SOME ADVENTURES IN STEREOCHEMISTRY

by

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Doctor of Science

University of Edinburgh

1979
Volume 2
An Appendix

Nae man can tether time nor tide

'Tam O'Shanter'  Robert Burns
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A List of Unpublished Works


The Unpublished Works
Preface to Volume 1

Chemistry assumes a ubiquitous status amongst the natural sciences. Not only does it seek, through the investigation of molecular structure and reaction mechanism, to answer questions posed by physical and chemical phenomena, but it also provides, through the medium of synthesis, a challenge to the innovative spirit and creative genius of man. It should always be a science and is sometimes an art. Often, the curiosity of the chemist in his quest to understand natural phenomena is surpassed only by his desire to emulate the chemical works of Nature. Nowhere across the wide spectrum of chemical disciplines has so much been accomplished by the practitioners in such a relatively short time span as within the domain—whatever that might be—of organic chemistry. A consideration in this volume to a range of topics which leads the reader through a somewhat arbitrary maze from hydrocarbons to quinones must, of necessity, pay some allegiance to the past glories of the subject. However, earlier achievements in no way overshadow more recent triumphs by organic chemists in manipulating molecular events involving the more mundane functional groups which will always provide the staple diet for chemical reactivity in organic compounds. Moreover, the last three decades have witnessed a technological revolution in the tooling of chemistry with the widespread introduction of, for example, chromatography and spectroscopy in their many and varied forms. In addition, interpretative and predictive powers have been increased enormously with the advent of modern high-speed electronic computers.

Stereochemistry has always provided a focal point within organic chemistry. It seemed not only reasonable but logical to allow recent conceptual developments in stereochemistry, coupled with the inevitable proliferation in nomenclature surrounding these advances, to provide a short introduction in Part 1 to this volume. Aside from their very considerable commercial importance, hydrocarbons, be they saturated or unsaturated, aliphatic or aromatic, have captured the imagination of theoreticians and experimentalists alike in recent years. Chapters 1–6 in Part 2 illustrate how the interplay of theory and practice has provided a much needed fillip to progress in this area. A discussion of reactive intermediates in Chapters 7 and 8 of Part 2 provides a useful bridge to the remainder of the volume. The early pre-eminence of carbocations has now given way to the recognition of the synthetic utility of other reactive species—particularly carbanions, but also radicals, carbenes, and arynes. Part 3 is given over entirely to halo compounds—a situation which reflects their importance from both academic and industrial viewpoints. In Part 4, alcohols, phenols, ethers, and peroxides are discussed in six separate chapters. Here, the importance of the oxygen atom in naturally occurring compounds is providing the organic chemist with the incentive, not only to understand, but also to mimic, e.g., the dramatic developments around crown ethers in a decade. Finally, of course, the carbonyl group is the centerpiece of organic chemistry. Chapters 1–5 in Part 5 must be viewed not only as individual contributions but also as introductions to much of the chemistry to be discussed in subsequent volumes of this work.

Circumstances eventually dictated that I was joined by no less than eighteen contributors in this mission to produce Volume 1 of Comprehensive Organic Chemistry. In so far as we are judged to have been successful in producing an interesting and readable account, the credit belongs to the authors. In so far as we are judged to have erred in our task through omissions or worse, the responsibility is mine. Whatever the judgement might be, I thank all those who have helped me to collate the material for this volume.

Sheffield

J. F. STODDART
1. INTRODUCTION AND STEREOCHEMISTRY

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1.1. SCOPE

There is little doubt that the emergence of stereochemical concepts over more than a century or so has been reflected intimately in the development of organic chemistry as a scientific discipline. Although stereochemistry is as old as organic chemistry itself, it provides, nonetheless, a suitable introductory theme to a treatise such as this devoted to modern organic chemistry. In more recent times, the advent of conformational analysis as a result of the pioneering paper published in 1950 by Barton heralded a new era of growth in organic chemistry. During almost three decades now, conformational ideas in particular and stereochemical concepts in general have fostered major advances in (i) our approach to structural elucidations, (ii) our knowledge of reaction mechanisms, and (iii) our development of new synthetic methods. In this brief introductory section, the more recent conceptual advances in stereochemistry will be brought under scrutiny since they impinge most directly upon structural aspects. Thereafter, some contemporary aspects of dynamic stereochemistry will be highlighted very briefly as a forerunner to the remainder of the work.
Inevitably, a short introduction must of necessity ignore many important stereochemical topics in specialised fields. Thus, at the outset, we refer the reader to a selection of numerous textbooks, monographs, and reviews on various aspects of stereochemistry in the hope that he might find there what he will not find here in this introductory Chapter.

1.2. SYMMETRY AND CHIRALITY

The symmetry properties of geometrical figures are characterised by symmetry operations which in turn define the symmetry elements (see Table 1) present in the particular simplex under examination. If molecules can be assumed— for the present at least—to generate geometrical figures, then it is possible to discuss their molecular structures in terms of their symmetry. In the first instance, it will be useful to restrict this discussion to (i) molecules which have defined structures by virtue of their rigidity and (ii) flexible molecules in which structures are defined as a consequence of selecting particular conformations. Basically, there are two kinds of symmetry elements—namely (i) axes of rotation and (ii) rotation-reflection axes which a molecule can display through inspection of symmetry operations. Molecules that witness superimposition of structures upon their original structures as a consequence of rotation by $2\pi/n$ radians about an axis possess a so-called $C_n$ axis (n.b. symmetry element descriptors are usually italicised). For example, dichloromethane (1) contains $C_2$ axis and chloroform (2), a $C_3$ axis. All molecules, of course, contain an infinite number of trivial $C_1$ axes and, for this reason, they are often referred to collectively as the identity element, $E$. Molecules whose structures are indistinguishable from the original structures only after rotation by $2\pi/n$ radians followed by reflection in a plane.
TABLE I

Symmetry elements and symmetry operations

<table>
<thead>
<tr>
<th>Symmetry elements</th>
<th>Symmetry operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_n$ (Axis of symmetry)</td>
<td>Rotation about an axis through $2\pi/n$ radians</td>
</tr>
<tr>
<td>$\sigma$ (Plane of symmetry)</td>
<td>Reflection in a plane</td>
</tr>
<tr>
<td>$I$ (Centre of symmetry)</td>
<td>Inversion through a centre</td>
</tr>
<tr>
<td>$S_n$ (Rotation-reflection axis of symmetry)</td>
<td>Rotation about an axis through $2\pi/n$ radians followed by reflection in a plane perpendicular to the axis.</td>
</tr>
</tbody>
</table>

a All molecules have an infinite number of trivial axes which can be referred to collectively as the identity element, $E$.

b A plane of symmetry corresponds to a $S_1$ symmetry element.

c A centre of symmetry corresponds to a $S_2$ symmetry element.

perpendicular to the chosen axis of rotation possess a so-called $S_n$ axis. When $n = 1$, the trivial $S_1$ axis corresponds to a plane of symmetry ($\sigma$) perpendicular to the rotation axis. A $\sigma$ plane is most easily recognised as a mirror plane which bisects the molecule such that the ligands on one side of the plane are reflected exactly upon those on the other side.

For example, dichloromethane (1) possesses two, and chloroform (2) three, $\sigma$ planes. When $n = 2$, the $S_2$ axis corresponds to a centre of inversion (1) which demands that all ligands in the molecule are capable of
inversion through a centre, i.e. any two particular ligands lie on a line going through the centre of the molecule such that the ligands are equidistant from the centre. The particular conformation (3) of meso-1,2-difluoro-1,2-dichloroethane contains a centre of symmetry. Higher order \( S_n \) (\( n \) must be an even number) axes are a relatively rare phenomenon but they do occur, for example, in spiro compounds of the type (4).

Molecules which contain \( S_n \) symmetry elements, i.e. a plane \((a \equiv S_1)\), or centre \((i \equiv S_2)\) of symmetry, or a higher order \( S_n \) (\( n = 4, 6, \text{etc.} \)) axis have reflection symmetry and are said to be nondissymmetric or achiral. Such molecules are devoid of handedness and therefore cannot exhibit enantiomerism and hence any of the chiroptical properties associated with this phenomenon. By contrast, molecules without reflection symmetry are said to be dissymmetric or chiral. Such molecules are not superimposable upon their mirror images and therefore exhibit enantiomerism. This means that, in principle at least, these molecules can display optical activity. However, it should be recognised that the absence of measurable chiroptical properties is possible in chiral molecules and that enantiomerism is not an empirically-based concept—it relates to a geometrical concept definable in terms of molecular symmetry. Thus, the description enantiomerism is always to be preferred to the term optical isomerism whose usage is not recommended. It should be noted that chiral molecules can be symmetric by virtue of containing a \( C_n \) (\( n > 1 \)) axis, e.g. in appropriate conformations, (+)-tartaric acid (5) and (-)-mannitol (6) both contain \( C_2 \) axes. When molecules are devoid of all symmetry elements apart from the identity element, e.g. (+)-\( \alpha \)-pinene (7) and (-)-cholesterol (8), they are said to be asymmetric. Thus, all asymmetric molecules are
chiral although not all chiral molecules are necessarily asymmetric. For this reason, the term asymmetric centre has been superceded by the term chiral centre, or more precisely, centre of chirality. The word chiral is derived from cheir, the Greek word for hand, and was first employed in 1884 by the physicist, Lord Kelvin, to describe geometrical figures or any group of points which exhibit handedness or what he preferred to call chirality. Although the meaning of the word had been discussed in a chemical context by Whyte in the 1950's, it took many decades for the term chirality to be accepted finally into the chemical literature by Cahn, Ingold, and Prelog in 1966 at the suggestion of Mislow.

Geometrical figures, and hence molecules, can be allocated symmetry point groups according to the combination of symmetry elements they possess. Since this classification of molecules proves to be useful in a much wider context within organic chemistry, the so-called Schoenflies notation (n.b. crystallographers usually employ the alternative Hermann-Mauguin notation) will now be discussed by reference to Table II which summarises the important symmetry point groups in relation to organic molecules. It should be noted that the boldface symbol employed to denote a point group tends to have its origins in the principle symmetry element with the numerical and italicised subscripts helping to identify other symmetry elements. Asymmetric molecules, e.g. α-pinene (7) and cholesterol (8), which contain no symmetry elements other than the identity element belong to the point group, $C_1$. Molecules without reflection symmetry which possess a $C_n$ ($n > 1$) axis belong to the $C_n$ point groups. By far the most common point group in this collection is the point group $C_2$, e.g. tartaric acid (5) and mannitol (6). Examples of molecules with $C_n$ symmetry of order higher than two are rare; they are provided by tri-α-thymotide (9).
### TABLE II

The important symmetry point groups

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<thead>
<tr>
<th>Point Group</th>
<th>Symmetry elements</th>
<th>Symmetry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_1$</td>
<td>$E$</td>
<td>1</td>
</tr>
<tr>
<td>$C_n$</td>
<td>$E, \frac{C_n}{2}$</td>
<td>$\frac{n}{2}$</td>
</tr>
<tr>
<td>$D_n$</td>
<td>$E, \frac{C_n}{2}, n \frac{C_2}{2}$</td>
<td>2n</td>
</tr>
<tr>
<td>$C_s$</td>
<td>$E, \sigma_v$</td>
<td>1</td>
</tr>
<tr>
<td>$C_1$</td>
<td>$E, i$</td>
<td>1</td>
</tr>
<tr>
<td>$S_n$</td>
<td>$E, \frac{C_n}{2}, \frac{S_n}{2}$ (collinear with the $\frac{C_n}{2}$ axis)</td>
<td>$\frac{n}{2}$</td>
</tr>
<tr>
<td>$C_{n+1}$</td>
<td>$E, \frac{C_n}{n}, n \sigma_v$</td>
<td>$n (n\leq\infty)$</td>
</tr>
<tr>
<td>$C_{\infty v}$</td>
<td>$E, \frac{C_\infty}{2}, \infty \sigma_v$</td>
<td>1</td>
</tr>
<tr>
<td>$C_{2h}$</td>
<td>$E, \frac{C_2}{2}, \sigma_h, i$</td>
<td>2</td>
</tr>
<tr>
<td>$D_2h$</td>
<td>$E, 3\frac{C_2}{2}$ (mutually perpendicular), $3\sigma$ (mutually perpendicular), $i$</td>
<td>4</td>
</tr>
<tr>
<td>$D_3h$</td>
<td>$E, \frac{C_3}{2}, 3 \frac{C_2}{2}$ (all perpendicular to the $\frac{C_3}{2}$ axis), $3\sigma_v, \sigma_h$</td>
<td>6</td>
</tr>
<tr>
<td>$D_{\infty h}$</td>
<td>$E, \frac{C_\infty}{2}, \infty \frac{C_2}{2}$ (all perpendicular to the $\frac{C_\infty}{2}$ axis), $\infty \sigma_v, \sigma_h, i$</td>
<td>2</td>
</tr>
<tr>
<td>$D_{2d}$</td>
<td>$E, 3\frac{C_2}{2}$ (mutually perpendicular), $2\sigma_d, S_4$ (collinear with one of the $\frac{C_2}{2}$ axes)</td>
<td>4</td>
</tr>
<tr>
<td>$D_{3d}$</td>
<td>$E, \frac{C_3}{2}, 3 \frac{C_2}{2}$ (all perpendicular to the $\frac{C_3}{2}$ axis), $3\sigma_d, i, S_6$ (collinear with the $\frac{C_3}{2}$ axis)</td>
<td>6</td>
</tr>
<tr>
<td>$T_d$</td>
<td>$E, 4\frac{C_3}{2}, 3 \frac{C_2}{2}$ (mutually perpendicular), $6\sigma, 3S_4$ (Coincident with the $\frac{C_3}{2}$ axis)</td>
<td>12</td>
</tr>
<tr>
<td>$O_h$</td>
<td>$E, 3\frac{C_4}{4}$ (mutually perpendicular), $4\frac{C_3}{3}, 6\frac{C_2}{6}, 9\sigma, 3S_4, 4S_6$</td>
<td>24</td>
</tr>
</tbody>
</table>

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**a** The number of indistinguishable but nonidentical positions through which a molecule may be rotated is known as the symmetry number.

**b** These point groups are termed the non-axial point groups because they do not contain any $C_n$ ($n > 1$) axes. All the other point groups are termed axial.
High symmetry chiral molecules have been reviewed recently by M. Farina and C. Morandi, Tetrahedron, 1974, 30, 1819.

If there is only one C_n axis, and if n σ planes intersect at that C_n axis, then the planes are designated σ^{v}_n (where v means vertical).

The commonly occurring examples correspond to n = 2 and 3, i.e., C_{2v} and C_{3v}. However, there are examples of molecules with C_{nν} symmetry where n > 3, e.g. the all-cis-1,2,3,4-tetrachlorocyclobutane belongs to point group C_{4ν}. Also, see ref. 36.

If there is only one C_n axis and no intersecting σ planes, but instead a σ plane perpendicular to the C_n axis, then the plane is designated σ^{h}_n (where h means horizontal). The commonly occurring examples correspond to n = 2, i.e., to C_{2h} as indicated above. However, there are examples of molecules with C_{nρ} symmetry where n > 2, e.g. iso-cis-perhydrotripticene has C_{3h} symmetry (see ref. in footnote c).

The commonly occurring examples correspond to n = 2 and 3, i.e., D_{2h} and D_{3h}. However, there are examples of molecules with D_{nρ} symmetry where n > 3, e.g. the eclipsed configuration of ferrocene belongs to point group D_{5h} and benzene has D_{6h} symmetry (see refs. 21 and 22).

When a set of σ planes bisect the angles between a set of C_2 axes, the planes are designated σ^{d}_n (where d means diagonal). The commonly occurring examples correspond to n = 2 and 3, i.e., to D_{2d} and D_{3d} as indicated above. However, there are examples of molecules with D_{nρ} symmetry where n > 3, e.g. the staggered configuration of ferrocene belongs to point group D_{5d}.

A few chiral molecules possess more than one C_n axis. In such cases, the molecules are said to have dihedral symmetry and belong to the D_n point groups. They have a principal C_n axis with nC_2 axes perpendicular to it. The D_2 point group is exemplified by twistane (11) and the rarely encountered D_3 point group by the trisbinaphthyl-24-crown-6 (12).

Molecules belonging to the C_n — including C_1 — and D_n point groups are...
chiral. Indeed, the vast majority of chiral molecules belong to these point groups. Molecules with reflection symmetry can be classified into a wide range of symmetry point groups. The simplest cases are those with either (i) a \( \sigma \) plane (S1 axis) — which have \( C_\infty \) symmetry — or (ii) an inversion (S2 axis) — which have \( C_1 \) symmetry. For example, ethanol (13) has \( C_\infty \) symmetry whereas the dichlorodifluorocyclobutane (14) has \( C_1 \) symmetry. In general, molecules which contain an \( S_n \) (\( n > 2 \)) axis in addition to collinear \( C_{n/2} \) axes belong to the \( S_n \) point groups, e.g. the spiro compound (14) has \( S_4 \) symmetry. Molecules which possess \( n \) \( \sigma \) planes which bisect a \( C_n \) axis belong to the \( C_{nv} \) point groups, e.g. dichloromethane (1) has \( C_{2v} \) symmetry and chloroform (2), \( C_{3v} \) symmetry. Linear molecules with conical symmetry such as chloroacetylene (15) belong to the point group \( C_{\infty v} \). Molecules which have a \( \sigma \) plane perpendicular to a \( C_n \) axis belong to the \( C_{nh} \) point groups, e.g. trans-butene (16) has \( C_{2h} \) symmetry. Molecules with reflection symmetry can also possess dihedral symmetry. When a \( \sigma \) plane is perpendicular to the principle \( C_n \) axis, the molecule belongs to the \( D_{nh} \) point groups, e.g. ethylene (17) has \( D_{2h} \) symmetry, cyclopropane (18) has \( D_{3h} \) symmetry, and benzene (19) has \( D_{6h} \) symmetry. Linear molecules with cylindrical symmetry such as acetylene (20) belong to the point group \( D_{\infty h} \). When \( \sigma \) planes intersect at a principal \( C_n \) axis and bisect the \( n \) \( C_2 \) axes, the molecule belongs to the \( D_{nd} \) point groups, e.g. allene (21) has \( D_{2d} \) symmetry and the chair conformation (22) of cyclohexane has \( D_{3d} \) symmetry. The highly symmetrical \( I_d \) and \( O_h \) point groups are exemplified by methane (23) and cubane (24), respectively.

So far in this discussion, it has been assumed that molecules can be equated with models based on geometrical figures. More detailed thought and analysis reveals, however, that this portrayal of real molecules...
in terms of abstract models is not really justified. For a full and 
stimulating discussion of the problems, the reader is referred to 'an 
epistemological note on chirality' by Mislow and Bickart. There now 
follows a summary of their appraisal of the problems and their conclusions. 
Let us begin by considering one mole of a monoatomic gas at room temperature. 
Although all possible means of measurement of the macroscopic sample 
indicate that it is achiral, it must, of course, at any particular instant 
be chiral. Statistical averaging on the time scale of any measurement 
made leads to the cancellation of the chiral effects and such a system is 
said to be stochastically achiral, i.e. the boundary between chirality 
and achirality is ill-defined for molecules. Similarly, the assignment 
of point groups to molecules very often represents the idealised situation 
which is probably never reached except on an averaging basis. For 
example, it has been stated already that the propeller conformation (g) 
of tri-o-thymotide has $C_3$ symmetry. In fact, in the crystal structure, 
deviations from $C_3$ symmetry are quite large; not surprisingly, on 
statistical—and hence entropic—grounds a lopsided asymmetrical ($C_1$) 
conformation is energetically more favourable. The fact that the low 
temperature $^1$H nuclear magnetic resonance (n.m.r.) spectra do not reveal 
this lack of symmetry in solution no doubt reflects an averaging process 
by this means of observation. It can be said that molecules of one 
chiral class, such as the propeller conformation (g) of tri-o-thymotide 
are homochiral just in the way right hands belonging to different people 
are alike but not identical. By the same token, enantiomerically-related 
molecules which exhibit a spectrum of chirality characteristics are said 
to be heterochiral. Another example of stochastic achirality is met in 
the ring inversion process which permits equilibration between enantiomeric
chair conformations, (25a) and (25a), of cis-1,2-disubstituted cyclohexanes (see Figure 1). It is unlikely that the enantiomeric mixture will ever be equimolar. Nonetheless, averaging processes on the time scale of observation reveal that the system is achiral. Furthermore, dynamic n.m.r. spectroscopy shows that although molecules of many 1,2-disubstituted cyclohexanes exhibit $C_1$ symmetry at low temperatures, they behave as if they had $C_5$ symmetry (25b), i.e. they are achiral, at room temperature. Extrapolating to cyclohexane, it often behaves as if it had $D_{6h}$ symmetry rather than the $D_{3d}$ symmetry of the chair conformation (22).

The absence of chirality can arise for reasons other than stochastic chirality. If chirality falls below the threshold of detection as it would in $\text{H}(\text{CH}_2)_n\text{CHD}(\text{CH}_2)_n\text{D}$ as the magnitude of $n$ increases, then a situation which is described as cryptochirality pertains. This phenomenon is met in the chemistry of triglycerides such as (26), which, although they are unquestionably chiral, do not exhibit chiroptical properties.

Thus, it is not only permissible but realistic to refer to degrees of chirality. As often happens in chemistry, the situation regarding a concept—in this case, chirality—is not black and white. It is various shades of grey. Whilst observable chirality phenomena allow us to conclude that a sample, i.e. an ensemble of molecules, is chiral, the lack of such phenomena do not permit the designation achiral to be made.

1.3. CHEMICAL TOPOLOGY

Following the critique at the end of the previous Section on the relationship between geometrical figures and molecules, this theme is now going to be considered again in more detail in order that different
sources of chirality within molecules can be identified and classified in Section 1.4. The practicalities of chemistry have to be recognised. Whilst it may be sufficient (or even insufficient!) to associate chirality with certain molecular symmetry characteristics at an abstract level, the fact is that experimentalists are often concerned with introducing stereochemical modifications into portions of organic molecules. Thus, it is useful — indeed essential — to be able to locate and designate elements of chirality within a molecule.

Prelog has drawn attention to the fact that chirality can be exhibited in either two- or three-dimensional space and has employed simplices in the form of triangles and tetrahedra to represent these situations. The irregular triangle is chiral in two-dimensional space since its mirror image by reflection across a straight line cannot be brought into congruence with it by translation or rotation in the plane (see Figure 2). Two-dimensional chirality is, however, lost in three-dimensional space. The block capital letters of the alphabet can be divided as shown in Figure 3 into those that are achiral and those that are chiral in two dimensions. In Figure 2, block capital letters have been introduced at the vertices of equilateral triangles to form different arrays; many of the simplices can be related to planar molecules, e.g. (28) to acetaldehyde (29), (30) to maleic acid (31), and (32) to fumaric acid (33). Thus, the chirality of acetaldehyde and fumaric acid in two-dimensions can be recognised by us and by enzymes (see Section 1.5). Concepts such as stereoheterotopism and prochirality are a consequence of two-dimensional chirality. Eight point group symmetries are possible (see Figure 4) for the three-dimensional simplex, the tetrahedron. The regular $T_4$
tetrahedron \((3^4)\) is the simplex for the familiar chiral centre—see \((4^2)\) in Figure 5—although simplices with \(D_2\) \((35)\), \(C_2\) \((36)\), and \(C_1\) \((37)\) symmetry can, in principle, incorporate a centre of chirality as well. Figure 5 shows that the regular \(T_d\) tetrahedron \((3^4)\) can also be considered as the simplex for centres of prochirality, e.g. \((4^3)\), pseudoasymmetry (or pseudochirality), \((4^2)\) e.g. \((4^4)\) and \((4^5)\), and propseudoasymmetry (or propseudochirality), e.g. \((4^6)\). The \(D_{2d}\) tetrahedron \((3^8)\) in Figure 4 is the simplex for axial chirality, prochirality, and pseudoasymmetry (pseudochirality) while the \(C_5\) tetrahedron \((3^9)\) in Figure 4 is the simplex for planar chirality, prochirality, and pseudoasymmetry (pseudochirality). For examples of axial and planar prochirality and pseudoasymmetry (pseudochirality), the reader is referred to the original literature. Although chiral centres, axes, and planes will be discussed in more detail in Section 1.4, it might be instructive to relate these to the general molecular phenomena at this juncture. Compounds of the type \(\text{Cab}cd\) \((4^7)\) contain the familiar chiral centre, whereas in appropriately-substituted allenes \((4^8)\) and biphenyls \((4^9)\), the element of chirality is an axis. A plane of chirality is present in \(\text{trans-cycloalkanes}\) \((5^0)\) and in appropriately-substituted paracyclophanes \((5^1)\).

1.4. ISOMERISM

1.4.1. Some Definitions

Although the concept of isomerism has been around in chemistry for more than 150 years, an element of vagueness and mystery still surrounds its usage by chemists. The IUPAC Commission on Nomenclature of Organic Compounds in their rules\(^{32}\) on stereochemistry carefully avoid the problems by merely stating that compounds with identical molecular formulae but differing in the nature or sequence of bonding of their atoms in space are termed isomers. The rules proceed to identify the
two major classifications of isomers, (i) those that differ in their 
constitution and (ii) stereoisomers which are inherent in the above 
definition of isomers. The constitution defines the nature and sequence 
of the bonding between atoms in molecules. Isomers differing in 
constitution are called constitutional isomers, e.g. butane (MeCH₂CH₂Me) 
and 2-methylpropane (MeCHMe₂), dimethyl ether (MeOMe) and ethanol (MeCH₂OH) 
and the keto (MeCOCH₂CO₂Et) and enol (MeCOH=CHCO₂Et) forms of acetoacetic 
ester. Isomers are called stereoisomers when they differ only in the 
arrangement of their atoms in space, e.g. D- and L- glyceraldehyde (52), 
cis- (53) and trans- (16) but-2-ene, gauche- (54) and anti- (55) butane, 
and the biphenyls, (R)-(56) and (S)-(56). Stereoisomers may be 
configurational or conformational in type. The term configuration 
relates to the particular spatial arrangement of atoms in molecules of 
defined constitution without regard to those arrangements which differ 
only on torsion about single bonds. Isomers differing in configuration 
are called configurational isomers, e.g. D- and L- glyceraldehyde (52), 
cis- (53) and trans- (16) but-2-ene, and (Z) and (E)- N-methylformamide 
(57). The term conformation relates to the different spatial arrange-
ments of atoms in molecules of defined configuration obtained on torsion 
about one or more single bonds, e.g. gauche- (54) and anti- (55) butane, 
and the biphenyls, (R)-(56) and (S)-(56). For most organic molecules, 
our knowledge of molecular shape—or structure—is only complete when 
the constitution, configuration, and conformation are known.

Stereoisomers—both configurational and conformational—are 
either enantiomers or diastereoisomers. Enantiomerism has already been 
discussed in conjunction with chirality in Sections 1.2 and 1.3. Suffice 
it to state here that molecules which are related as object is to mirror
image and yet non-superimposable upon one another are enantiomers. Diastereoisomers are any stereoisomers which are not enantiomers of each other. This dichotomous subdivision first suggested by Wheland has now gained general acceptance although it produces some surprises for those versed in the old definition. For example, it means that not only are stereoisomers such as \(-\) (5) and meso- (58) tartaric acid, and cis- (59) and trans- (60) 1,3-dimethylcyclohexane, which contain chiral centres, classified as diastereoisomers but so are cis- (61) and trans- (62) 1,4-dimethylcyclohexane, and cis- (53) and trans- (16) butene, which are devoid of chirality. Although the term cis-trans isomerism remains acceptable as a sub-class of diastereoisomerism, it is to be hoped that terms such as optical and geometrical isomers will soon disappear from the scene. Prelog has drawn attention to a rather novel example of stereoisomerism amongst some cyclopeptides and has coined the terms cycloenantiomer and cyclodiastereoisomer to describe this rather specialised phenomenon. In addition, cyclic molecules are capable of another type of structural isomerism which has been referred to as topological isomerism. This is exhibited by, for example, catenanes which are formed by the interlocking of cyclic atomic arrays.

Finally, the situation governing synthetic and natural polymers requires some comment. The term primary structure defines the constitution of a polymer as well as the configuration of all the chiral centres along the chain and in the side chains. The secondary structure is known when the conformation of the chain is defined. In the case of polymers—some proteins, nucleic acids, and polysaccharides in particular—ordering of structure by a multitude of many weak non-covalent interactions between two or more chains in the same or separate molecules can occur.
The term tertiary structure can be employed to describe molecules of known primary and secondary structure which interact intermolecularly, e.g. to form double or triple helices.

1.4.2. Designation of Constitution

The designation of the constitution of an organic molecule is perhaps most readily communicated by means of a formula presented in two-dimensional space. However, this form of presentation, whilst highly precise is demanding on space and so the need for names and a system of nomenclature arises. The literature in this area is vast and IUPAC has attempted over the years to introduce some rhyme and reason into chemical nomenclature. The reader is referred to the literature on IUPAC nomenclature of organic chemistry but is reminded of the need to come to terms with reality and trivial nomenclature, e.g. 'glucose' is going to be 'glucose' for a long time to come!

1.4.3. Designation of Absolute Configuration

The term absolute configuration is used to describe the known three dimensional arrangement of ligands around a chiral element. It became possible after 1951 by the use of a technique based on X-ray fluorescence to determine the absolute stereochemistry of a chiral molecule. In a particular case, the absolute configuration of a molecule can be represented on two-dimensional paper using the familiar 'wedge' and 'dot' notation or some suitably defined projection formula, e.g. the Fischer projection formula. Once again, however, there is a need to designate absolute configuration by means of a symbolism which can be coupled to the name of a compound. In recent years, the (RS)-convention introduced by Cahn, Ingold, and Prelog in 1951 and modified subsequently in 1956.
and 1966 has tended to replace the older DL-convention in many areas of organic chemistry.

1.4.3.1. The (RS)-convention. The Cahn-Ingold-Prelog system for assigning absolute configuration depends upon a sequence rule procedure to specify the chirality of each chiral element (centre or axis) in a configurationally-chiral molecule.

In its most familiar form, the system has been employed with the chiral carbon (Cabcd) atom although it can equally well be applied to other atoms (e.g. N,S,P, etc.) carrying four different ligands (abcd) — even lone pairs of electrons can be accommodated! A sequence rule (see below) is employed in order to arrange the ligands a, b, c, and d with the priority: a > b > c > d. The chiral centre is then viewed (Figure 6) from the side remote from ligand d of lowest priority. If the ligands a, b, and c describe a clockwise array, the descriptor (R) (Latin, rectus = right) is used and if they describe an anticlockwise array the descriptor (S) (Latin, sinister = left) is used. In order to deduce the priority a > b > c > d, the sequence rule is invoked according to the following simplified procedure. First of all, ligands are arranged in order of decreasing atomic number so that, in bromochloroiodomethane, for example, a > b > c > d corresponds to I > Br > Cl > H and hence it has the (S)-configuration. If the atoms in two or more of the ligands attached to the chiral centre are the same, then decisions regarding their priorities are reached by working outwards concurrently atom by atom until the first point of difference is reached. The procedure is illustrated by considering the priority a > b > c > d assigned to the ligands in which is Cl > CH(CH₂I)CH₃ > CH(CHBrCH₃)₂ > CH₂OH > H and hence the chiral centre C* in has the (R)-configuration.
Note that as soon as the atom—iodine, in this case—of highest atomic number in the two ligands under comparison is reached, it claims precedence for its ligand over the other ligand where there might be an accumulation of atoms—in this case, bromine and oxygen—with smaller atomic numbers. Multiple bonded atoms in double or triple bonds are split formalistically into two and three bonds, respectively. The examples given in Figure 7 illustrate the practice of denoting the duplicated or triplicated atoms in parentheses. In D-glyceraldehyde D-(52), the priority $a > b > c > d$ assigned to the ligands is $\text{OH} > \text{CHO} > \text{CH}_2\text{OH} > \text{H}$ and so it has the (R)-configuration. Finally, when isotopes are present, the atom of higher mass number takes priority, e.g., $\text{D} > \text{H}$ (see Section ). Compounds can, of course, contain more than one chiral centre. In these cases, the descriptors (R) and (S) are associated with their IUPAC locants, e.g., the enantiomeric pentan-2,4-diols $\text{CH}_3\text{CH(OH)}\text{CH}_2\text{CH(OH)}\text{CH}_3$ (65) are differentiated as (2R,4R) and (2S,4S).

 Appropriately-substituted allenes, e.g., (48), are configurationally chiral and the element of chirality is an axis based on the $\text{D}_2\text{d}$ simplex (38). A comparison of (47) with (48) indicates that fewer ligand differences are required to produce chirality around an axis than are necessary to produce a chiral centre. The chiral allene can be viewed along its chiral axis in either direction, and, in assigning the priority $a > b > c > d$ to the four ligands, it is assumed that near ligands precede far ligands. Thus, applying the sequence rules to the dimethylallene (66) in Figure 8 establishes that it has the (R)-configuration. Other examples of axial chirality are found amongst alkyldenecycloalkanes, spiro compounds, and adamantoids. Also, the allenic fragment can be part of a cyclic system as in (+)-cyclonona-1,2-diene, which is shown in
Section 2.2.1 to have the \((R)\)-configuration.

1.4.3.2. **The DL-convention.** This much older convention is still used with \(\alpha\)-amino acids,\(^{53}\) cyclitols,\(^{54}\) and carbohydrates.\(^{55}\) It can be applied to molecules of the type \(R^1\text{CHXR}^2\) which can be oriented in a Fischer projection formula such that the most highly oxidised carbon-containing ligand is at the top. Then, if \(X\) is on the right, the configuration is \(D\), whereas if \(X\) is on the left the configuration is \(L\). Thus, \((+)-\text{glyceraldehyde} \,(+)-(52)\) has the \(D\)-configuration and \((-)-\text{glyceraldehyde} \,(-)-(52)\), the \(L\)-configuration. Difficulties can arise in applying this convention when more than one chiral centre is present. In such cases, it is conventional to number the carbon chain of the Fischer projection from top to bottom and allow the absolute configuration of the highest-numbered chiral carbon atom to determine the nature of the configurational descriptor. Thus, \((-)-\text{threose} \,(-)-(67)\) has the \(L\) configuration and \((-)-\text{arabinose} \,(-)-(68)\) the \(D\)-configuration. The relative configurations at the other chiral centres in \(\alpha\)-\((67)\) and \(\delta\)-\((68)\) are defined by the generic prefixes, threo and arabino, respectively. It is probably desirable\(^{29,32}\) that these 'local' systems of nomenclature be retained since the adoption of the \((RS)\)- convention would be both confusing and cumbersome. However, there is no reason\(^{29,32}\) why the \((RS)\)- cannot be 'mixed' with the DL-convention when the need arises.

1.4.3.3. **The \(\alpha\beta\)-convention.** The only other convention of major importance nowadays is the \(\alpha\beta\)-system employed\(^{56}\) with a series of trivial names for steroids and related compounds. When the rings of a steroid are denoted as projections on to the plane of the paper, the formula is oriented as in cholesterol \((\alpha)\), for example. A ligand attached to a ring is termed alpha (\(a\)) if it lies below the plane of the paper, \(e.g.,\) the \(H\) atom at C-9,
and beta (β) if it lies above the plane of the paper, e.g. the Me group at C-10.

1.4.4. Designation of Relative Configuration

The term relative configuration is used\(^{32}\) to describe the relative positions of ligands on different atoms in a molecule. Relative configuration differences can occur in both chiral and achiral molecules.

1.4.4.1. In molecules with chiral centres. When only the relative configurations of a number of chiral centres in a molecule are known, the (RS)-convention is used on the arbitrary assumption that the chiral centre with the lowest locant according to the IUPAC nomenclature rules has chirality (R). In the case of a racemic modification, the prefix rel is also used, e.g. the racemic cyclohexane derivative (\(\dagger\))-(69) is rel-(1R,3S,5S)-1-bromo-3-chloro-5-iodocyclohexane and racemic CH\(_3\)CH(OH)CH\(_2\)CH(OH)CH\(_3\) (65) is designated rel-(2R,4R)-pentan-2,4-diol. In optically active or meso compounds, the prefix rel is also employed, e.g. the cis-isomer (59) of 1,3-dimethytcyclohexane becomes rel-(1R,3S)-1,3-dimethylcyclohexane and meso-CH\(_3\)CH(OH)CH\(_2\)CH(OH)CH\(_3\) (65) is called rel-(2R,4S)-pentan-2,4-diol.

1.4.4.2. The (EZ)-convention. Although the terms cis and trans are adequately well defined in the case of disubstituted olefins, their use becomes\(^{30,32}\) ambiguous with trisubstituted olefins and impracticable with tetrastubstituted olefins. It is better to adopt a system of nomenclature\(^{30,32}\) based on the sequence rules for structures of the type abcC=Ccd. If the priorities are a > b and c > d and a and c are cis to each other, then the configuration is seqcis and the descriptor (Z) (German, zusammen = together) is used in naming the compound. If the priorities are the same and a and c
are trans to each other, then the configuration is seqtrans and the descriptor (E) (German, entgegen = opposite) is used in naming the compound. Thus, cis-but-2-ene (53) has the (Z)-configuration and trans-but-2-ene (16), the (E)-configuration. The convention can be applied to other double bonds, e.g., C=N and N=N bonds, and, in relation to the stereochemistry of oximes, the use of the terms syn and anti should now be discontinued. Finally, if a molecule contains several double bonds then the necessary prefix is associated with the relevant locant prescribed by the IUPAC nomenclature rules, e.g., compound (70) is (2E,4Z)-5-chloro-2,4-hexadienoic acid.

1.4.4.3. In monocyclic systems with substituents. In compounds such as cis- (59) and trans- (60) 1,3-dimethylcyclohexane, the prefixes define their diastereoisomeric relationship unequivocally. The (RS)-convention can be employed to define absolutely the configuration of a particular enantiomer of trans-1,3-dimethylcyclohexane (60). However, the (RS)-convention when applied to racemic modifications is cumbersome (see Section 1.14.1) and it is often more convenient to apply the prefixes, cis and trans, e.g., for the 1,4-dimethylcyclohexanes (61) and (62), respectively. Unfortunately, in more highly substituted examples, the cis-trans nomenclature becomes equivocal; e.g., in the dimethylcyclohexanol derivative (71), is the 4-methyl substituent considered to be trans to the hydroxyl group at C-1 or cis to the methyl group at C-1? In ambiguous situations such as this, the relative configurations of the substituents are expressed by adding r (for reference ligand) before the locant of the lowest-numbered of these substituents according to the IUPAC nomenclature rules of numbering, e.g., the tribromocyclopentane derivative (72) becomes r-1, cis-2, cis-4-tribromocyclopentane. When two different substituents are attached
to the lowest-numbered ring atom, then the ligand with preference under
the IUPAC nomenclature system is designated as the reference ligand, e.g.
the dimethylcyclohexanol derivative \( (71) \) becomes \( _{\text{trans}}^{1\text{-trans}}4\text{-dimethylcyclo-
hexan-r-1-ol} \).

1.4.4.4. In fused-ring systems. Bicyclic systems can be treated as
examples of \textit{cis}-\textit{trans} isomerism just like disubstituted monocyclic systems,
\textit{e.g.} \textit{trans}-decalin \( (73) \). The use of the prefixes \textit{exo} and \textit{endo} to indicate
relative stereochemistry in bicyclic systems such as \([2,2,1]\)bicycloheptane
(norbornane) \( (74) \) is well established by contemporary usage. When the rela
tive configuration at more than one bridgehead has to be specified, the
descriptors \textit{cisoid} and \textit{transoid} are employed, \textit{e.g.} the tricyclic hydrocarbon
\( (75) \) is referred to as \textit{cis-transoid-cis-}perhydroanthracene. See also
Section 4.4.5.2, for a discussion of the relative stereochemistry of the
seven configurational isomers of dicyclohexyl-18-crown-6.

1.4.5. Designation of Conformation

The designation of the conformation of a molecule is potentially
even more hazardous and challenging to the chemist than is the designation
of its constitution or configuration. As conformational considerations
represent the most recent level of structure to have been considered
stereochemically, the nomenclature system is still at an embryonic stage.

Appropriately-substituted biphenyls, \textit{e.g.} \( (49) \), have been treated
as examples of axially-chiral systems and the \((RS)\)-convention has been
employed\( ^{29,30,32} \) to designate their chirality as \((R)\) or \((S)\). The need
for their absolute conformational properties to be defined has arisen out
of the fact that many biphenyls containing bulky \textit{ortho} substituents have
been resolved into their enantiomeric pairs, e.g. 6,6'-dinitrodiphenic acid. It will be recalled that the $D_{2d}$ simplex in Figure 4 forms the basis for designating axial chirality. In tetra-ortho-substituted biphenyls the apices of this elongated tetrahedron correspond with C-2, C-6, C-2', and C-6'. The chiral biphenyl can be viewed along its axis in either direction and in assigning the priority $a > b > c > d$ to the four ligands, it is assumed—as with chiral allenes (see Section 1.4.3.1)—that near ligands precede for ligands. Thus, applying the sequence rules to the 6,6'-dinitrodiphenic acid (76) in Figure 9 establishes that (76) has chirality (R). Occasionally, this kind of axial chirality is found in biphenyls which also have chiral centres associated with them (see Section 4.2.3.2).

For the few specialised cases in which planar chirality has to be specified using the (RS)-convention, the reader is referred to the original literature. 29,32

A number of molecules are conformationally chiral on account of their helicity, e.g. the propeller conformation (9) of tri-o-thymotide and hexahelicene (77). In such situations, according as the identified helix is left-handed or right-handed, it is designated (M) (for minus) and (P) (for plus), respectively. It has been shown by circular dichroism that (+)-tri-o-thymotide has the (M)-propeller conformation (9). Nucleic acids, proteins, and polysaccharides also exhibit helicity (see ref. 29) in their tertiary structure.

In 1,2-disubstituted ethanes ($XCH_2CH_2X$), conformations are described (see Figure 10) as synperiplanar (sp), synclinal (sc), anticlinal (ac), or antiperiplanar (ap) according as the torsional angle is within $\pm 30^\circ$ of $0^\circ$, $\pm 60^\circ$, $\pm 120^\circ$, or $\pm 180^\circ$, respectively. In more
complicated situations, the ligands which define the torsional angle are selected on the following basis: (i) when all three ligands on a carbon atom are different that given priority by the sequence rule is chosen, (ii) when one ligand out of the three is unique, it is chosen, and (iii) when all three ligands are the same, the one which provides the smallest torsional angle is chosen. It should be noted that, whereas synclinal and antiperiplanar conformations can correspond to ground state conformations (i.e. isomers), synperiplanar and anticlinal conformations correspond to transition state conformations, at least in \( \ce{C(sp^3)} \) bonding situations. This system of designating relative conformation can be extended to \( \ce{C(sp^3)} \) bonding situations. Examples of both kinds are given in Figure 11. The absolute conformation of a particular torsional angle can be analysed through its helicity. The smaller rotation required to eclipse the front ligand with the back ligand is noted as shown in Figure 12. If the rotation is right handed, the conformation is described as \( \text{(P)} \); if the rotation is left-handed, the conformation is described as \( \text{(M)} \).

A flexible ring system will seek its minimum energy conformation where the sum of the classical components (bond deformation strain, torsional strain, nonbonded interactional strain, and electronic interactional strain) of strain energy are minimised with respect to the molecular geometry (see Section ). For six-membered saturated ring compounds, the rigid chair conformation is the most stable conformational isomer, e.g. the chair conformation \( \text{(22)} \) of cyclohexane which has \( \ce{D_{3d}} \) symmetry. If the chair conformation is assumed to have idealised tetrahedral geometry (which does not quite have!) then the bonds that are parallel to the principal \( \ce{C_3} \) axis are termed axial (a) and those which, on projection towards this
axis, define tetrahedral angles with it are termed equatorial (e). In less symmetrical ring systems, e.g. the half-chair conformation (78) of cyclohexene the terms pseudoaxial (a') and pseudoequatorial (e') are often employed. When it is necessary to define the absolute conformation of ring compounds then the (MP)-convention can be applied to the synclinal ring bonds, e.g. the chair conformation (22) of cyclohexane has alternate (M) and (P) synclinal ring bonds as has trans-decalin (79).

1.4.6. Concept of Isomerism

It has been pointed out that the concept of isomerism only takes on practical significance when there is some means of distinguishing between isomers. However, the time scale of observation is often important in this connection. If isomers can be isolated physically, they can usually be distinguished by spectroscopic and/or diffraction methods. Even when they are too unstable to be isolated, they can sometimes be observed by, say, n.m.r. spectroscopy (see Figure 1). Chlorocyclohexane exhibits both axial and equatorial C-Cl stretching frequencies in its infrared spectrum at room temperature, although the ^1H n.m.r. spectrum shows no indications of the presence of diastereoisomeric conformations until the temperature is lowered to -100°C. Finally, at -150°C, it is possible to separate the axial and equatorial conformations into noncrystalline and crystalline samples, respectively.

Recently, Eliel has recommended that isomers should be defined independently of the conditions of their observation. In order to do this, it must be agreed that only molecules in their lowest electronic, vibrational, and torsional states qualify to be isomers (cf. Section 1.4.5), i.e. they must correspond to a minimum on a potential energy hypersurface.
species with the same molecular formula are considered to be isomeric if the energy barrier separating them is higher than $RT \text{ mol}^{-1}$ ($2.47 \text{ kJ mol}^{-1}$ at 25°C). When the energy barrier is smaller than $RT \text{ mol}^{-1}$, they are identical. For example, the barrier to inversion in cyclobutane is approximately 5.9 kJ mol$^{-1}$ and so it is capable of conformational isomerism. By contrast, the barrier to inversion in oxetane is approximately 0.17 kJ mol$^{-1}$ and so it exists as one species at room temperature (see Section 4.4.2).

Acceptance of this definition of isomerism would remove many of the inconsistencies and some of the terminology of the past. An arbitrary distinction has been drawn between conformational isomers—called atropisomers—which are separated by sufficiently high torsional energy barriers to permit their isolation—for example, the enantiomers of 6,6'-dinitrodiphenic acid (76) (in Figure 9)—and those which are rapidly inverting or interconverting at room temperature. Also, a qualitative distinction is often drawn between constitutional isomers such as n-butane and isobutane and the readily interconvertible constitutional isomers known as tautomers, e.g. the keto and enol forms of acetoacetic ester.

Although it is probably desirable from the point of view of teaching that redundant imprecise terminology of this kind be discontinued for the sake of clarity and simplification, it seems likely that its use will persist for some time to come.

It often transpires that the number of isomers that can be observed by a particular means of detection falls short of the number of isomers expected on the basis of the above definition. The number of observable isomers or species corresponds to 61,62 the so-called residual isomers or species. Examples of both residual constitutional isomerism, e.g. the valence bond isomerisation between 7-cyano-7-trifluoromethylcycloheptatriene...
and 7-cyano-7-trifluoromethylnorcaradiene (81) (see Figure 13) and residual stereoisomerism, e.g. the conformational isomerisation of 1,2-dichloroethane (see Figure 13) are known. Molecular propellers of the triarylmethane type—for example, 1-(2-methoxynaphthyl)-1-(2-methylnaphthyl)-1-(3-methyl-2,4,6-trimethoxyphenylmethane (82) which is a 32-isomer system with three different aryl groups lacking local \( C_2 \) symmetry—can exhibit residual diastereoisomerism. Two diastereoisomers of (82) have been separated by fractional crystallisation; they are interconvertible but the energy barrier is high (128 kJ mol\(^{-1}\)).

### 1.5. Topism

#### 1.5.1. Some Terminology

Just as isomerism is concerned with comparisons between molecules so a whole branch of stereochemistry can be built around internal comparisons of ligands within molecules. However, it is only in comparatively recent times that this aspect of stereochemistry concerned with so-called topic relationships has received adequate expression although the concept has been illustrated in the glorious multitude of reactions catalysed by enzymes since time immemorial. Topism, which is derived from the Greek word \textit{topos} meaning place, relates to a form of analysis which compares ligands in relation to their environment. Thus, two ligands in a molecule are said to be homotopic if their superimposition can be achieved by (i) rotation about a \( C_n \) axis, e.g. the two hydrogen atoms (and the two chlorine atoms) in dichloromethane (1) are homotopic on account of \( C_2 \) symmetry, (ii) rapid changes in configuration or conformation, e.g. the methyl hydrogen atoms in toluene are homotopic as a result of rapid torsional changes about the \( C(sp^3) \)--\( C(sp^2) \) bond, or (iii) translational
motion in the case of infinite polymers. Ligands which are not homotopic by any of these criteria are said to be heterotopic. If heterotopic ligands are in constitutionally different environments they are said to be constitutionally heterotopic, e.g. the methylene protons (H) at C-1 and C-2 in propan-1-ol, \( \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \), whereas heterotopic ligands in stereoisomERICally different environments are said to be stereoheterotopic. Finally, the class of stereoheterotopic ligands can be divided into (i) enantiotopic and (ii) diastereotopic ligands depending on (i) whether the ligands can be exchanged by an \( \frac{s}{n} \) symmetry operation—e.g. the methylene hydrogens in ethanol (13) are enantiotopic—or (ii) whether the ligands cannot be exchanged by any symmetry operation on the molecule at all—e.g. the methyl groups on C-8 of \( \alpha \)-pinene (7) are diastereotopic. Figure 14 illustrates clearly the close conceptual correspondence between isomerism and topism.

A substitution criterion (see Figure 15) can be used to establish or confirm the nature of the topic relationship between stereoheterotopic ligands. Consecutive replacement of the homotopic hydrogens in dichloromethane (1) by deuterium gives only one deuterated compound (83). Consecutive replacement of the enantiotopic ligands in ethanol (13) by deuterium leads to the enantiomers (R)-(84) and (S)-(84). Consecutive replacement of the diastereotopic hydrogens in (R)-malic acid (2R)-(85) by deuterium leads to the diastereoisomers (2R,3R)-(86) and (2R,3S)-(87).

An understanding of topic relationships between ligands in molecules is useful when interpreting n.m.r. spectra. Under all circumstances, homotopic nuclei exhibit the same chemical shifts and the signals are said to be isochronous. However, diastereotopic nuclei can exhibit different chemical shifts and if they do the signals are said to be anisochronous. Enantiotopic nuclei exhibit isochronous behaviour in achiral solvents but...
in the presence of chiral solvents or complexing agents—including enzymes—which may be regarded as chiral reagents—enantiotopic ligands can be distinguished. Thus, enantiotopic nuclei may exhibit anisochronous behaviour in a chiral environment.

Topic relationships are also useful for describing regions of space around atoms and bonds in molecules. In particular, the faces of double bonds associated with \( \text{sp}^2 \) hybridised carbon atoms can be homotopic or stereoheterotopic. As illustrated in Figure 16, the faces of carbonyl groups can be homotopic, enantiotopic, or diastereotopic. Formaldehyde (88) only forms one hemiacetal (89) because its two faces are equivalent or homotopic. However, in benzaldehyde (90) the two faces are enantiotopic and so addition of cyanide ion to either face is equally probable and gives rise to two enantiomeric mandelonitriles (91) and (91). In the presence of emulsion, only one of these enantiomers is formed, i.e. enzymes can distinguish between enantiotopic faces. Finally, the two faces of 3-phenylbutan-2-one (92) are diastereotopic and hence it gives rise to two diastereoisomeric alcohols in unequal proportions on addition of phenyl Grignard reagent to the carbonyl group. Many years ago, Cram formulated his well-known rule which allows predictions of the preferentially formed product to be made in these situations of so-called asymmetric induction. More recently, this kind of stereoselectivity has been subjected to detailed mathematical treatment.

1.5.2. Prochirality

Just as compounds which contain chiral centres of the type Cabcd (47) can display enantiomerism and diastereoisomerism so those which contain a centre of the type Caabc (95), where the ligands a are either
enantiotopic or diastereotopic, are said\textsuperscript{70,71} to contain a prochiral
centre. In addition to centres of prochirality, axes and planes may also
constitute prochiral elements (cf. chiral elements). Thus, a general
definition of prochirality can be given. If a chiral assembly is obtained
when a ligand in an assembly of ligands is replaced by a different ligand,
then the original assembly is prochiral. Hence, centres of prochirality
\text{Caabc (95) in molecules can carry either enantiotopic or diastereotopic}
ligands, and since these stereoheterotopic ligands can be distinguished by
chiral reagents, e.g. enzymes, it is useful to have symbols based on the
Cahn-Ingold-Prelog sequence rule\textsuperscript{29} to differentiate between heterotopic
ligands (see Section 1.5.2.1). However, we have seen that faces in
molecules containing double bonds, for example, can also be stereoheterotopic.
Consequently, a kind of prochirality also exists for assemblies of the type
\text{abC—c (96). Since stereoheterotopic faces can be distinguished by enzymes,
it is also useful to have a system of nomenclature based on the Cahn-Ingold-
Prelog sequence rule\textsuperscript{29} (see Section 1.5.2.2).

1.5.2.1. The pro-R/pro-S convention. The relationship between prochirality
and chirality is well-defined and hence the sequence rule\textsuperscript{29} can be used\textsuperscript{70}
to specify the paired stereoheterotopic ligands associated with prochiral
elements. If replacement of one of the paired ligands by a ligand of
higher priority leads to \text{(R)}-chirality, then the ligand is designated
pro-\text{R} and given the descriptor LR (L for ligand). If \text{(S)}-chirality results
from this test then the ligand is designated \text{pro-\text{S}} and given the descriptor
LS. The notation is illustrated for ethanol (13a) and (2R)-malic acid
(2R)-(85a) in Figure 15.

1.5.2.2. The re/si convention. Stereoheterotopic faces may be specified\textsuperscript{70}
by using the Cahn-Ingold-Prelog sequence rule in two dimensions (see Figure 17). If the arrangement of the ligands according to the priority \( a > b > c \) is clockwise, the face is designated a \textit{re}-face, whereas an anticlockwise arrangement defines a \textit{si}-face. The use of the convention is illustrated with benzaldehyde (90) and 3-phenylbutan-2-one (92) in Figure 16 (see also Section 5.1.5). It can also be employed with carbon-carbon double bonds where the arrangement of ligands about both carbon atoms is specified. Thus, maleic acid (31) has \textit{re-si-} and \textit{si-re-} faces and fumaric acid (33) has \textit{re-re-} and \textit{si-si-} faces.

1.5.3. Pseudoasymmetry (Pseudochirality)

Centres of the type \( \text{Caabc} \) (95) are not always prochiral. If the paired ligands a each contain a source of chirality and are enantiomerically related by internal comparison then a molecule containing such a centre is said to have a centre of pseudoasymmetry (or pseudochirality) \(^{29,32} \). For example, the alditols, ribitol (97) and xylitol (98) shown in Figure 18 both have pseudoasymmetric centres at C-3. Although they are examples of achiral molecules since ligands b and c are devoid of chirality, compounds containing a centre of pseudoasymmetry can be chiral if either or both of these ligands contains a source of chirality. In common with the elements of chirality and prochirality, the phenomenon of pseudoasymmetry manifests itself in axes and planes of pseudoasymmetry as well (see refs. 26-29 and 72 for a discussion of these rather specialised situations). In order to specify the intramolecular relative configurations about a centre of pseudoasymmetry using the Cahn-Ingold-Prelog convention, a sub-rule \(^{29,32} \) to the sequence rule, which states that for the paired chiral ligands \( \text{L}_R \) precedes \( \text{L}_S \), is employed. The intramolecular relative configurations of
pseudoasymmetric elements are then specified by the descriptors \((r)\) and \((s)\) in a manner similar to that used in the specification of absolute configurations at chiral elements by the descriptors \((R)\) and \((S)\). Figure 18 illustrates the use of the descriptors \((r)\) and \((s)\) to specify the intramolecular relative configurations at C-3 of xylitol (98) and ribitol (97), respectively.

### 1.6. TOPOMERISM

Following on the conceptual advances described in the previous Section, a nomenclature system has been proposed\(^7^3\) for intramolecular exchange processes which do not involve any change in structure and can frequently be followed by dynamic n.m.r. spectroscopy.\(^7^4\) The system identifies a process which leads to interchange of identical ligands between distinguishable chemical or magnetic environments as a topomerisation. It is suggested that the indistinguishable species involved in the exchange are called topomers. The most common type of topomerisations which can occur are illustrated in Figure 19. Bullvalene (100) represents an example of valence bond or constitutional topomerisation in which one and the same ligand (carbon or hydrogen) visits four constitutionally different positions (allylic, two kinds of vinylic, and cyclopropanoid) during equilibration. Diastereotopomerisations are also well known, e.g. the ring inversion of 1,1-difluorocyclohexane (101), and examples of enantiotopomerisations and homotopomerisations, although much less common, are known.

### 1.7. DYNAMIC STEREOCHEMISTRY: A BRIEF COMMENT

The dynamic aspects of stereochemistry are concerned with how reactions depend upon configurational and conformational properties of
reactants and products and the transition states separating them. There is little doubt that stereoelectronic effects in substitutions, additions, eliminations, and rearrangements are best discussed within the context of reaction mechanisms and no attempt has been made in this introductory Chapter to cover this vast and growing field of stereochemistry. Indeed, the stage of development in dynamic stereochemistry is such that inconsistencies abound in the use of terminology and nomenclature. It will be obvious to the reader of this work that different authors attach different meanings to terms such as stereoselectivity and stereospecificity although attempts\(^3,75\) have been made to restrict their use to the description of particular phenomena. At the constitutional level of structure, terms such as chemoselectivity and regioselectivity have been widely adopted by many authors. Suggestions for the designations of reaction mechanisms have also been made.\(^76\)

Dynamic stereochemistry has, of course, impinged upon developments in synthesis, particularly chiral or asymmetric synthesis.\(^12\) During the last 25 years,\(^77\) conformational analyses has had much influence in this field. Most recently the high stereoselectivity exhibited by most so-called pericyclic reactions has been interpreted\(^78,79\) in a number of ways. At the constitutional level of structure, computer assisted synthesis\(^80,81\) promises much for the future.
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Captions to Figures

Figure 1. Ring inversion in 1,2-disubstituted cyclohexanes

Figure 2. Some examples of two-dimensional chirality

Figure 3. The chirality of the block capital letters of the alphabet in two dimensional space.

Figure 4. The eight point group symmetries of the tetrahedron

Figure 5. The regular $T_d$ tetrahedron ($\text{34}$) as a simplex for chirality, prochirality, pseudoasymmetry, and propseudoasymmetry

Figure 6. The designation of the absolute configuration of a chiral centre using the (RS)- convention

Figure 7. The representation of multiple bonded atoms in the Cahn-Ingold-Prelog system of nomenclature

Figure 8. The designation of the absolute configuration of chiral axis of the dimethylallene ($\text{66}$) using the (RS)- convention

Figure 9. The designation of axial chirality in 6,6'-dinitrodiphenic acid ($\text{76}$) using the (RS)- convention

Figure 10. The terminology for describing conformations of 1,2-disubstituted ethanes. Older terms which are still in use are shown in brackets

Figure 11. The designation of relative conformation. The circled ligands are the reference ligands

Figure 12. The designation of the absolute conformation of synclinal 1,2-disubstituted ethanes
Figure 13. Examples of residual constitutional isomerism (a) and residual stereoisomerism (b).

Figure 14. The conceptual correspondence between isomerism and topism.

Figure 15. The use of the substitution criterion to establish topic relationships between ligands. The designation of $\text{pro}^{\sim}R$ and $\text{pro}^{\sim}S$ ligands.

Figure 16. The use of nucleophilic additions to carbonyl groups in establishing topic relationships between faces. The designation of $\text{re}$- and $\text{si}$- faces.

Figure 17. The designation of stereoheterotopic faces using the $\text{re}/\text{si}$- convention.

Figure 18. Examples of compounds containing pseudoasymmetric centres. The designation of nitramolecular relative configurations using the $(\text{rs})$- convention.

Figure 19. Examples of constitutional topomerisation (a) and diastereotopomerisation (b).
Figure 3

Achiral: ABCDEHIKMOUVWXYZ

Chiral: FGJLNQRSZ
Figure 4

$T_d$

$(34)$

$D_2$

$(35)$

$C_2$

$(36)$

$C_1$

$(37)$

$D_{2d}$

$(38)$

$C_5$

$(39)$

$C_{2v}$

$(40)$

$C_{3v}$

$(41)$
Figure 5

\[ C_1 \]

(42)

\[ C_1 \]

(42)

\[ C_2 \]

(43)

\[ C_5 \]

(44)

\[ C_5 \]

(45)

\[ C_\infty \]

(46)
Figure 6

(R)-(47)

(S)-(47)
Figure 8

View from A

View from B

(R)-(66)

(R)-(66)

(R)-(66)
Figure 9

View from A

(Far) NO₂
(Near) HO₂C ——— NO₂ (Near)

View from B

(Near) O₂N ——— CO₂H (Far)

(R) - (76)

(R) - (76)
Synperiplanar
(Cis or syn)

Synclinal
(Gauche)

Anticlinal

Antiperiplanar
(Trans or anti)
Figure 11

Synclinal

Synperiplanar

Anticlinal
Figure 12
Figure 13

(a) 

\[ \text{Cl} \quad \text{Cl} \quad \text{Cl} \]

(b) 

\[ \text{H} \quad \text{H} \quad \text{Cl} \]

\[ \text{Cl} \quad \text{H} \quad \text{H} \]
(a) Compound with the same molecular formula

Identical Isomers

Constitutional isomers Stereoisomers

Enantiomers Diastereoisomers

(b) Ligands within a molecule

Homotopic Heterotopic

Constitutionally heterotopic Stereoisotopic

Enantiotopic Diastereotopic
Figure 15

Each H-b/D in turn

(1)
Homotopic hydrogens

or

Identical

Each H-b/D in turn

(13)
Enantiomers

Diastereoisomers

Each H-b/D in turn

Diastereoisomers

(Figure 15)
Figure 16

H \quad C = O \quad + \quad MeOH \quad \xrightarrow{\text{(88)}} \quad H \quad C - OMe

Homotopic faces

H \quad C = O \quad + \quad HCN \quad \xrightarrow{\text{(90)}} \quad HO - C - H \quad + \quad H \quad C - OMe

Enantiotopic faces

H \quad C = O \quad + \quad PhMgBr \quad \xrightarrow{\text{(92)}} \quad HO - C - Ph \quad + \quad HO - C - Me

Diastereotopic faces

Attack from the front or re-face

Attack from the back or si-face
Figure 18
Figure 19

(a) 

(b)
(±)-(69)  
(Only one enantiomer shown)
The Design and Development of Enzyme Analogues

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1. Preamble

2. Binding Forces

3. Primary binding

4. Secondary binding

5. Chiral Recognition at the Ground State

6. Catalysis

7. Concluding remarks

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The Design and Development of Enzyme Analogues

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1. Preamble

Recently, in an "ICI at 50 Supplement to Chemistry and Industry," Lord Todd (1976) made the following comment in relation to the chemical industry:

"I also regard wholly synthetic enzyme analogues designed to carry out specific reactions as likely to be produced on a large scale. These could revolutionise processes in many areas of the industry and they will be attractive not just from the environmental but also from the energy-sparing point of view."

This prediction coincides with a rapidly increasing awareness amongst chemists in academia, as well as in industry, that the realisation of enzyme analogues is within our grasp at long last. Our mechanistic and sterechemical understanding of chemical reactions has now reached a stage of development where the synthetic art of chemistry can be harnessed to build wholly synthetic catalysts which will exhibit the characteristics of enzymes, i.e. they will promote high velocities in chemical reactions and induce high regioselectivities and/or stereoselectivities with appropriate substrates. In so far as there are no chemical reactions and no appropriate substrates which are not amenable to this kind of treatment, the concept of designing
enzyme analogues has no bounds other than the limitations of our scientific knowledge and imagination. Hence, the term enzyme analogue has connotations that the term enzyme model lacks. Whereas, an enzyme model seeks to mimic a known enzyme in its catalytic function, an enzyme analogue is merely a practical expression of the lessons learnt from Nature.

2. Binding Forces

The highly structured molecular complexes of Nature have their origins in a myriad of different noncovalent forces. Enzyme-substrate and antibody-hapten complexes are invariably built up of different and many weak interactions, including (Jencks, 1967; Guthrie, 1976) some of an electrostatic nature. In aqueous solution, however, van der Waals interactions—the attractive London dispersion term—often combine with an imperfectly solvated hydrophobic cavity in the host (Griffiths & Bender, 1973) to bind relatively nonpolar guests with binding energies of the order of \(-10 \text{ kcal mol}^{-1}\) (Jencks, 1967). The naturally occurring cycloamyloses, e.g. (1), are probably the best known and most extensively studied (Griffiths & Bender, 1973; Tabushi et al., 1978a) enzyme analogues to date which depend upon hydrophobic bonding for binding of guests. They bind a whole range of organic substrates—including many which contain aromatic rings—in aqueous solution. Recently however, a number of synthetic hosts have been made (Tabushi et al., 1976a, b, 1978b) which show some potential as hydrophobic binders of appropriately chosen guests in water. Water soluble heterocyclophanes of the type \(\frac{2}{5}\) \(4\text{BF}_4^-\), (3), and (4) \(4\text{BF}_4^-\) form large enough cavities—\(7\text{R}\) for \((2) \cdot 4\text{BF}_4^-\) and \(5.5\text{R}\) for (3)—to include a phenyl group or a naphthyl moiety. Using the
fluorescent hydrophobic guest, sodium-1-anilino-8-naphthalenesulphonate (5),
strong enhancements have been observed (Tabushi et al., 1976, a,b) in the
intensities of the fluorescent spectra in the presence of these heterocyclo-
phanes. For example, the tetrasulphonium salt (2).4BF₄⁻ binds (Tabushi et al.
1976a) with (5) in water at pH 7 with an association constant of 1.6 x 10³ M⁻¹
which is 28 times higher than that observed for cycloheptaamylose (1) and (5).
Moreover, the tetraamonium salt (4).4BF₄⁻ exhibits (Tabushi et al., 1978b)
catalysis in the hydrolysis (phosphate buffer 1/15M, pH 8.10, 20.2°C) of
p-nitrophenyl (6) (k_cat/k_uncat, 2.6), α-naphthyl (7) (k_cat/k_uncat, 10.6) and
β-naphthyl (8) (k_cat/k_uncat, 25) chloroacetates. However, the requirements
and conditions for hydrophobic binders are (i) for large rigid molecules which
may require a lot of time and effort in order to synthesise and (ii) for
subsequent complexation studies to be conducted in a largely aqueous environ-

[Insert Formulae (5) - (8) here]

In organic solvents, the range of weak interactions available for
exploitation is much greater. To date, the most productive in terms of synthe-
hosts has been hydrogen bonding and other electrostatic forces including
charge transfer interactions. A combination or an assembly of weak interactions
is generally required in order to overcome solvation and/or lattice forces
associated with the guest. Hydrogen bonds come in many different forms—
pole-pole, e.g. (9), pole-dipole, e.g. (10), and dipole-dipole, e.g. (11)—

[Insert Formulae (9) - (11) here]

and have been subjected recently to a general analysis by Kollman (1977).
In discussing the nature of hydrogen bond directionality, the most important
contributing factor seems to be the electrostatic energy. Underneath each
formula—where data are available—are listed the total interaction energies
ΔE, in kcal. mol⁻¹ calculated at the energy minimum distances, R(X···Y),
in \( R \) by \textit{ab initio} molecular orbital approaches after the style \((\Delta E; R(X\cdots Y))\). In the case of (10), the interaction shown in which the \( \text{NH} \cdots \text{OH}_2 \) group has local \( C_{2v} \) symmetry is more stable than any interactions where the water molecule becomes tilted and the \( \text{NH} \cdots \text{OH}_2 \) group assumes \( C_5 \) symmetry. In the water dimer (11), Umeyama and Morokuma (1977) have found that the minimum energy geometry corresponds to \( \theta = 30^\circ \) for the angle between the axis collinear with the hydrogen bond and the bisector in the acceptor molecule. This is probably a result of repulsions between the three hydrogens not involved in the hydrogen bond. The dipole-dipole type of hydrogen bond is also exemplified (Pimentel & McClellan, 1960; Jencks, 1967) in carboxylic acids, e.g., (12) and in secondary amines, e.g., (13). In addition, the ability of C-H groups in, for example, chloroform, nitromethane, and acetonitrile, to serve as hydrogen bonding acids (Pimentel & McClellan, 1960; Green, 1974) and aromatic rings to act as hydrogen bonding bases (Pimentel & McClellan, 1960) will almost certainly be exploited in the near future. Electrostatic bonding of the pole-pole type is met not only in ion-pairing between a metal cation and its counterion but also, for example, in the formal approach of a chloride ion along the two-fold axis (14) or along the three-fold axis (15) of an ammonium ion (Kollman, 1977). These interactions involve less energy than the hydrogen bonding approach already described in (9). The formal approach of a water molecule along the two-fold axis (16) and along the three-fold axis (17) of an ammonium ion provide (Kollman, 1977) examples of the pole-dipole variety of electrostatic bonds. Once again, however, the
preference for the hydrogen bonding approach already described in (10) is marked. The complex (18) formed between a lithium cation and a water molecule has a minimum energy geometry corresponding to $C_{2v}$ symmetry.

\[ \text{[Insert Formula (18) here]} \]

(Kollman, 1977). We shall shortly be meeting examples of pole-dipole electrostatic interactions in relation to both metal cations and substituted ammonium ions. The intramolecular interaction between a carbonyl group and the lone pair on a heteroatom in medium-sized rings, e.g., (19) - (22), provides an additional example (Leclard, 1956; Sicher, 1962; Ollis et al., 1974) of dipole-dipole binding forces. In the case of (22), there is evidence (Gellatly, 1976) that the stabilisation could amount to as much as $-8 \text{kcal/mol}$. A detailed structural analysis supported by ab initio calculations has shown (Burgi et al., 1974) that the approach of the nucleophile (Nu) towards the electrophilic carbon of the carbonyl group is accompanied by a displacement ($\Delta$) of the carbon atom out of the plane defined by its three bonded ligands ($R$, $R'$, and $0$) towards the nucleophile (see Figure 1). The nucleophile is found to lie in the plane bisecting the $RCR'$ angle at distances less than 3Å and approaches linearly at an angle of $107^0$ to the carbon-oxygen bond. When oxygen is the nucleophile, $\Delta$ is about one-third that of when nitrogen is the nucleophile reflecting the fact that the oxygen-carbon interaction is about 10 times weaker than the nitrogen-carbon interaction. Coupled with the fact that a lone pair on nitrogen also reacts intramolecularly in medium-sized ring compounds—usually, but not always, under conditions of acid catalysis—with carbon-carbon double bonds (23) (Ollis et al., 1974;
Jeffs & Scharver, 1976; Brickwood et al., 1978) as well as with carbonyl groups (24), this kind of dipole-dipole interaction will probably become a happy hunting ground for secondary binding interactions in molecular complexes. The observation that dipole-induced dipole interactions between (i) 1,3-dioxans, e.g. (25) (Anderson, 1965; Cookson et al., 1968), and (ii) 1,3-dioxolans, e.g. (26) (Carlson, 1970), and benzene leads to the formation of weak 1:1 complexes in solvents such as carbon tetrachloride can also be exploited — as we shall see presently — to provide secondary binding sites. The classical charge transfer interaction between a π-acceptor and a π-donor (Andrews & Keefer, 1964; Jencks, 1967; Foster, 1969, 1973, 1974, 1976), e.g. (27), is typically rather weak (-1 to -2 kcal. mol.\(^{-1}\) of stabilisation) but, unlike the electrostatic interactions already discussed, this source of binding is relatively independent of the nature of the solvent (Guthrie, 1976). Along with other weaker interactions not involving hydrogen bonding, charge transfer forces promise to play a significant role as secondary and tertiary interactions within molecular complexes. In so doing, they equip the chemist with a means of building order and structure into his synthetic hosts. The ultimate goal must surely be to employ every facet of weak bonding available: this goal will probably be realised, initially at least, as much by accident as by design.

3. Primary Binding

History records (Pedersen, 1971a) that serendipity played a crucial role in the discovery by Pedersen (1967) of the so-called crown ethers. The
accidental synthesis of dibenzo-18-crown-6 (28) led directly to the recognition

[Insert Formulae (28) and (29) here]

that this compound forms stable complexes both in the crystalline state and in solution with metal, ammonium, and substituted ammonium salts. The crystal structure of the complex (29) has been determined (Seiler et al., 1974). It has approximately D_{3d} symmetry (ignoring the counterion) with the potassium ion entering into pole-dipole interactions with all six oxygens as well as being ion-paired to the thiocyanate ion (see Figure 2). In methanolic solution at 25°C the association constant for 1:1 complex formation between

[Insert Figure 2 here]

the potassium ion (chloride ion) and 18-crown-6 is $1.26 \times 10^6 \text{ M}^{-1}$ (Frensdorff, 1971) corresponding to a free energy of complexation of $-8.3 \text{ kcal.mol}^{-1}$.

The complex (30) between 18-crown-6 and t-butylammonium thiocyanate is

[Insert Formula (30) here]

believed (Cram & Cram, 1974; Cram et al., 1975; Cram, 1976; Cram & Cram, 1978) to involve (i) hydrogen bonding of the three hydrogens of the ammonium ion with alternate oxygens on the 18-crown-6 macrocycle with (ii) ion-dipole stabilisation of the positively charged nitrogen by the other three oxygens. These two components of binding in this so-called three point binding model are reminiscent of the interactions in (10) and (16) between an ammonium ion and a water molecule. In deuteriochloroform solution at 25°C, the association constant for 1:1 complex formation between the t-butylammonium cation and 18-crown-6 is $3 \times 10^6 \text{ M}^{-1}$ corresponding to a free energy of complexation of $-8.8 \text{ kcal.mol}^{-1}$ (Timko et al., 1977). Many factors have been recognized to contribute towards stabilising complexes in solution: they include (i) the nature and size of the cation, (ii) the constitution and size of the
ligand, (iii) the steric compatibility between the cation and the ligand, (iv) the nature of the anion, and (v) the nature of the solvent. At the present stage of development of the subject, a good initial approach to designing complexes is to examine Corey-Pauling-Koltun (CPK) space-filling molecular models. If a complex can be built there is a good chance it can be made! This guiding principle has proved highly productive in several laboratories. It led Kyba et al., (1977), for example, to discover that complexes, e.g., (31) and (32), are formed readily (i) between 18-crown-6 and arenediazonium salts and (ii) between benzo-27-crown-9 and guanidinium salts.

It also provided the incentive for us (Metcalfe et al., 1977, 1978) to demonstrate that 12-crown-4 and a \( N,N \)-dimethyldiaza analogue both form strong complexes, e.g., (33) and (34), with secondary dialkylammonium ions as well as with primary alkylammonium ions. This observation is significant in view of the importance of secondary amines physiologically and pharmacologically.

In addition, the ability of diazacaraparacyclophanes to form stronger complexes, e.g., (35), with primary alkylammonium ions than with secondary dialkylammonium ions indicates (Beckford et al., 1978) that there might be a stabilising interaction between the \( \pi \)-system of the phenylene ring and one of the hydrogen on the primary alkylammonium ion. This kind of interaction where the aromatic ring possibly acts as a hydrogen bonding base was suggested to us by inspection of CPK space filling molecular models and is supported by the observation of hindered rotation of the phenylene ring in the complex (35). Complexes (34) and (35) illustrate the utility of crowns containing tertiary amine functions to bind substituted ammonium ions (Leigh & Sutherland, 1975; Hodgkinson et al.)
Amide carbonyl groups can also be employed as a primary binding source: witness the fact that a stable complex (36) is formed (Bartman et al., 1977) between cyclo(L-Pro-Gly)$_3$ and (S)-valine methyl ester hydrochloride. Returning to the 18-crown-6 constitution, it is intriguing to note (i) that dibenzo-18-crown-6 (28) forms (Pedersen, 1971) complexes with thiourea and related compounds and (ii) that 18-crown-6 binds (El Basony et al., 1976) CH-acidic compounds such as acetonitrile and nitromethane. In fact, 18-crown-6 is most readily isolated upon its preparation as its crystalline complex with acetonitrile (Gokel et al., 1974) whilst the X-ray crystal structure analysis of the complex with dimethyl acetylenedicarboxylate reveals (Goldberg, 1975a) attractive interactions between the methyl groups and the crown ether oxygens (see Figure 3). It seems inevitable that good synthetic host molecules to bind neutral molecules containing CH acidic functions will be designed in the very near future.

Modification to the constitution of 18-crown-6 (37) allows (Timko et al., 1977) the strength of complexing with t-butylammonium thiocyanate in chloroform at 24°C to be varied almost at will in a highly predictable manner within a given range of structural types. Thus, replacement of a CH$_2$CH$_2$OCH$_2$CH$_2$ unit in (37) by a furan-2,5-dimethyl unit to give (38), a m-xylyl unit to give (39), and a pentamethylene unit to give (40) leads to a progressive decrease in complexing strength in accordance with the hypothesis of additivity of contact site free energies (Cram & Cram, 1978). The free energy contributions given in parentheses in kcal mol$^{-1}$ after the interaction.
type $[(\text{CH}_2)_2\text{O}--\text{HN}^+ (2.10); (\text{CH}_2)_2\text{O}--\text{N}^- (0.84); (\text{CH}≡\text{C})_2\text{O}--\text{HN}^+ (1.85);$ $(\text{CH}≡\text{C})_2\text{O}--\text{N}^- (0.74); (\text{CH}_2)_2\text{CH}_2--\text{N}^+ (3.59);$ and $\text{m-xylyl}--\text{N}^- (3.19)]$ can be used (Timko et al., 1977) to calculate free energies of complexation ($\Delta G$) which are in good agreement with the experimental values given in brackets beneath (37) - (40). The calculations do not, however, reproduce the high $\Delta G$ value observed for cis-monomotetrahydrofuranyl-18-crown-6 (41). This suggests that stereochemical factors are important and must also be taken into consideration in discussing strengths of complexes. This realisation takes on even more significance when we consider the range of $\Delta G$ values obtained (Coxon et al., 1978) (i) for the cis-syn-cis (42), cis-anti-cis (43), and trans-syn-trans (44) isomers of dicyclohexyl-18-crown-6 and (ii) for the 18-crown-6 derivatives $\alpha-\text{D}$-(45) and $\beta-\text{D}$-(45) which incorporate methyl 4,6-O-benzyldene $\alpha$- and $\beta$-$\text{D}$-glucopyranoside residues respectively and the 18-crown-6 derivatives $\alpha-\text{D}$-(46) and $\beta-\text{D}$-(46) which incorporate methyl 4,6-O-benzyldene $\alpha$- and $\beta$-$\text{D}$-galactopyranoside residues, respectively. The $\Delta G$ values are considerably less for all of these derivatives than for 18-crown-6 (37). This observation cannot be explained on steric grounds alone. In fact, some [$\alpha-\text{D}$-(45) and $\alpha$- and $\beta-\text{D}$-(46)] of the carbohydrate derived 18-crown-6 derivatives form (Laidler & Stoddart, 1977; Pettman & Stoddart, 1978) stronger complexes than they might otherwise because of the participation of non-crown ether oxygens in binding substituted ammonium ions. The trans-anti-trans isomer (47) of dicyclohexyl-18-crown-6, together with isomers (42)-(44), also exhibit (Frensdorff, 1971; Burden et al., 1977; Coxon et al., 1978) destabilisation of their 1:1 complexes formed with sodium.
that ion-dipole interactions as well as hydrogen bonding interactions are dependent on stereochemistry. Available X-ray crystal structure data (Truter, 1973, Dunitz et al., 1974; Goldberg 1975 a,b) indicates that complexes of 18-crown-6 (37) and its derivatives prefer, if possible, to take up "all-gauche OCH₂CH₂O" conformations in which the oxygens are displaced alternately above and below the mean plane of the ring. In the trans-anti-trans isomer (47) of dicyclohexyl-18-crown-6, such a conformation cannot be attained and consequently cooperativity of binding sites towards both metal cations and substituted ammonium ions is impaired. Although the "all-gauche OCH₂CH₂O" conformation is attainable in the trans-syn-trans isomer (44), and in the carbohydrate derivatives α-D-(45) – β-D-(46), they are all conformationally-biased systems in which ring inversion of the 18-membered ring cannot occur. Thus, three oxygens can be defined as being on one side of the mean plane of the ring and three on the other. In (44) – β-D-(46), I have employed a dot (.) and circle (0) notation: the dot (.) indicates "up" oxygens, the circle (0) "down" oxygens. In the cis-syn-cis (42) and cis-anti-cis (43) isomers of dicyclohexyl-18-crown-6, not only can the "all-gauche OCH₂CH₂O" conformation be attained but 18-membered ring inversion can also occur. I have indicated this feature in (42) and (43), as well as in 18-crown-6 (37), by the symbolism, .0.0. The differences observed in ΔG values in both the metal and t-butylammonium cation series are believed (Coxon et al., 1978) to be enthalpic in origin. The question then arises as to where these differences originate. We have already noted that both hydrogen bonding—the electrostatic component—and ion dipole interactions have directionality. Furthermore, ab initio molecular orbital calculations have shown (Timko
et al., 1977) that for interactions between an ammonium ion and a dimethyl ether molecule, the situation is qualitatively similar to that already discussed for the interaction between an ammonium ion and water. In the hydrogen bonding approach of a dimethyl ether molecule to an ammonium ion, the one, i.e. (48) which preserves local $C_{2v}$ symmetry for the $\text{NH}--\text{O(CH}_3)_2$ group is more stabilising than the $\overline{C_2}$ approach in (49). The two-fold approach (50) of a dimethyl ether molecule to an ammonium ion is also stabilising when the interaction has $C_{2v}$ symmetry. However, the interaction energy is

[Insert Formulae (48) - (50) here]

only about one-third of that available in the hydrogen bonding approach (48) (cf. (16) with (13), where qualitatively at least the same difference emerges).

The results of these calculations lead one to predict that a t-butylammonium ion will be more highly stabilised by hydrogen bonding to the "up" oxygens (see Figure 4) in 18-crown-6 (34) since this particular match allows the favourable interaction (48) to be approached. The available X-ray crystallographic data (Goldberg, 1975b) is in accordance with this prediction.

The strong preference towards hydrogen bonding of the t-butylammonium ion to the "up" oxygens leaves the "down" oxygens in poor stereochemical alignment in the "all-gauche $\text{OCH}_2\text{CH}_2\text{O}" conformation to act as efficient electrostatic stabilisers of the positive charge on nitrogen. Clearly, the complex has to partition its energy of formation between (i) seeking the best hydrogen bonding array at the expense of (ii) not being able to maximise its ion-dipole stabilisation because of (iii) conformational constraints—mainly torsional—involving the 18-membered ring. A compromise is inevitably reached in maximising the free energy of formation of the complex. The crystal structure data (Goldberg, 1975b) for the salt formed between the
2-carboxy-1,3-xylyl-18-crown-5 (51) and t-butylamine—here the counterion is part of the primary binding site—shows (Figure 5) that (i) the hydrogen bonds to the "up" oxygens (0-8 and 0-14) are in the planes bisecting the \(-\text{CH}_2\text{OCH}_2\)- angles with \(\theta = 42^\circ\) whereas, (ii) the weaker ion dipole interactions to the "down" oxygens (0-5 and 0-17) have to settle for the larger distortion with \(\theta = 60^\circ\). Amongst other factors, it is clear that the "all-gauche-\text{OCH}_2\text{CH}_2" conformation of 18-crown-6 (37) with \(D_{3d}\) symmetry does not have the most favourable stereochemistry for binding substituted ammonium ions. Inspection of framework molecular models indicates, for example, that cis-monotetrahydrofuranyl-18-crown-6 (41) can adopt a conformation—also all-gauche—with a better alignment of binding sites for substituted ammonium ions. Future designs of 18-crown-6 derivatives must take into consideration the fact that small conformational differences in synthetic hosts lead to large differences in free energies of complexation. By the same token, it should be possible to build more highly structured complexes by exercising control over the synthetic host conformation. The ultimate in sophistication in synthetic host design will probably be realised by exercising configurational control to locate certain constitutional features in particular conformational environments. It seems not only reasonable but logical that constitution, configuration, and conformation must define the structures of noncovalently bonded species in much the same way as they define the structures of covalently bonded species.

4. **Secondary Binding**

The uncovering of secondary binding sites has been realised in crown ether complexes sometimes by accident and sometimes by design. Let us consider some examples which illustrate both historical backgrounds.
The complex (52) between 2,2′-binaphthyl-20-crown-6 and p-nitrophenyl
diazonium tetrafluoroborate exhibited (Kyba et al., 1977) a red colour
characteristic of the existence of a charge transfer interaction between a
π-acceptor (a p-nitrophenyl group) and a π-donor (a naphthalene ring).
Inspection of CPK space filling molecular models indicates that such an
interaction is indeed possible in the complex (52). Variable temperature
1H n.m.r. spectroscopy, in conjunction with deuterium studies, has provided
evidence (Laidler & Stoddart, 1978) in complexes of the type (53) that primary
alkylammonium ions which contain a phenyl group with the appropriate constituting
disposition, enter into a dipole-induced dipole interaction with one of the
1,3-dioxan rings in the 20-crown-6 derivative incorporating a 1,3:4,6-di-O-
methylene-D-mannitol residue. A similar kind of secondary interaction is also
thought (Laidler & Stoddart, 1977) to be responsible for the relative
stabilisation of one (54) of the anisometric (Mislow, 1977) complexes between
α-D-(45) and benzylammonium thiocyanate. In this case, the dipole-induced
dipole interaction involves the 4,6-O-benzylidene ring in α-D-(45) and the
phenyl group in the guest. A further manifestation of this interaction is
believed to operate in complexes through a kind of secondary anomeric effect
(Stoddart, 1978) involving the anomeric centre in a β-glycoside, say, β-D-(46)
and the phenyl group in, say, benzylammonium thiocyanate. Once again, a
dipole-induced dipole interaction is thought (Pettman & Stoddart, 1978) to be
responsible for the relative stabilisation of one (55) of the anisometric
complexes. The classical intramolecular dipole-dipole interaction in a
β-glycoside, which can be invoked (Stoddart, 1971) to explain why a β-glycoside is destabilised with respect to an α-glycoside is believed to interact favourably with the phenyl group in the guest in this instance. Although none of these secondary interactions amount to much stabilisation (< 2 kcal.mol\(^{-1}\) of a complex, they do provide an extremely valuable means of introducing additional order into a complex. In all cases, their existence emerged accidentally—rather than by design—from experimental investigations.

The synthetic host (S)-(56) has been prepared (Helgeson et al., 1973) in an optically pure state and shown to complex preferably with (S)-amino acids as illustrated in (57). In addition to the primary binding site, the [Insert Formulae (S)-(56) and (57) here] side chains on C-3 and C-3' of the binaphthyl residue provide (i) a carboxyl group to hydrogen bond with the carboxyl group of the amino acid and (ii) a carboxylate ion to act as the internal counterion centred under the positively charged nitrogen. In this case, the complex (57) was designed by recourse to the examination of CPK space filling molecular models, i.e. the secondary binding sites were planned prior to the experimental investigations.

5. Chiral Recognition at the Ground State.

Two approaches have been employed in order to introduce chirality into crown ether hosts. One involves (Cram & Cram, 1974, Cram et al., 1975; Cram, 1976; Cram & Cram, 1978) the use (vide supra) of axially chiral 2,2'-dihydroxy-1,1'-binaphthyl which is optically stable after resolution. The other appeals (Curtis et al., 1975, 1977) directly to Nature and uses carbohydrates which are readily available in enantiomerically pure form. The attributes of carbohydrates as sources of chirality have been discussed elsewhere (Stoddart, 1978). Appropriately substituted L-tartaric acid, L-threitol, D-mannitol, L-iditol, D-glucose, D-galactose, D-mannose, and D-altrose have all been
incorporated into 18-crown-6 derivatives. CPK space filling molecular models indicate that tetraisopropylidenedi-D-mannitol-18-crown-6 $D_2D$-(58) with eight chiral centres is topologically related (see Figure 6) to (SS)-bisbinaphthyl-22-crown-6 (SS)-(59) with two chiral axes. Both these chiral synthetic hosts exhibited (Kyba et al., 1973, Curtis et al., 1975, 1977) enantiomeric differentiation in complexation equilibria towards (RS)-$\alpha$-phenylethylammonium hexafluorophosphate in favour (62%) of the (R)-guest. Figure 7 illustrates the less stable diastereoisomeric complex in each case: both can accommodate the "large" phenyl group in the (S)-guest over a region of the crown free of substituent groups whilst leaving the "medium" methyl group to interact severely with a chiral barrier: thus, this diastereoisomeric complex is destabilised relative to the other one in each case. The chiral recognition properties of (SS)-bisbinaphthyl-22-crown-6 (SS)-(59) can be substantially improved (Peacock & Cram, 1976) by locating methyl groups at the C-3 and C-3′ positions on one of the binaphthyl residues. It is also important to employ (Cram, 1976) a counterion such as hexafluorophosphate or perchlorate which will not compete with the crown ether oxygens for hydrogen bonding to the ammonium ion and hence destructure the complex. Under suitably designed conditions using (SS)-(59), or its enantiomer, total optical resolutions of racemic amine and amino ester salts have been realised (Cram, 1976) by liquid-liquid (Sousa et al., 1974) and solid-liquid (Sogah & Cram, 1975) chromatography.

Improvements in the design of chiral synthetic hosts built around the crown ether constitution will undoubtedly make use of (i) the principles of stereochemical control of complex structure and stability (see Section 3),
(ii) the incorporation of appropriate secondary binding sites (see Section 4), and (iii) the strategic positioning of chiral barriers in relation to the steric demands of the racemic guest. One obvious design - which is under investigation in our laboratory at the moment - is to arrange substituent groups trigonally around the 18-crown-6 framework such that large (L), medium (M), and small (S) cavities are created to match (see Figure 8) the large (L'), medium (M'), and small (S') ligands attached to the chiral centre of one enantiomer of a guest cation. A variation on this theme based on the incorporation of three binaphthyl residues into a 21-crown-6 derivative was frustrated (de Jong et al., 1975) by the failure of the synthetic hosts to complex with substituted ammonium salts as a result of the reduced basicity of the crown ether oxygens.

6. Catalysis

To date, only a limited number of potentially catalytic systems have been investigated which rely on the crown ether constitution to provide the primary binding site. Recently, Behr & Lehn (1978) have shown that complexes (see, for example, Figure 9) formed between a chiral 1,4-dihydropyridine-bearing receptor molecule and a pyridinium substrate display enhanced rates of internal hydride transfer which may be inhibited by addition of potassium or tetramethylenediammonium tetrafluoroborates. Enhanced rates of hydride transfer have also been observed (van Bergen & Kellog, 1977) from an achiral 1,4-dihydropyridine-18-crown-6 derivative (van Bergen & Kellog, 1976) to a sulphonium salt. Enantioselective transacylations between α-amino acid p-nitrophenyl ester salts and axially-chiral crown ethers containing sulphhydryl groups as catalytic sites have been reported (Chao & Cram, 1976). More
recently, the dependence of the rates of transacylations of $\alpha$, $\beta$, $\gamma$, and $\varepsilon$-amino acid $p$-nitrophenyl ester salts by thiol-containing 18-crown-6 derivatives synthesised from $L$-tartaric acid on the length and constitutional nature of the catalytic side arms has been investigated (Matsui & Koga, 1976). The results demonstrate the feasibility of obtaining regioselectivity in reactions catalysed by crown ethers carrying suitable functional groups.

Transition state stabilisation of activated complexes is likely to be an important prerequisite in the design of potentially catalytic systems of the enzyme analogue type. The directionality of noncovalent interactions is almost certain to be of paramount importance in achieving this end.

7. Concluding Remarks

In designing and developing enzyme analogues the ultimate goal is to realise efficient catalysts which will be regioselective and/or stereoselective in their chemical reactions with appropriate substrates. Each reaction, and indeed each substrate, present their own problem to be solved. I believe solutions will be found and enzyme analogues will become commonplace reagents in the laboratory before the turn of the century.

Acknowledgements

This review was written during March 1978 in the intellectually stimulating atmosphere provided by the Department of Chemistry in the University of California at Los Angeles. I thank the Science Research Council for the award of a Senior Visiting Fellowship to take me there and Professor D.J. Cram, his colleagues, and research collaborators for their time talking chemistry with me while I was there.


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Table 1. The log $K_a$ (based on $K_a$ in M$^{-1}$) and $\Delta G$ values for the formation of 1:1 complexes between sodium, potassium, and caesium chlorides in methanol

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$\log K_a^a$</th>
<th>$\Delta G^b$</th>
<th>$\Delta \Delta G^b$</th>
<th>$\log K_a^a$</th>
<th>$\Delta G^b$</th>
<th>$\Delta \Delta G^b$</th>
<th>$\log K_a^a$</th>
<th>$\Delta G^b$</th>
<th>$\Delta \Delta G^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-Crown-6 (37)</td>
<td>4.32$^d$</td>
<td>-5.9</td>
<td>-</td>
<td>6.10$^d$</td>
<td>-8.3</td>
<td>-</td>
<td>4.70</td>
<td>-6.3</td>
<td>-</td>
</tr>
<tr>
<td>cis-syn-cis-isomer ($\phi_2$)$^c$</td>
<td>4.08$^d$</td>
<td>-5.5</td>
<td>0.4</td>
<td>6.01$^d$</td>
<td>-6.2</td>
<td>0.1</td>
<td>4.61$^d$</td>
<td>-6.2</td>
<td>0.1</td>
</tr>
<tr>
<td>cis-anti-cis-isomer ($\phi_3$)$^c$</td>
<td>3.68$^d$</td>
<td>-5.0</td>
<td>0.9</td>
<td>5.38$^d$</td>
<td>-7.3</td>
<td>1.0</td>
<td>3.49$^d$</td>
<td>-4.7</td>
<td>1.6</td>
</tr>
<tr>
<td>trans-syn-trans-isomer ($\phi_4$)$^c$</td>
<td>2.99$^e$</td>
<td>-4.0</td>
<td>1.9</td>
<td>4.14$^e$</td>
<td>-5.6</td>
<td>2.7</td>
<td>3.00$^e$</td>
<td>-4.0</td>
<td>2.3</td>
</tr>
<tr>
<td>trans-anti-trans-isomer ($\phi_7$)$^c$</td>
<td>2.52$^e$</td>
<td>-3.4</td>
<td>2.5</td>
<td>3.26$^e$</td>
<td>-4.3</td>
<td>4.0</td>
<td>2.27$^e$</td>
<td>-3.0</td>
<td>3.3</td>
</tr>
</tbody>
</table>

$^a$ Obtained for the equilibrium, $M^++$nMeOH + Ligand $\rightleftharpoons M$ Ligand$^+$ + nMeOH at 20-25°C by potentiometry with ion selective electrodes (Burden et. al., 1977; Frensdorff, 1971).

$^b$ In kcal mol$^{-1}$. The $\Delta \Delta G$ values correspond to the differences in the $\Delta G$ values between the particular ligand and 18-crown-6 (37).

$^c$ Isomers of dicyclohexyl-18-crown-6.

$^d$ Values from Frensdorff (1971).

$^e$ Values from Burden et al. (1977).
Captions to Figures

Figure 1. The geometry of the approach of a nucleophile (Nu) towards the electrophilic carbon of a carbonyl group.

Figure 2. A qualitative representation of the crystal structure of the 1:1 complex formed between 18-crown-6 and potassium thiocyanate.

Figure 3. A qualitative representation of the crystal structure of the complex of 18-crown-6 with dimethyl acetylenedicarboxylate. The indicated interatomic distance of 3.08 Å is shorter by 0.3 Å than the usually quoted van der Waals contact between carbon and oxygen.

Figure 4. The preferred stereochemistry of the 1:1 complex formed between 18-crown-6 and a t-butylammonium cation.

Figure 5. A qualitative representation of the salt formed between the 2-carboxy-1,3-xylyl-18-crown-5 (51) and t-butylamine.

Figure 6. A topological comparison between the tetraisopropylidenedi-ß-D-mannitol-18-crown-6 ß-D-(58) and the (SS)-bisbinaphthyl-22-crown-6 (SS)C–C(59).

Figure 7. The less stable diastereoisomeric complexes formed between (i) ß-D-(58) and (S)-PhCHRNH₃⁺ cations, and (ii) (SS)-(59) and (S)-PhCHRNH₃⁺ cations.

Figure 8. The three-residue 18-crown-6 derivative.

Figure 9. The complex between a 3-acetylpyridinium cation and a dihydropyridine-bearing receptor molecule synthesised from L-tartaric acid.
Nu Lies in a plane bisecting the \( RCR' \) angle

\[ \angle < 3^\circ \]

\[ \theta = 107^\circ \]

Figure 1

![Figure 1](image1)

SCN\(^-\) ions disordered

Figure 2

![Figure 2](image2)

3.08 Å

Figure 3

![Figure 3](image3)
Figure 4
HYDROGEN BONDS

"Up" oxygens \(0-8/0-14\)

"Down" oxygens \(0-5/0-17\)

ION-DIPOLE INTERACTIONS

Figure 5
Figure 6
Figure 7
Figure 8
Figure 9
(2) \( 4 \text{BF}_4^- \)  \( X = \overset{+}{\text{SMe}} \)

(3)  \( X' = \overset{+}{\text{NMe}} \)

(4) \( 4 \text{BF}_4^- \)  \( X = \overset{+}{\text{NMe}}_2 \)

\( \overset{+}{\text{NaO}_3\text{S}} \) \( \overset{+}{\text{NH}_2} \)

\( \overset{+}{\text{O}_2\text{CCH}_2\text{Cl}} \) \( \overset{+}{\text{NO}_2} \)
\[(13)\]

\[(14)\]
\((-116.8; 2.77)\)

\[(15)\]
\((-116.0; 2.74)\)

\[(16)\]
\((-21.8; 2.69)\)

\[(17)\]
\((-20.4; 2.65)\)
(19) $X' = O$
(20) $X = \text{NCH}_3$
(21) $X = S$
(53)

(54)

(55)
TATE AND LYLE LECTURE

From Carbohydrates to Enzyme Analogues

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TATE AND LYLE LECTURE*

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1. Why not

One of the pleasures of belonging to our profession is that its membership provides us with a licence to dream. To my mind, dreaming is not only a professional privilege accorded to us all, it is an honourable duty to be performed by all of us objectively. Above all, it raises our expectations and encourages us to tackle problems which, one might say, are almost beyond our wildest dreams! Nobody has captured the spirit of dreaming more vividly or with as much feeling and hopefulness as did Robert Kennedy¹ in his much quoted lines: Some men see things as they are and say, why. I dream things that never were and say, why not.

In this context of "why not", I have a dream, "I have a dream that one day² we shall be able to make molecules which will vie with Nature's receptor molecules in their ability to exhibit selective binding and to display recognition functions towards chosen target molecules. If, initially at least, I agree to moderate my vision of the man-made receptor molecules of the future, then the concept of enzyme modelling, for example, is not a new

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one, I grant, especially to those of us familiar with carbohydrates. Indeed, Nature has provided us with one of the most intensively investigated enzyme model systems to date in the shape of the cycloamyloses. This group of homologous oligosaccharides which are comprised of $\alpha$-$1,4$ linked $D$-glucopyranosyl residues in a cyclic constitution is elaborated by the action of Bacillus macerans amylase on starch. The best known and studied representatives are those built up from six and seven glucose units. The results of X-ray crystallographic studies and an analysis of space filling molecular models reveal that cyclohexaamylose (1) is a doughnut-shaped molecule in which (i) the six $D$-glucopyranosyl residues are in the $4C_1(D)$ chair conformation, (ii) the six glycosidic oxygens surrounded by four hydrogens (on C-3 and C-5 of neighbouring residues) are all pointing into the centre of the cavity, (iii) the hydroxymethyl groups on C-5 line one rim of the cavity, and (iv) the secondary hydroxyl groups (on C-2 and C-3) line the other rim. As a result of the work of Cramer in Germany, and Bender and Breslow in The United States, and others, it is now well established that cyclohexaamylose (1) serves as a host molecule in aqueous solution for a whole range of organic guest molecules including aliphatic and aromatic hydrocarbons, alcohols, phenols, ethers, carboxylic acids, esters, amines, and so on. Since the cavity diameter of 4.5 Å in (1) is just sufficient to accommodate a benzene ring, these inclusion complexes, e.g. (2) and (3), can be viewed as owing their existence to a kind of hydrophobic bonding. Association constants are moderately high ($10^2 - 10^4$ M$^{-1}$) and they have been shown, for example, to exhibit covalent catalysis with maximal rate enhancement.
of the order of several hundred times that of the uncatalysed reaction (e.g. the hydrolysis of m-t-butylphenylacetate can be accelerated \(260\)-fold) as well as noncovalent catalysis—the \textit{para}-chlorination of anisole with hypochlorous acid proceeds \(5.3\) times faster with high regioselectivity (\textit{para} : \textit{ortho}, \(96:4\)) when \(72\%\) of the anisole is bound\(^{10}\) in \((1)\). Enantiomeric differentiations have also been observed\(^{11}\) during the catalytic hydrolysis of racemic esters by cyclohexaamylose \((1)\) which belongs to the rare chiral point group with \(\mathcal{C}_6\) symmetry.\(^{12}\)

Whilst research aimed at uncovering the potential of the cycloamyloses as enzyme models will no doubt continue to thrive, it would appear that rapid progress in this area is going to be hampered by a number of factors, not least of them \((i)\) the lack of sufficient structuring of the guests in their binding sites, \((ii)\) the low degree of chirality inherent in their axial symmetry (despite the fact that \((1)\) contains 30 chiral centres!), \((iii)\) the constitutional difficulties associated with their chemical modification, and \((iv)\) the constraints of always having to start with the same one or two basic building blocks. And so it seems obvious now that we must at least face up to the challenge of designing and synthesising our own receptor molecules. For more than a century now, chemists have been elucidating the structures of natural products and unravelling the mechanisms of quite complex reactions. More often than not, synthetic objectives have emerged out of the harvested information from Nature's apparently boundless store. Occasionally, preparative goals have been pursued on molecules designed by the chemists' own imagination usually to test some structural or mechanistic hypothesis and sometimes just to indulge in an aesthetic vagary. It is only very recently that we have been able to contemplate the design and preparation of synthetic hosts to complex in a highly structured manner with both synthetic
and naturally-occurring guests. As a result, I am willing to predict that synthetic chemistry is about to enter a new and exciting era and I want to try and explain how and why I believe that carbohydrates are going to play an important role in this renaissance. First of all, however, we must digress to meet the new building blocks.

2. The Break and Some Facts

A great opportunity was afforded to us with the accidental synthesis by Pedersen\(^13\) of dibenzo-18-crown-6 (4) and his reports\(^14\) in 1967 that this compound forms stable complexes—both in the crystalline state and in solution—with a whole range of metal (e.g. Na\(^+\)NO\(_2^-\), K\(^+\)I\(^-\), Rb\(^+\)SCN\(^-\), Cs\(^+\)SCN\(^-\), Ca\(^{2+}\)Cl\(_2^-\), Ba\(^{2+}\)(SCN)\(_2^-\), Cd\(^{2+}\)Cl\(_2^-\), Hg\(^{2+}\)Cl\(_2^-\)), ammonium, and substituted ammonium (e.g. HONH\(_3^+\)Cl\(^-\), H\(_2\)NNH\(_3^+\)Cl\(^-\), Me\(_2\)CHCH\(_2\)NH\(_3^+\)Cl\(^-\), and HO\(_2\)CCH\(_2\)NH\(_3^+\)Cl\(^-\)) salts. In particular, the ability of the so-called crown ethers to complex with substituted ammonium cations forms a basis for building synthetic organic host molecules to bind organic cations in a highly structured manner. In ingenious fashion, Cram\(^15\)-\(^{21}\) suggested that binding in such complexes arises from hydrogen bonds involving the three hydrogens of the substituted ammonium cation with alternate oxygens on the 18-crown-6 constitution. The atomic dipoles associated with the lone pairs of electrons on the other three oxygens lend\(^21\) some additional ion-dipole stabilisation to the positively charged nitrogen of the cation. Inspection of framework molecular models of the complex (5)-(6).HSCN between 18-crown-6 (5) and Me\(_3\)CNH\(_3^+\)SCN\(^-\) (6).HSCN, employing an N—H.....O distance of 2.88 Å for the three N—H.....O hydrogen bonds,\(^22\) indicates

[Formula (4) here]
that the complex is of a face-to-face type. The drawings in Figure 1,

which are based on photographs of C.P.K. space-filling molecular models of the cationic complex (5)-(7).H⁺ formed between 18-crown-6 (5) and the MeNH₃⁺ cation (7).H⁺ reveal a good "fit" between the crown ether and the cation with an obvious convergence of donor sites in (5) towards receptor sites in (7).H⁺. In nonpolar solvents, the anion will often form a contact ion pair with the cationic complex if it can compete (e.g. Cl⁻, ArCO₂⁻, CF₃CO₂⁻, and SCN⁻ ions) with the crown ether oxygens for hydrogen bonding with the cation. Nonetheless, Cram's three point binding model provides a very useful working hypothesis for investigating the structures of these complexes and is supported by crystal structure data on complexes of 18-crown-6 derivatives. It also allows us to interpret and predict the strengths of complexes formed in nonpolar solvents. The stabilities of complexes in CDC₁₃ can be measured spectroscopically by a procedure which involves partitioning of Me₃CNH₃⁺SCN⁻(6).HSCN between D₂O and CDC₁₃ in the absence and the presence of the crown compound. From the ratio of Me₃CNH₃⁺SCN⁻(6).HSCN to crown in the CDC₁₃ layer — obtained conveniently from the ¹H n.m.r. spectrum of the CDC₁₃ layer—the association constant (Kₛ/M⁻¹) for the equilibrium in Equation (1) can be determined and the corresponding free energy of complexation can be calculated using Equation (2). Where these thermodynamic parameters are known for complexes cited in
First of all, let us consider the strengths of the complexes formed between ligands (8) - (SS)-(18) and Me$_3$CNH$^+$SCN$^-$ (6).HSCN in relation to the strong complex formed between 18-crown-6 (5) and Me$_3$CNH$^+$SCN$^-$ (6).HSCN in CDCl$_3$. In the case of the open-chain analogue (8), the need to have the binding sites already organised to act cooperatively is demonstrated by the factor of $>10^4$ in the $K_a$ compared to that obtained for the cycle (5). The formal "removal" of one of the oxygens in (5) by replacing a diethylene glycol unit in (5) in turn by (i) a pentamethylene unit to give (9), (ii) a meta-xylyl unit to give (10), and a 2-methoxy-carbonyl-meta-xylyl unit to give (11) also has a drastic effect upon complex strengths and brings about reductions in $K_a$ of the order of $>10^3$, $10^3$, $<10^2$, respectively. In fact, both the CH$_2$...N and 7t-aryl...N interactions are believed to be repulsive. The CO$_2$Me group in (11) provides an additional binding site to stabilise its complex relative to that of (10). The ortho-phenylyl unit in (12) reduces the basicity of the ligand as a result of the delocalisation of the aryl oxygen lone pairs into the $\pi$-system of the aryl ring and is probably responsible for most of the reduction of ca. 5 in its $K_a$ value relative to that for (5). A factor of $>10$ in $K_a$ is conceded when a furan-2,5-dimethylyl unit in (13) replaces a diethylene glycol unit in (5). No doubt this reflects the fact that the furanyl oxygen lone pairs are delocalised into the furanyl ring. Not only is their effect removed when (13) is reduced to give the tetrahydrofuranyl derivative (14) but inspection of molecular models shows that the 5-membered
ring oxygen is turned in towards the cavity in such a way that the ion-dipole interaction with the positively charged nitrogen can be maximised. Thus, for this reason - at least in part - it is believed that (114) forms a slightly stronger complex than does (5). So does (15) which incorporates a 2,6-pyridine dimethyl unit in place of a diethylene glycol unit in (5). In this case, the reason for the slightly better complex probably resides in the ability of the pyridyl nitrogen to form a stronger hydrogen bond to the ammonium hydrogens than to an ether oxygen. In the sym-dipyridyl-18-crown-6 (16), only one pyridyl nitrogen can be involved in hydrogen bonding within a three-point binding model leaving the other pyridyl nitrogen to fulfil the function of stabilising electrostatically the positive charge on nitrogen. Since nitrogen is less electronegative than oxygen it will be less efficient at this task and so (16) has a $K_a$ value which is just less than that for (5) and ca. one-third smaller than that for (15). The (5)-2,2'-binaphthyl-20-crown-6 (5)-(17) and the (SS)-bisbinaphthyl-22-crown-6 (SS)-(18) both form very weak complexes on account of (i) steric interactions between the naphthalene rings and the tert-butyl group of the cation (6).$H^+$ and (ii) the reduced basicity of the aryl oxygens due to inductive effects and delocalisation of their lone pairs into the naphthalene rings. Compounds (5)-(17) and (SS)-(18) illustrate the use of the 1,1'-binaphthyl unit as a source of axial chirality in optically-active crown ethers.

An added advantage of building synthetic receptor molecules around crown ethers is that relatively high yields can be obtained in the synthesis of these compounds. Table 1 shows that 18-crown-6 (5) can be synthesised in 33-93% yields from condensation of triethylene glycol (19) with its bistosylate (20) in the presence of $Me_3COK$ depending on the nature of the solvent. With less expensive reagents such as (i) triethylene glycol (19), its dichloride (21) and KOH in aqueous tetrahydrofuran or
Table 1: High yields in the synthesis of 18-crown-6 (5)

<table>
<thead>
<tr>
<th>Diol</th>
<th>Other reactant</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield(%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(19)</td>
<td>(20)</td>
<td>Me₃CO</td>
<td>Me₃COH/Benzene</td>
<td>33d</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me₃CO</td>
<td>THF a</td>
<td>30-60e</td>
<td>38</td>
</tr>
<tr>
<td>(19)</td>
<td>(21)</td>
<td>Me₃CO</td>
<td>DMSO b</td>
<td>84f</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me₃CO</td>
<td>DME c</td>
<td>93f</td>
<td>38</td>
</tr>
<tr>
<td>(19)</td>
<td></td>
<td>KOH</td>
<td>THF a/H₂O</td>
<td>40-60g</td>
<td>39</td>
</tr>
<tr>
<td>(22)</td>
<td>(23)</td>
<td>KOH</td>
<td>THF a</td>
<td>30h</td>
<td>41</td>
</tr>
</tbody>
</table>

a. Tetrahydrofuran; b. Dimethyl sulphoxide; c. Dimethoxyethane; d. Obtained on heating for 5 hours; e. Reaction carried out at 35°C; f. Reaction conditions not described; g. Obtained on refluxing and stirring for 18 hours; h. Obtained on refluxing for 18 hours.

(ii) Tetraethyleneglycol (22) and diethyleneglycol dichloride (23) in anhydrous tetrahydrofuran, yields of 30-60% can be achieved. These are remarkably high yields for the formation of an 18-membered ring. One asks, "why". The reasons are probably at least two fold. First of all, there is the so-called gauche effect which characterises the conformations of bismethylenedioxy units in so many different guises (43-52) (see Figure 2). In systems close to "home", the conformational free energy of the acetoxy group in 3-acetoxytetrahydropyran
(24) lies \(^{43}\) in the range \(-0.27\) to \(+0.17\) kcal mol\(^{-1}\) depending on the nature of the solvent and is much smaller than the estimated value of \(+0.5\) kcal mol\(^{-1}\) based on steric considerations alone. Clearly, an effect of an electronic nature is operating in favour of the axial conformation \((24a)\). A similar kind of solvent dependence is observed \(^{44,45}\) in the acid-catalysed equilibration of cis \((25a)\) and trans \((25b)\) 5-methoxy-2-isopropyl-1,3-dioxans. Almost equal amounts of the two configurational isomers are present \(^{45}\) in acetonitrile at 25\(^{\circ}\)C. Infrared spectroscopy indicates \(^{46}\) that, although 1,2-dimethoxyethane \((26)\) contains both gauche \((26a)\) and anti \((26b)\) conformations about the C-C bond in the liquid at 25\(^{\circ}\)C, it adopts only the gauche conformation \((26a)\) about the C-C bond in the crystal at \(-195^{\circ}\)C. Polyoxymethylene \((27)\) has a helical "all-gauche" conformation about the C-C bonds in the crystal, \(^{47}\) and comparisons between calculated and experimentally-determined physical properties indicate \(^{48}\) that this is also the preferred conformation in solution. \(^{53}\) Moreover, the propensity during boron-trifluoride catalysed cyclooligomerisations of ethylene oxide \((28)\) for macrocycle formation \(^{51,54}\) to give 12-crown-4 \(^{55}\) \((30)\) in particular, is compatible with a helical shape for the growing oligooxymethylene chain in \((29)\), Equation (3). In the synthetic approaches to 18-crown-6 \((5)\)

[Insert Equation (3) here]

summarized in Table 1, a template effect \(^{13,20,35-38,40,42,51,54,56,57}\) involving the K\(^{+}\) ion probably augments the helicity in the intermediates, \(\text{e.g. (31)}\), by entering into ion-dipole interactions with the oxygens and stabilising the "all-gauche OCH\(_2\)CH\(_2\)O" conformation. \(^{58}\) This can then be envisaged to undergo fast intramolecular reaction to give the cyclised product, \(\text{e.g. (32)}\) in Equation (4). Thus, the gauche effect and the template effect can be considered to

[Insert Equation (4) here]
operate in unison to enhance the entropy of activation and hence lower the free energy of activation for cyclisation. The existence of a template effect is also supported by additional thermodynamic and kinetic evidence insofar as (i) comparative yields in competition experiments and (ii) rates of cyclisations reflect a close correspondence between a catalytic effect and the relative complexing ability of crown ethers towards the cations used in their synthesis. We shall return to this point later. Now that we are armed with some facts, we are ready to pay a visit to dreamland!

3. A Visit to Dreamland

A few years ago, we decided to meet the challenge of building synthetic receptor molecules around the crown ether constitution as the provider of the primary binding site for complexation with substituted ammonium cations. However, we had to go out in search of two other basic requirements, namely chirality and functionality. Where better to go in this instance than to carbohydrates? Amongst their many attributes are the following seven:

(i) They are rich in substituted bismethylenedioxy units for incorporation into the crown ether constitution. (ii) They are unusually well-endowed with functionality which can be used to build in secondary binding sites as well as catalytic sites. (iii) They are gifted with a high degree of chirality. (iv) They are available in enantiomerically-pure form with known chiroptical properties. (v) They are more often than not conformationally-biased (i.e. they are examples of anancomeric systems), a feature which permits the design of both convergent and divergent side arms. (vi) They are blessed with good $^1$H and $^{13}$C n.m.r. probes. (vii) They are cheap! This is important. More than any other attribute, it ensures a bright future for carbohydrates in this field of endeavour.
We are now in a position to give these attributes some real expression. Figures 3 and 4 list a number of suitably substituted carbohydrate derivatives which can serve as precursors to chiral crown ethers. Some we have used, some we are using, and some we plan to use. We recognised at the outset that the attractions of selecting carbohydrates with $\tilde{C}_2$ symmetry are considerable because of the relative ease and efficiency this introduces into the synthesis of symmetrical crown ethers incorporating more than one sugar residue. For example, $\tilde{L}$-tartaric acid has been incorporated into the 18-crown-6 constitution as its bis-(N,N-dimethylamide) $\tilde{L}$-(33). While both tetritols and hexitols have the required constitutional symmetry, only threitol, mannitol and iditol fulfil the $\tilde{C}_2$ symmetry requirement. The 1,4-dibenzyl ether $\tilde{L}$-(34) of $\tilde{L}$-threitol can be obtained from $\tilde{L}$-tartaric acid and the 1,2,5,6-di-O-isopropylidene derivatives $\tilde{D}$-(35) and $\tilde{L}$-(36) of $\tilde{D}$-mannitol and $\tilde{L}$-iditol are available beginning with $\tilde{D}$-mannitol and $\tilde{L}$-sorbitose, respectively. Diols $\tilde{L}$-(34) to $\tilde{L}$-(36) are all examples of conformationally "flexible" sources of "chiral ethyleneglycol" units. $\tilde{D}$-Glucosamine and $\tilde{D}$-sorbital are inexpensive starting materials for the syntheses of the 2,5-anhydro derivatives $\tilde{D}$-(37) and $\tilde{L}$-(38) of $\tilde{D}$-mannitol and $\tilde{L}$-iditol, respectively. These derivatives have potential as sources of "chiral diethyleneglycol" units as well as "chiral ethyleneglycol" units. The conformational freedom of both these units is somewhat impaired by their association with a 5-membered ring. The restrictions on finding suitable derivatives of asymmetric carbohydrates to employ in the preparation of asymmetric crown ethers is not nearly so great (see Figure 4). $\tilde{D}$-Mannitol is a potential source of
1-0-benzyl-D-glycerol D-(39)\(^ {75-77}\) containing only one chiral centre and a conformationally "flexible" monosubstituted ethyleneglycol unit. Figure 4 also draws attention to the fact that the 4,6-0-benzylidene derivatives \(\alpha-D-(40), \beta-D-(40), \alpha-D-(41), \beta-D-(41), \alpha-D-(42),\) and \(\beta-D-(42)\) of the methyl \(\alpha-\) and \(\beta-\) glycosides of D-glucose, D-galactose, and D-mannose are readily available.\(^ {78}\) These derivatives are all sources of conformationally "rigid" gauche "chiral ethyleneglycol units." Methyl 4,6-0-benzylidene-\(\alpha-D-\)altroside \(\alpha-D-(43)\) can be obtained\(^ {79}\) from D-glucose and provides a ready source of conformationally "rigid" anti "chiral ethyleneglycol units." D-Galactosamine is \(^ {80}\) a precursor of 2,5-anhydro-D-talitol D-(44) and 1,5-anhydro-D-ribose D-(45) can be synthesised\(^ {81}\) from D-ribose. These derivatives provide a ready chiral source of near to eclipsed and formally eclipsed C-O bonds for incorporation into chiral crown ethers. Finally, the benzyloxycarbonyl derivative \(\alpha-D-(46)\) of methyl 4,6-0-benzylidene-\(\alpha-D-\)glucosamine provides\(^ {82}\) a ready entry into chiral aza-crown ethers from D-glucosamine.

Now that the principle is established and the scene is set, let me add a comment on nomenclature. In looking for words to describe our chemistry I could not resist recalling Fischer's famous lock and key metaphor in which he likened an enzyme to a lock and its substrate (in the specific case under consideration, a "glucoside") to a key. This analogy was drawn in 1894 by Fischer\(^ {83}\) in the statement:

\[
\text{Um ein Bild zu gebrauchen, will ich sagen, dass Enzym und Glucosid wie Schloss und Schlüssel zu einander passen müssen, um eine chemische Wirkung auf einander ausüben zu können.}
\]

In the present context, the lock will refer to the crown ether and the key to the substituted ammonium ion. To my mind, it almost seems appropriate that a synthetic host molecule should be likened to an inanimate lock. Fischer must have had vision!
13. Reality

Our first practical ventures were greeted with beginners' luck. The tetra-O-isopropylidenedi-D-mannitol 18-crown-6 derivative \( \text{DD}(48) \) was obtained from D-(35) and diethyleneglycol bistosylate (47) in 24\% yield together with the 9-crown-3 and 27-crown-9 homologues by the route outlined in Scheme 1. It was isolated pure as an oil after chromatography on alumina. It solubilises primary alkylammonium salts in \( \text{CD}_2\text{Cl}_2 \) and the formation of 1:1 complexes were indicated by significant changes in the \( ^1\text{H} \) n.m.r. spectrum of the lock as well as in the appearance of additional signals for the key. The lock has \( D_2 \) symmetry and hence its faces are homotopic. Thus, complexation of achiral or optically pure keys to either face affords identical complexes. On the other hand, complexation of enantiomeric keys to either face results in the formation of diastereoisomeric complexes. The big question was would our chiral lock exhibit differentiation under equilibration conditions towards enantiomeric keys in a racemic salt? After partitioning \( (\text{RS})-\alpha\)-phenylethylammonium hexafluorophosphate \( (\text{RS})(49) \cdot \text{HPF}_6 \) between \( \text{D}_2\text{O} \) and \( \text{CDCl}_3 \) in the presence of \( \text{DD}(48) \), the \( ^1\text{H} \) and \( ^{13}\text{C} \) n.m.r. spectra of the \( \text{CDCl}_3 \) layer were recorded. Although we only obtained rather modest chiral recognition—the \( (R):(S) \) ratio was 62:38—we were excited about the result because it meant our first chiral lock had "worked." The broad-band decoupled \( ^{13}\text{C} \) n.m.r. spectrum (see Figure 5) of the \( \text{CDCl}_3 \) layer provides the best visual representation of the enantiomeric differentiation. The spectrum displayed the expected eight resonances for the heterotopic carbons in the lock indicating
fast exchange between the lock and the enantiomeric keys on the $^{13}$C n.m.r. time scale. The methyl, methine, and quaternary aromatic carbons in the previously enantiomeric keys exhibit chemical shift non-equivalence. Assignments to diastereoisomeric complexes $\text{DD}-(48)-(R)-(49).\text{HPF}_6$ and $\text{DD}-(48)-(S)-(49).\text{HPF}_6$ were made on the basis of "blank" experiments using the pure enantiomeric keys. Assuming three-point binding models for the diastereoisomeric complexes and selecting Newman projections which orient the phenyl groups over a region of the 18-crown-6 cycle free of substituent groups, the methyl group in the key is seen to interact more severely with a 2,2-dimethyl-1,3-dioxolanyl group in $\text{DD}-(48)-(S)-(49).\text{HPF}_6$ than in $\text{DD}-(48)-(R)-(49).\text{HPF}_6$. Since $\text{DD}-(48)$ forms a very weak complex with $\text{Me}_3\text{CNH}_3{+}\text{SCN}^- (6).\text{HSCN}$ in $\text{CDCl}_3$—presumably mainly for steric reasons—we decided to investigate the effect upon chiral recognition of increasing the complexing ability by incorporating nitrogen atoms in the form of pyridyl residues$^{25,31}$ and tertiary amine functions$^{27,33,86}$ into the lock. In particular, the nitrogen atoms in the latter form stronger hydrogen bonds with $\text{N}^+\text{H}$ bonds than do oxygen atoms. Accordingly, we prepared$^{87}$ the sym-dipyridyl $\text{DD}-(50)$ and sym-$\text{N, N}$-dimethylidiza $\text{DD}-(51)$ derivatives of $\text{DD}-(48)$ and found that they do indeed form appreciably stronger complexes with $\text{Me}_3\text{CNH}_3{+}\text{SCN}^- (6).\text{HSCN}$ in $\text{CDCl}_3$ than does $\text{DD}-(48)$. However, neither lock showed any chiral recognition towards $(RS)$-$\text{PhCHMeNH}_3{+}\text{PF}_6^- (RS)-(49).\text{HPF}_6$ indicating that increasing binding strengths and chiral recognition do not necessarily go hand in hand. $^{88}$ This observation was also borne out by
experiments on the tetra-o-isopropylidenedi-l-iditol-18-crown-6 derivative $\text{LL}-(52)$ which is a factor of ca. 60 more efficient than $\text{DD}-(48)$ at binding

[Formula $\text{LL}-(52)$ here]

Me$_3$CNH$_3^+\text{SCN}^-$ (6).HSCN and does not show any chiral recognition towards $(\text{RS})-\text{PhCHMeNH}_3^+\text{PF}_6$ (RS)-(49).HPF$_6$. However, $\text{LL}-(52)$ does exhibit enantiomeric differentiation to the extent of 60:40 for $(R):(S)$ in equilibration experiments with $(\text{RS})-\text{PhCHCO}_2\text{MeNH}_3^+\text{ClO}_4^- (\text{RS}-(53)).\text{HClO}_4$. In the face of these apparent contradictions and only limited success on this front, we noted that, in relation to its chiral recognition properties, the lock $\text{DD}-(48)$ is on a par with the $(SS)$-binaphthyl-22-crown-6 $(SS)-(18)$ popularised by Cram.$^{15-19,90}$ This led us to forge a link between the approaches developed independently at UCLA and Sheffield by carrying out a "synthetic resolution" of the 1,1'-binaphthyl unit through incorporation of $(\text{RS})-2,2'$-dihydroxy-1,1'-binaphthyl $(\text{RS}-(54))$ and di-o-isopropylidene-$\alpha$-mannitol $\alpha-(35)$ into the

[Formula $(S)-(54)$ here]

synthesis of the diastereoisomeric locks $\alpha-(R)-(55)$ and $\alpha-(S)-(55)$.

[Formulae $\alpha-(R)-(55)$ and $\alpha-(S)-(55)$ here]

The assignments of the absolute configurations to these locks were made on the basis of repeating the synthesis with $(S)-2,2'$-dihydroxy-1,1'-binaphthyl $^{92}$ $(S)-(54)$ to afford only the $\alpha-(S)-(55)$ isomer. In view of the topological similarities between $(SS)-(18)$, $\text{DD}-(48)$, and $\alpha-(S)-(55)$—evident upon inspection of CPK space-filling molecular models—we were not surprised to find the $\alpha-(S)-(55)$ isomer exhibited similar chiral recognition characteristics. What did surprise us was the competitive nature of the $\alpha-(R)-(55)$ isomer$^{93}$ as
a chiral recogniser. But then, surprises abound in this field!

It was now clear to us that a much wider survey of carbohydrate derived locks was called for if we were to gain some real understanding in this area of lock and key chemistry. We decided at this stage to turn our attention to the incorporation\textsuperscript{28} of 1,3:4,6-di-0-methylene-D-mannitol D-(56)—which is readily accessible\textsuperscript{94} from D-mannitol—into 22-crown-6 DD-(57) and 20-crown-6 D-(58) derivatives. Examination of CPK space filling molecular models indicates that they are not too different topologically from the corresponding (RR)-bisbinaphthyl-22-crown-6 (RR)-(18) and (R)-2,2'-binaphthyl-20-crown-6 (R)-(17) derivatives, respectively. Although the 22-crown-6 derivative DD-(57) forms exceedingly weak complexes with substituted ammonium salts in CDCl\(_3\), the 20-crown-6 derivative D-(58) binds reasonably well with the thiocyanate and/or perchlorate salts derived from MeNH\(_2\) (7), Me\(_2\)CHNH\(_2\) (59), Me\(_3\)CNH\(_2\) (6), PhCH\(_2\)NH\(_2\) (60), (R)- and (S)-PhCHMeNH\(_2\) (R)- and (S)-(49), (S)-PhCHO\(_2\)MeNH\(_2\) (S)-(53), and (R)- and (S)-PhCH\(_2\)CHCO\(_2\)MeNH\(_2\) (R)- and (S)-(61). The association constant for 1:1 complex formation with Me\(_3\)CNH\(_3\)\(^+\)SCN\(^-\) (6).HSCN in CDCl\(_3\) is 520. By this time we had acquired at Sheffield a superconducting \(^1\)H n.m.r. spectrometer operating at 220 MHz and so we were in a good position to study the kinetics of the complexation-decomplexation processes of locks with a range of keys by variable temperature \(^1\)H n.m.r. spectroscopy.\textsuperscript{95} The lock DD-(58) has \(C_2\) symmetry and so the faces are homotopic. Figure 6 illustrates in general terms the kind of degenerate equilibration process of [Insert Figure 6 here]

keys between homotopic faces that can be studied by dynamic \(^1\)H n.m.r.
spectroscopy in locks with $C_2$ symmetry. Homotopic protons (H) in such locks become heterotopic ($H_C$ and $H_D$) when 1:1 complexes with keys are formed. Furthermore, when dissociation of the key from the lock becomes slow on the $^1H$ n.m.r. time scale, anisochronous behaviour of the heterotopic protons can be observed on account of a site exchange process involving $H_C$ and $H_D$. The $^1H$ n.m.r. spectra reproduced in Figure 7 demonstrate the power of this technique for investigating (i) the thermodynamics of complexation-decomplexation processes and (ii) the structures of complexes. Figure 7a shows the spectrum of the pure lock B-(58) in CD$_2$Cl$_2$ at +30°C. The AB system can be assigned to the dioxymethylene protons, the A portion arising from the equatorial protons and the B portion from the axial protons. The other assignments were made on the basis of homonuclear INDO spectroscopy. Small chemical shift changes occur (see Figure 7b) in the signals for the lock when 1 molar equivalent of PhCH$_2$NH$_3^+$ClO$_4^-$ (60).HClO$_4$ is added. Additional signals, of course, appear in the spectrum and they can be attributed to protons in the key. Most significant is the observation that the previously enantiotopic benzylic methylene protons in (60).HClO$_4$ become diastereotopic (in the chiral environment as exhibited by their appearance as an AB system. This kind of observation gives one confidence that a molecular complex has been formed in solution. On lowering the temperature of the CD$_2$Cl$_2$ solution, line broadening occurs in all regions of the spectrum, a phenomenon characteristic of the kind of equilibration and site exchange processes described in Figure 6. The line shape behaviour of the AB system for the dioxymethylene protons is most informative (see Figure 7c). The B part becomes very broad, goes through a coalescence temperature at -55°C, and eventually divides out into two signals.
of equal intensity separated by 64 Hz at -80°C. The A part behaves similarly with a lower coalescence temperature of -65°C and a smaller chemical shift difference of 18 Hz at -80°C. Since the 20-membered ring in the lock P-(58) cannot ring invert, the free energies of activation (both 10.5 kcal mol\(^{-1}\)) calculated at the coalescence temperatures for both these spectral changes can be associated with the free energy of activation (\(\Delta G^+_d\)) for dissociation of the complex. The \(\Delta G^+_d\) values for all the 1:1 complexes investigated are listed in Table 2. If we assume that the transition state

Table 2. The free energies of dissociation (\(\Delta G^+_d\)) for the 1:1 complexes formed between RNH\(_3^+\) keys and the lock P-(58)

<table>
<thead>
<tr>
<th>Key</th>
<th>SCN(^-)</th>
<th>CIO(^-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeNH(_3^+) (7).H(^+)</td>
<td>&lt;8.2</td>
<td>&lt;8.2</td>
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<tr>
<td>Me(_2)CHNH(_3^+) (59).H(^+)</td>
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<td>9.7</td>
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<td>9.2</td>
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<tr>
<td>PhCH(_2)NH(_3^+) (60).H(^+)</td>
<td>8.8</td>
<td>10.5</td>
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<tr>
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<td>&lt;9.3</td>
<td>-</td>
</tr>
<tr>
<td>(S)-PhCHMeNH(_3^+) (S)-(49).H(^+)</td>
<td>&lt;8.8</td>
<td>10.2</td>
</tr>
<tr>
<td>(R)-PhCHCO(_2)MeNH(_3^+) (R)-(53).H(^+)</td>
<td>9.3</td>
<td>-</td>
</tr>
<tr>
<td>(R)-PhCH(_2)CHCO(_2)MeNH(_3^+) (R)-(61).H(^+)</td>
<td>-</td>
<td>9.9</td>
</tr>
<tr>
<td>(S)-PhCH(_2)CHCO(_2)MeNH(_3^+) (S)-(61).H(^+)</td>
<td>-</td>
<td>10.4</td>
</tr>
</tbody>
</table>

free energies in the complexation-decomplexation processes are characteristic of the locks more so than of the keys, then the values for \(\Delta G^+_d\) will reflect the relative binding energies for different keys. On this basis, we may draw the following conclusions: (i) The MeNH\(_3^+\)X\(^-\) (7).HX salts form the least stable complexes of all with P-(58), probably on account of the relative
accessibility of their cation for ion pairing with the anion when the substituent on N⁺ is small. (ii) Complexes involving the ClO₄⁻ ion are stronger than those involving the SCN⁻ ion. "Destructuring" of complexes by the SCN⁻ ion through its ability to hydrogen bond with the cation is probably responsible (cf. refs. 27, 33, and 86) for this effect. (iii) The difference of 500 cal mol⁻¹ in the ΔG° values for the diastereoisomeric complexes D-(8)-(R)-(61).HClO₄ and D-(8)-(S)-(61).HClO₄ suggests that D-(8)-(R)-(61).HClO₄ and D-(8)-(S)-(61).HClO₄ suggests that D-(8)-(R)-(61).HClO₄ and D-(8)-(S)-(61).HClO₄ suggests that D-(8) is showing a small amount of chiral recognition towards (RS)-PhCH₂CHCO₂MeNH₃⁺ClO₄⁻ (RS)-(61) at low temperatures. (iv) Those complexes involving cations which contain phenyl groups are ca. 1 kcal mol⁻¹ stronger than those without phenyl groups in the cations. This observation suggested to us that a secondary binding site is present within the complex. Recalling the weak 1:1 complexes (e.g. 62) formed between variously substituted 1,3-dioxans in CCl₄, we examined space-filling molecular models of the complexes between D-(8) and a generalised substituted ammonium ion of the type PhCHR¹NH₃⁺ (R¹ = H, Me, or Ph). Sure enough, it is possible for the phenyl group in such a cationic key—assuming a three-point binding model—to orient itself above one of the 1,3-dioxan rings in the lock so that it meets the directional requirements for a dipole-induced dipole interaction as shown in the complex D-(8)-PhCHR¹NH₃⁺. Two observations in the low temperature [Formulae (62) and D-(8)-PhCHR¹NH₃⁺ here] ¹H n.m.r. spectra leave us feeling very confident about this structural proposal for the complex. First of all, the chemical shift differences for H_B are larger (44-64 Hz) for the complexes D-(8)-(S)-(49).HClO₄,
which contain a phenyl group than they are (15-22 Hz) for the complexes D-(58)-(59).HSCN, D-(58)-(59).HClO₄, and D-(58)-(60).HClO₄ where the substituent groups on the ammonium cation are Me₂CH and Me₃C. It is clear from the low temperature spectra that the phenyl group is shielding preferentially one of the axial protons Hₖ in these complexes listed above. Even more intriguing is the emergence at high field (6 2.50-3.00) of a signal which integrates for one proton in the low temperature spectra of the complexes D-(58)-(60).HClO₄, D-(58)-(R)-(53).HClO₄, and D-(58)-(60).HClO₄ but not in the corresponding thiocyanate complexes. Next we carried out a deuteration study to clinch the argument. The tetradeuterio-20-crown-6 derivative D-(58)-d₄ was prepared from [1,1,6,6-2H₄]mannitol and the low temperature spectrum of the complex D-(58)-d₄-(60).HClO₄ was recorded (see Figure 7c). The high field signal which integrated previously for one proton was absent. Thus, it can be assigned to H-1a which falls under the shielding influence of the phenyl group in the complex D-(58)PhCHR[NH₃]⁺. It is significant that the above chemical shift effects are absent in the less highly structured thiocyanate complexes and also in the PhCH₂CHCO₂MeNH₃⁺ClO₄⁻ complexes, D-(58)-(R)-(61).HClO₄ and D-(58)-(S)-(61).HClO₄, which contain an "extra" methylene group.

The demonstration of the power of dynamic H n.m.r. spectroscopy to probe the structures of complexes in solution, and to provide a rapid semi-quantitative assessment of the relative strengths of complexes in relation to particular locks leads logically into a discussion of our chiral asymmetric locks. To date, our efforts have been confined largely to a detailed investigation of the locks α-D-(63) to α-D-(69) incorporating

[Formulae α-D-(63) to α-D-(69) here]
the 4,6-O-benzylidene derivatives of methyl α- and β-D-glucosides, methyl α- and β-D-galactosides, methyl α-D-mannoside, and methyl α-D-altroside. Before we examine the complexing ability of these two classes (i.e. α and β) of diastereoisomerically related 18-crown-6 derivatives, let us consider how we prepared them by reference to one example, that of the α-galactoside-mannitol-18-crown-6 α-DD-(66) shown in Scheme 2. Treatment of methyl 4,6-O-benzylidene α-D-galactopyranoside α-D-(41) with an excess of allyl bromide and potassium hydroxide in toluene gave the diallyl ether of α-D-(41) in good yield. Ozonolysis of the diallyl ether in methanol, followed by borohydride reduction afforded the "half-crown" diol α-D-(70).

[Insert Scheme 2 here]

1,2:5,6-Di-O-isopropylidene-D-mannitol D-(35) was also converted into its diallyl ether which was subjected to ozonolysis followed by reduction with borohydride to give the "half-crown" diol of D-(35). Conversion of the "half-crown" diol into the "half-crown" ditosylate D-(71) was followed by condensation of equimolar proportions of α-D-(70) with D-(71) to afford the α-D-galactoside-D-mannitol-18-crown-6 derivative α-DD-(66) in 29% yield. The compound is crystalline and optically active. Two points regarding the stereochemistry of this class of chiral asymmetric locks can be made by reference to α-DD-(66): (i) It has heterotopic faces. In keeping with established carbohydrate nomenclature, I shall refer to the "bottom" face as being the α-face and the "top" face as being the β-face. (ii) The 18-membered ring is "rigid" as a result of its trans fusion to an anancomeric system. I shall adopt the "dot and circle" notation introduced earlier to identify "up" and "down" oxygen atoms, respectively. In addition, the torsional angles associated with the carbon-carbon bonds will be denoted
[see $\alpha$- and $\beta$-$\alpha$-(63), $\alpha$- and $\beta$-$\beta$-(65), $\alpha$-$\beta$-(67), and $\beta$-$\alpha$-(69)] as $g$ and $a$ for gauche and anti, respectively. In accordance with the convention employed by Dale $^{51,106}$ the helicity of the gauche bonds will be described (see Figure 8) as $g^+$ if they are clockwise and $g^-$ if they are anticlockwise. $^{107}$ Let us now return to a comparison of the association constants for complex formation of $\alpha$-$\alpha$-(63) to $\alpha$-$\alpha$-(69) with Me$_3$CNH$_3^+$SCN$^-$ (6).HSCN in CDC$_3$. Two features in relation to the $K_a$ values did not surprise us. They are: (i) The decrease in the strengths of the complexes which arise from disubstitution of $\alpha$-$\alpha$-(63), $\beta$-$\alpha$-(63), $\alpha$-$\beta$-(65), $\beta$-$\beta$-(65), and $\beta$-$\alpha$-(67) with bulky 2,2-dimethyl-1,3-dioxolanyl groups affording $\alpha$-$\alpha$-(64), $\beta$-$\beta$-(64), $\alpha$-$\beta$-(66), $\beta$-$\beta$-(66), and $\alpha$-$\alpha$-(68) in turn. This trend is to be expected on steric grounds. (ii) The very weak complexes formed by $\alpha$-$\alpha$-(69). This was also to be expected since introduction of one anti carbon-carbon bond into an 18-crown-6 derivative removes the opportunity for six oxygens to act cooperatively in binding substituted ammonium ions. However, another two features in relation to the $K_a$ values were surprising. They were: (i) All the glucoside, galactoside, and mannoside crowns form much weaker complexes with Me$_3$CNH$_3^+$SCN$^-$ than does 18-crown-6 ($^5$) ($K_a$, 3,000,000) itself. A discussion of this important and highly significant observation will be deferred until later. (ii) Despite the fact that in the galactoside and mannoside crowns one of the faces is more sterically hindered - this is obvious on examination of CPK space-filling molecular models - they form much stronger complexes than the glucoside crowns. The clue to the reasons for these unexpected observations came from an investigation (see Figures 9 and 10) of the
chemical shift dependences in the $^1$H n.m.r. spectrum of H-1, H-4, and PhCH in the galactoside portion of $\alpha$-D-(65) and H-1 and PhCH in the glucoside portion of $\alpha$-DD-(64) on stepwise additions of $\text{Me}_3\text{CNH}_3^+\text{SCN}^-\ (6).\text{HSCN}^-$.

In all cases, the chemical shifts of these protons attain their limiting values at a 1:1 molar ratio of lock-to-key providing evidence for 1:1 complex formation. However, the relative magnitudes of the downfield shifts are also important. First of all, we notice in Figure 9 that H-1, H-4, and PhCH all experience substantial downfield shifts indicating that O-1 and O-4 are participating along with the crown ether oxygens in hydrogen bonding and/or ion-dipole electrostatic stabilisation with the ammonium hydrogens of the $\text{Me}_3\text{CNH}_3^+\ (6).\text{H}^+$ ions in two distorted face-to-face complexes. Indeed, inspection of CPK space-filling molecular models shows that the axial orientations of the carbon-oxygen bonds at C-1 and C-4 render both O-1 and O-4 available to participate in the weak noncovalent to the cations in these complexes. Secondly, we notice (cf. Figures 9 and 10) that the downfield shifts for H-1 and PhCH are smaller for $\alpha$-DD-(64) than for $\alpha$-D-(65). This indicates that although O-1 is probably participating in complex stabilisation in $\alpha$-DD-(64), it is not doing so to the same extent as it does in $\alpha$-D-(65). The influence on the chemical shift of the PhCH proton is, as expected, very slight since the equatorial orientation of the carbon-oxygen bond at C-4 in $\alpha$-DD-(64) denies it the opportunity to cooperate with the crown ether oxygens in weak bonding to the cation. In a rather qualitative manner, the potential number of oxygens which are available as binding sites for the $\text{Me}_3\text{CNH}_3^+\ (6).\text{H}^+$ ion can be correlated with the relative strengths of the complexes formed between the locks $\alpha$-D-(63), $\beta$-D-(63), $\alpha$-D-(65), $\beta$-D-(65), and $\alpha$-D-(67) and the cationic key. We display in parentheses inside these
locks the potential number of total binding sites that can be utilised in complex formation and we indicate by means of arrows (→) those oxygens which can serve as binding sites assuming that a minimum of two crown ether oxygens are always utilised in a three-point binding array. A problem in nomenclature now arises. Although the equilibration between α- and β-complexes on the $^1$H n.m.r. time scale is fast (see Figures 9 and 10), they have now been identified (vide supra) as being "different" in their weak noncovalent bond connectivity as well as in their stereochemistry. In anticipation of being able to identify α- and β-complexes in the low temperature $^1$H n.m.r. spectra (vide infra) of 1:1 complexes in CD$_2$Cl$_2$, we have decided to adopt the classification of pairwise relations between isomeric structures proposed recently by Mislow. Hence we shall refer to a pair of α- and β-complexes as being anisometric in recognition of the fact that they may display the characteristics of constitutional isomerism as well as being distinguishable in a stereochemical sense. Thus, locks α-D-(63) to α-D-(69) all have heterotopic faces and can form anisometric α- and β-complexes [cf. α-D-(65)-α-(6).HSCN and α-D-(65)-β-(6).HSCN in Figure 9 and α-DD-(64)-α-(6).HSCN and α-DD-(64)-β-(6).HSCN in Figure 10] with both achiral and chiral keys. Figure 11 illustrates in general terms the kind of equilibration process of keys between heterotopic faces that can be studied by dynamic $^1$H n.m.r. spectroscopy in chiral asymmetric locks. All protons in asymmetric locks are heterotopic. Hopefully, a suitable candidate (H)—preferably one which resonates as a singlet and is chemically shifted from the others—emerges as a suitable $^1$H n.m.r. probe for studying the equilibration between the α- and β-complexes by giving rise to
anisochronous signals in the low temperature spectra attributable to say $H_C$ and $H_D$ in the anisometric complexes. Since the $\alpha$- and $\beta$-complexes can have different free energies of complexation, the ratios of the signals at low temperature in the $^1H$ n.m.r. spectra will reflect the relative stabilities of the anisometric complexes. Moreover, the temperature dependent spectra resulting from the site exchange process involving $H_C$ and $H_D$ in equally or unequally populated sites can be subjected to line shape analysis to give activation parameters for the equilibrium between the anisometric complexes. The spectra reproduced in Figures 12-16 serve to illustrate the mine of information that can be uncovered using this technique. Figure 12a shows the $^1H$ n.m.r. spectrum of the pure lock $\alpha-D-(65)$ in CD$_2$Cl$_2$ at $+30^\circ$C. The assignment of peaks to the PhCH$_2$, H-1, H-4, and OCH$_3$ protons can be made unambiguously and demonstrates the enormous potential of carbohydrate derivatives to provide good $^1H$ n.m.r. probes. In addition to the appearance of additional signals for the key, dramatic chemical shift changes occur (Figure 12b) in the resonances for the lock when 1 molar equivalent of PhCH$_2$NH$_3$$^+$SCN$^-$ (60).HSCN is added. As indicated previously (see Figure 9), the PhCH$_2$, H-1, and H-4 protons witness marked downfield shifts which signify the involvement of O-1 and O-4 in the weak noncovalent bonding pattern within the $\alpha$- and $\beta$-complexes. On lowering the temperature of the CD$_2$Cl$_2$ solution, line broadening occurs in all regions of the spectrum and the behaviour of the signals for the PhCH$_2$, H-1, and OCH$_3$ protons is particularly interesting. In all cases the signals separate out into two signals at $-70^\circ$C in the ratio of 55:45 and the free energies of activation (12.0, 11.9, and 11.8 kcal mol$^{-1}$) calculated at the coalescence temperatures are in excellent agreement with each other (see Figure 12c). Let me now make some general points by summarising in Table 3
Table 3. The complex ratios at low temperatures in \( \text{CD}_2\text{Cl}_2 \) and the free energies of dissociation \( (\Delta G_d^\ddagger) \) for the \( 1:1 \) complexes formed between \( \text{RNH}_3^+X^- \) salts and the chiral asymmetric locks \( \alpha-D-(63) \) to \( \alpha-D-(69) \) 

<table>
<thead>
<tr>
<th>Lock</th>
<th>( \text{RNH}_3^+X^- )</th>
<th>( R )</th>
<th>Complex ratio(( T/\degree\text{C} ))</th>
<th>( \Delta G_d^\ddagger ) (kcal mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha-D-(63) )</td>
<td>(60).HSCN</td>
<td>CH(_2)Ph</td>
<td>67 : 33 (-70)</td>
<td>11.6</td>
</tr>
<tr>
<td>( \beta-D-(63) )</td>
<td>(60).HSCN</td>
<td>CH(_2)Ph</td>
<td>78 : 22 (-90)</td>
<td>10.2</td>
</tr>
<tr>
<td>( \alpha-DD-(64) )</td>
<td>(60).HSCN</td>
<td>CH(_2)Ph</td>
<td>75 : 25 (-70)</td>
<td>12.2</td>
</tr>
<tr>
<td>( \beta-DD-(64) )</td>
<td>(60).HSCN</td>
<td>CH(_2)Ph</td>
<td>86 : 14 (-90)</td>
<td>10.8</td>
</tr>
<tr>
<td>( \alpha-D-(65) )</td>
<td>(6).HSCN</td>
<td>CMe(_3)</td>
<td>55 : 45 (-90)</td>
<td>10.2</td>
</tr>
<tr>
<td>( \beta-D-(65) )</td>
<td>(6).HSCN</td>
<td>CMe(_3)</td>
<td>76 : 24 (-100)</td>
<td>10.0</td>
</tr>
<tr>
<td>( \alpha-DD-(66) )</td>
<td>(60).HSCN</td>
<td>CH(_2)Ph</td>
<td>50 : 50 (-90)</td>
<td>11.5</td>
</tr>
<tr>
<td>( \alpha-D-(67) )</td>
<td>(60).HSCN</td>
<td>CH(_2)Ph</td>
<td>74 : 26 (-75)</td>
<td>11.1</td>
</tr>
<tr>
<td>( \alpha-DD-(68) )</td>
<td>(6).HSCN</td>
<td>CMe(_3)</td>
<td>88 : 12 (-95)</td>
<td>10.3</td>
</tr>
<tr>
<td>( \alpha-D-(69) )</td>
<td>(6).HSCN</td>
<td>CMe(_3)</td>
<td>50 : 50 (-108)</td>
<td>8.3</td>
</tr>
</tbody>
</table>

all the results we have obtained to date on our chiral asymmetric locks. Since the 18-membered ring in locks \( \alpha-D-(63) \) to \( \alpha-D-(69) \) cannot ring invert, the free energies of activation, calculated (i) at the coalescence temperatures in the case of \( \alpha-D-(65) \), \( \alpha-DD-(66) \), and \( \alpha-D-(69) \) and (ii) by line shape analysis at

\( (\text{RNHF}_3 \) salts and the chiral asymmetric locks \( \alpha-D-(63) \) to \( \alpha-D-(69) \).
selected temperatures in the case of all the other locks, can be equated with the free energies of activation ($\Delta G^\ddagger_d$) for dissociation of the anisometric complexes. Figure 17 portrays an energy profile diagram

[Insert Figure 17 here]

which illustrates the general situation. The $\Delta G^\ddagger_d$ values, which are listed in Table 3 are those relating to dissociation of the major anisometric complex where inequalities in complex populations are observed. The Table also records the ratios of the anisometric complexes formed at low temperature in CD$_2$Cl$_2$. The following general observations can be made: (i) The temperature dependences of both the lock and key signals in the $^1$H n.m.r. spectra are interpretable in terms of equilibrations between two, and only two, anisometric complexes. At this stage, the most reasonable explanation of our results is that these are the $\alpha$- and $\beta$-complexes. This means that there is no evidence with this range of locks for other than rapid reorganisation of the noncovalent bonding pattern within each of the anisometric complexes on the $^1$H n.m.r. time scale at temperatures down to $-110^\circ$C. This realisation prompts us to use the analogy that the key is spinning in the lock! (ii) As indicated in Figure 17, dissociation of the complexes is the slow rate determining step in the complexation-decomplexation process. In those cases - that is $\alpha$-$D$-(65), $\beta$-$D$-(65), $\alpha$-$DD$-(68), and $\alpha$-$D$-(69) - where we have values for the free energies of complexation of Me$_3$CNH$^+$SCN$^-$ (6).HSCN in CDCl$_3$ comparisons with the $\Delta G^\ddagger_d$ values obtained in CD$_2$Cl$_2$ lead us to the conclusion that the free energies of activation ($\Delta G^\ddagger_a$) for association lie in the range of 3 - 6 kcal. mol.$^{-1}$ This implies
that the rate of association, although fast is short of being a diffusion controlled process as observed for 18-crown-6 (5) and Me$_3$CNH$_3^+$SCN$^-$ (6).

In the wake of these general observations we can return to the consideration of some more specific points. In contrast with the $\alpha$-galactoside locks $\alpha$-D-(65) and $\alpha$-DD-(66), the $\alpha$-glucoside locks $\alpha$-D-(63) and $\alpha$-DD-(64) bind all the keys examined stereoselectively (2:1, or better) to one of their heterotopic faces. Figure 13 records the now familiar sequence of experiments — namely, the $^1$H n.m.r. spectrum (Figure 13a) of the pure lock $\alpha$-DD-(64) and the temperature dependent $^1$H n.m.r. spectra (Figure 13b and c) of the 1:1 complex $\alpha$-DD-(64)-(S)-(49).HSCN formed between $\alpha$-DD-(64) and (S)-PhCHMeNH$_3^+$SCN$^-$(S)-(49).HSCN in CD$_2$Cl$_2$ solution. However, on this occasion there is strong evidence that one of the anisometric complexes is being formed with high stereoselectivity (>97 : <3) at -70°C. We believe that complexation occurs preferentially at the $\beta$-face because of the close similarities in the chemical shifts of the signals for H-1 in $\alpha$-DD-(64) (δ 4.79) and for the major peak (δ 4.83) arising from H-1 in the complex at -70°C. This observation suggests that O-1 is not involved in complexing in the major anisometric complex. However, the appearance of a minor peak (δ 5.08) at much lower field suggests that O-1 is involved in complexing in the minor anisometric complex. Inspection of CPK space-filling molecular models has led us to ascribe the high stereoselectivity of binding to the $\beta$-face to a dipole-induced dipole interaction between the 2-phenyl-1,3-dioxan ring in $\alpha$-DD-(64) and the phenyl group in (S)-PhCHMeNH$_3^+$SCN$^-$(S)-(49).HSCN. Support for this proposal comes from the observation that when we replace (S)-PhCHMeNH$_3^+$SCN$^-$(S)-(49).HSCN in the $\alpha$-DD-(64)-β-(S)-(49).HSCN complex with (R)-PhCHMeNH$_3^+$SCN$^-$(R)-(49).HSCN, the stereoselectivity of
binding to the β-face is reduced to 72:28 in accordance with the steric interaction in the α-DD-(54)-β-(R)-(49).HSCN complex of the methyl group in the cationic key with the 2,2-dimethyldioxolanyl group in the lock.

[Formulae α-DD-(54)-β-(S)-(49).HSCN and α-DD-(54)-β-(R)-(49).HSCN here]

We conclude that the major complex in all cases (see Table 3) involving the α-glucoside locks α-D-(63) and α-DD-(54) is the β-complex. For the most part, the same conclusion has been reached on the basis of a similar argument for the α-mannoside locks α-D-(67) and α-DD-(68), which also form 1:1 complexes at +30°C with selected SCN⁻ and ClO₄⁻ salts derived from Me₃CNH₂ (6), PhCH₂NH₂ (60), and (R)- and (S)-PhCHMeNH₂ (60) and (R)-(49) as indicated by the significant changes in the ¹H n.m.r. spectra of the locks. The signals for the H-1 protons are shifted downfield (0.23 - 0.28 p.p.m.) on 1:1 complex formation. Much smaller downfield shifts (0.03 - 0.07 p.p.m.) are observed for the OMe protons and significant upfield shifts (up to 0.11 p.p.m.) are experienced by the PhCH protons. These results indicate that the pyranosidic ring oxygens in α-D-(67) and α-DD-(68) participate along with the six crown oxygens in complex formation. The ¹H n.m.r. spectrum (Figure 14a) of the pure lock α-D-(67) and the temperature dependent ¹H n.m.r. spectra (Figure 14b and c) of the 1:1 complex α-D-(67)-(60).HSCN serve to illustrate the more general case. At -75°C the signals for the PhCH proton appear (Figure 14c) as a higher intensity singlet at high field and a lower intensity singlet at low field while the signal for the anomeric proton is seen to have separated into a higher intensity low field signal and a lower intensity high field signal.
These observations suggest that the major complex is associated with the β-face of α-D-(67). Support for this hypothesis comes from inspection of CPK space-filling molecular models which reveals that the phenyl ring in the α-D-(67)-β-(60).HSCN complex can enter into a stabilising dipole-

\[ \text{[Formula α-D-(67)-β-(60).HSCN here]} \]

induced dipole interaction with the 4,6-O-benzylidene ring. This introduces the PhCH proton into the shielding zone of the phenyl ring. Thus, we can account for the upfield shift of this proton at +30°C (see Figure 14b) as well as the emergence (see Figure 14c) at -75°C of the higher intensity singlet for the major β-complex at δ 5.54. So far in the α-series of locks we have considered the complexing ability of (i) anancomerically trans-fused 18-crown-6 locks in which the gauche crown oxygens at the ring junctions are diequatorial with respect to the pyranosidic rings [i.e., α-D-(63), α-DD-(64), α-D-(65), and α-DD-(66)] and (ii) anancomerically cis-fused 18-crown-6 locks in which the gauche crown oxygens at the ring junctions are axial-equatorial with respect to the pyranosidic rings [i.e., α-D-(67) and α-DD-(68)]. In order to complete this stereochemical investigation it was necessary to study the complexing ability of the α-D-altroside lock α-D-(69). This anancomerically trans-fused 18-crown-6 derivative has anti crown oxygens with, of course, a diaxial arrangement at the pyranosidic ring junction. The Δ_c^1 value (8.3 kcal mol⁻¹) for the α-D-(69)-HSCN complex in CD₂Cl₂ in conjunction with the low association constant for this complex in CDCl₃ indicate that stereochemical factors can play a crucial role in determining the thermodynamic and kinetic stabilities of organic cationic complexes of 18-crown-6 derivatives. In the α-series, the selectivity of binding to the heterotopic faces was found to be poor to non-existent for the
α-galactoside and α-altroside locks and good to excellent for the α-glucoside and α-mannoside locks. Since the axial O-1 is involved in primary binding of the NH$_3^+$ ionic centre we reasoned that selectivity in favour of the β-face should be increased by inverting the configuration at C-1 and hence reducing the oxygens involved in the α-complexes to the six crown oxygens. Once again there was a surprise waiting for us when this speculation was put to the test. As observed previously in the α-series, β-D-(63), β-DD-(64), β-D-(65) and β-DD-(66) form 1:1 complexes with selected SCN$^-$ and ClO$_4^-$ salts derived from Me$_3$CNH$_2$ (6), PhCH$_2$NH$_2$ (60), and (R)- and (S)-PhCHMeNH$_2$ (R)- and (S)-(L9) at +30°C in CD$_2$Cl$_2$. The usual substantial changes in the $^1$H n.m.r. spectra of these complexes relative to those of the pure locks was noted. The temperature dependent behaviour of the spectra of the β-D-(65)-(66)·HSCN complex serves to illustrate (see Figure 15) the general situation that exists for the β-galactoside locks. At +30°C (Figure 15b), the signals for the PhCH, H-1, and H-4 protons are shifted considerably downfield in relation to their original chemical shifts in the spectrum (Figure 15a) of the pure lock. This observation indicates that O-14 participates along with the six crown oxygens in complex formation. On cooling the CD$_2$Cl$_2$ solution down to -90°C, the signals for the PhCH and H-4 protons both separate (Figure 15c) into high (δ 5.63 and 4.56, respectively) and low (δ 5.76 and 4.75, respectively) intensity signals. The fact that the lower field signals are the lower intensity signals in both cases suggests that the minor complex is associated with the β-face of β-D-(65). Hence, against all apparent reason, the major complex appears to involve binding to the α-face of β-D-(65). This finding is general for all the 1:1 complexes studied (see Table 3) involving phenyl-containing substituted ammonium keys.
As far as the β-D-glucoside locks are concerned, the $^1H$ n.m.r. spectral behaviour of the $\beta-D-(6\beta)-(6\alpha).HClO_4$ complex with temperature serves to illustrate (see Figure 16) the general situation. Although the influence

[Insert Figure 16 here]

upon the chemical shift of the PhCH proton on complex formation is much less pronounced than in the β-galactoside locks, nonetheless this useful $^1H$ n.m.r. probe shows temperature dependence. This is presumably as a result of the dipole-induced dipole interaction present in the $\beta-D-(6\beta)-(6\alpha).HClO_4$ complex which undoubtedly brings the PhCH proton under the influence of the
diamagnetic ring current of the phenyl ring. At $-90^\circ C$, a triplet ($J = 10$ Hz with a peak area corresponding to ca. 0.8 of a proton emerges (Figure 16c) at high field (δ 2.62) and can be assigned to H-3 in the major α-complex on the basis of double irradiation studies. Since this upfield shift of H-3 is characteristic of nearly all the low temperature spectra of 1:1 complexes involving $\beta-D-(6\beta), \beta-D-(6\alpha), \beta-D-(6\delta)$, and $\beta-D-(6\sigma)$ and phenyl-containing substituted ammonium ions, we are led inexorably to propose the existence of a stabilising secondary anomeric effect in α-complexes such as $\beta-D-(6\beta)-(6\alpha).HClO_4$ and $\beta-D-(6\delta)-(6\alpha).HSCN$ which involves the dipole associated with the anomeric region of β-glycosides. Inspection of CPK space-filling molecular models shows that the acetal group associated with

[Formulae $\beta-D-(6\beta)-(6\alpha).HClO_4$ and $\beta-D-(6\delta)-(6\alpha).HSCN$ here]

the anomeric centre in the $\beta-D-(6\beta)-(6\alpha).HClO_4$ complex is more accessible sterically to the phenyl ring of the PhCH₂NH₃⁺ ion than is the acetal group
of the 1,3-dioxan ring in the $\beta$-$D$-$\text{f}(63)$-$\beta$-$\text{g}(60) . \text{HClO}_4$ complex. Naturally, we find the possibility that the anomeric effect, which destabilises $\beta$-glycosides intramolecularly may be a source of stability "intermolecularly within complexes of $\beta$-glycosides, an intriguing prospect. If this hypothesis is vindicated then serendipity will once again have played an important role in our science.

5. Why

Previously, I have drawn attention to the fact that all the glucoside, galactoside, and mannioside locks form relatively weak complexes with $\text{Me}_3\text{CNH}_3^+\text{SCN}^-$ (6).HSCN in CDCl$_3$. The time has come to pose the question, "why." Before I do this, let me introduce some model compounds on to the scene. They are four of the five possible diastereoisomers of dicyclohexano-18-crown-6. Catalytic hydrogenation of dibenzo-18-crown-6 (4), followed by column chromatography of the product on alumina, yields the cis-cisoid-cis (72) and cis-transoid-cis (73) isomers as crystalline compounds, Equation (5). The trans-cisoid-trans (74) and trans-transoid-trans (75) isomers have been synthesised (Scheme 3) stereospecifically from (±)-cyclohexane-trans-1,2-diol.

This approach was made possible because of the following properties of the diastereoisomeric meso- (76) and (±)- (77) 2,2'-methylenedioxy-dicyclohexanols: (i) Their ready separation by fractional crystallisation and (ii) the symmetry properties of their dioxymethylene protons which are reflected in their $^1\text{H}$ n.m.r. spectra.

The association constants and the corresponding free energies of complexation for the 1:1 complexes formed between $\text{Me}_3\text{CNH}_3^+\text{SCN}^-$ (6).HSCN
in CDC\textsubscript{3} and the isomers (72) to (74) of dicyclohexano-18-crown-6 and the chiral asymmetric locks \(\alpha-D-(63)\), \(\beta-D-(63)\), \(\alpha-D-(65)\), \(\beta-D-(65)\), and \(\alpha-D-(67)\) are given in Table 4. They are seen to be considerably less than the corresponding \(K_a\) and \(\Delta G\) values for 18-crown-6 (5) and \(\text{Me}_3\text{CNH}_3^+\text{SCN}^-\) in CDC\textsubscript{3}. A similar situation is found\textsuperscript{113} to exist (Table 5) for the 1:1 complexes formed between \(\text{Na}^+,\ \text{K}^+,\ \text{and Cs}^+\) chlorides in MeOH and the four isomers (72) to (75) of dicyclohexano-18-crown-6. In both Tables, I have expressed the extent of the destabilisation of the complexes relative to those formed by 18-crown-6 (5) in terms of \(\Delta\Delta G\) values. The following observations can be made: (i) Fusion to the 18-crown-6 constitution of either one, or two diametrically opposed 6-membered ring leads to weaker complexes. (ii) When the ring junctions are trans-fused as in \(\alpha-D-(63)\), \(\beta-D-(63)\), \(\alpha-D-(65)\), \(\beta-D-(65)\), (74), and (75), or cis-fused as part of an anancomeric system as in \(\alpha-D-(67)\), the strengths of complexes are generally speaking reduced to a much greater extent than they are when the ring junctions are cis-fused in conformationally "flexible" systems such as (72) and (73). It is believed\textsuperscript{120} that lower enthalpy changes rather than very large decreases in entropy on complexation of the cations by all of the locks discussed under heading (ii) are responsible for their lower free energies of complexation. The question then arises as to where these appreciable differences in enthalpy originate. We believe\textsuperscript{121} they are stereochemical in origin.

Electrostatic interactions – including hydrogen bonds – are expected to exhibit directional characteristics. Recent, \textit{ab initio} molecular orbital calculations on model systems by Kollman\textsuperscript{123} have shown that in attempting to discuss hydrogen bond directionality, the most important contribution appears to come from the electrostatic component. Moreover,
Table 4. The association constants ($K_a$) and free energies of complexation ($\Delta G$) for the formation of 1:1 complexes between $\text{Me}_3\text{CNH}_3^+\text{SCN}^-$ (6), HSCN and 18-crown-6 (5) and the derivatives (72) to (74) and $\alpha$-$\text{D}$-(63), $\beta$-$\text{D}$-(63), $\alpha$-$\text{D}$-(65), $\beta$-$\text{D}$-(65), and $\alpha$-$\text{D}$-(67) in CDC13

<table>
<thead>
<tr>
<th>Lock</th>
<th>$K_a (M^{-1})$</th>
<th>$\log K_a$</th>
<th>$\Delta G^a$ (kcal mol$^{-1}$)</th>
<th>$\Delta \Delta G^a$ (kcal mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-Crown-6 (5)</td>
<td>3,000,000$^b$</td>
<td>6.48</td>
<td>-8.80</td>
<td></td>
</tr>
<tr>
<td>cis-cisoid-cis-DCH-18-C-6 (72)</td>
<td>17,000$^{c,d}$</td>
<td>4.23</td>
<td>-5.75</td>
<td>3.05</td>
</tr>
<tr>
<td>cis-transoid-cis-DCH-18-C-6 (73)</td>
<td>900,000$^{c,d}$</td>
<td>5.95</td>
<td>-8.09</td>
<td>0.71</td>
</tr>
<tr>
<td>trans-cisoid-trans-DCH-18-C-6 (74)</td>
<td>7,100$^c$</td>
<td>3.85</td>
<td>-5.23</td>
<td>3.57</td>
</tr>
<tr>
<td>$\alpha$-$\text{D}$-Glu-18-C-6 $\alpha$-$\text{D}$-(63)</td>
<td>2,000$^c$</td>
<td>3.30</td>
<td>-4.49</td>
<td>4.31</td>
</tr>
<tr>
<td>$\beta$-$\text{D}$-Glu-18-C-6 $\beta$-$\text{D}$-(63)</td>
<td>1,300$^c$</td>
<td>3.11</td>
<td>-4.23</td>
<td>4.57</td>
</tr>
<tr>
<td>$\alpha$-$\text{D}$-Gal-18-C-6 $\alpha$-$\text{D}$-(65)</td>
<td>201,000$^c$</td>
<td>5.30</td>
<td>-7.21</td>
<td>1.59</td>
</tr>
<tr>
<td>$\beta$-$\text{D}$-Gal-18-C-6 $\beta$-$\text{D}$-(65)</td>
<td>5,800$^c$</td>
<td>3.76</td>
<td>-5.11</td>
<td>3.69</td>
</tr>
<tr>
<td>$\alpha$-$\text{D}$-Man-18-C-6 $\alpha$-$\text{D}$-(67)</td>
<td>39,000$^c$</td>
<td>4.59</td>
<td>-6.24</td>
<td>2.56</td>
</tr>
</tbody>
</table>

$^a$ The $\Delta \Delta G$ values correspond to the differences in the $\Delta G$ values between the particular lock and 18-crown-6 (5).

$^b$ Value from ref. 21;

$^c$ Values from ref. 118;

$^d$ For a mixture of these isomers, $K_a = 360,000$ is reported (ref. 21).
<table>
<thead>
<tr>
<th>Lock</th>
<th>( \log K_a )</th>
<th>( \Delta G^b )</th>
<th>( \Delta \Delta G^b )</th>
<th>( \log K_a )</th>
<th>( \Delta G^b )</th>
<th>( \Delta \Delta G^b )</th>
<th>( \log K_a )</th>
<th>( \Delta G^b )</th>
<th>( \Delta \Delta G^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-Crown-6 (5)</td>
<td>4.32&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-5.9</td>
<td>-</td>
<td>6.10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-8.3</td>
<td>-</td>
<td>4.70</td>
<td>-6.3</td>
<td>-</td>
</tr>
<tr>
<td>cis-cisoid-cis-DCH-18-C-6 (72)</td>
<td>4.08&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-5.5</td>
<td>0.4</td>
<td>6.01&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-8.2</td>
<td>0.1</td>
<td>4.61&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-6.2</td>
<td>0.1</td>
</tr>
<tr>
<td>cis-transoid-cis-DCH-18-C-6 (73)</td>
<td>3.68&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-5.0</td>
<td>0.9</td>
<td>5.38&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-7.3</td>
<td>1.0</td>
<td>3.49&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-4.7</td>
<td>1.6</td>
</tr>
<tr>
<td>trans-cisoid-trans-DCH-18-C-6 (74)</td>
<td>2.99&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-4.0</td>
<td>1.9</td>
<td>4.14&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-5.6</td>
<td>2.7</td>
<td>3.00&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-4.0</td>
<td>2.3</td>
</tr>
<tr>
<td>trans-transoid-trans-DCH-18-C-6 (75)</td>
<td>2.52&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-3.4</td>
<td>2.5</td>
<td>3.26&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-4.3</td>
<td>4.0</td>
<td>2.27&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-3.0</td>
<td>3.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Obtained for the equilibrium, \( M^+n\text{MeOH} + \text{Lock} \rightleftharpoons M\text{Lock}^+ + n\text{MeOH} \), at 20-25°C by potentiometry with ion selective electrodes; <sup>b</sup> In kcal mol\(^{-1}\). The \( \Delta \Delta G \) values correspond to the differences in the \( \Delta G \) values between the particular lock and 18-crown-6 (5); <sup>c</sup> Values from H.K. Frensdorff, J. Amer. Chem. Soc., 1971, 93, 600; <sup>d</sup> Values from ref. 118.
in the case of the approach of a water molecule to an ammonium ion, the interaction (76) in which the \( \text{NH}_2 \cdots \text{OH}_2 \) component has local \( C_{2v} \) symmetry is more stabilising than any of the other approaches where the water molecule becomes tilted so that the \( \text{NH}_2 \cdots \text{OH}_2 \) component assumes \( C_2 \) symmetry. The pole-dipole variety of electrostatic interactions met in the formal approach of a water molecule along the two-fold axis (77) and the three-fold axis (78) of an ammonium ion are much less stabilising than the hydrogen bonding approach (76). The minimum energy geometries corresponding to (local) \( C_{2v} \) symmetry is also preferred in (i) the approach (79) of a lithium cation to a water molecule,\(^{123}\) (ii) the hydrogen bonding approach (80) of a dimethyl ether molecule to an ammonium ion,\(^{21}\) and (iii) the two-fold pole-dipole approach (81) of a dimethyl ether molecule to an ammonium ion.

\[ \text{Formulae (76) - (78) here} \]

It is significant, however, that the interaction energy calculated for (81) is only about one-third that calculated for (80). This preference for the "bisector" approach coupled with the additional strength of a hydrogen bond over a simple electrostatic bond is thought\(^{121}\) to be responsible for the Me\(_3\)CNH\(_3\)\(^+\) (6) H\(^+\) ion choosing to hydrogen bond (cf. ref. 23) with "up" oxygens rather than with "down" oxygens in crown ethers, e.g. the crystal structure data\(^{29}\) for the salt formed between the 2-carboxy-1,3-xylyl-18-crown-5 (82) and Me\(_3\)C\(_2\)NH\(_2\) (6).\(^{126,127}\)

\[ \text{Formula (82) here} \]

Let us address ourselves to the question "why" again. In view of the directional characteristics of non-covalent bonds—and the dependence
of conformation upon configuration — relatively small differences in the
torsional angles associated with the bismethylenedioxy and substituted
bismethylenedioxy units in the 18-membered rings might account for the
observed changes (see Tables 4 and 5) in the ΔΔG values when 6-membered
ring systems are fused to the macroring as in (72) to (75) and in
α-Đ-(63), α-Đ-(63), α-Đ-(65), β-Đ-(65), and α-Đ-(67). In Figure 18, the
top view notation53 has been employed to represent (72) to (75), α-Đ-(63),
and 18-crown-6 (5). These representations serve to highlight the following
important stereochemical differences: (i) When it is involved in complex
formation, 18-crown-6 (5) adopts the diamond lattice "all-gauche-OCH2CH2O"
conformation with D3d symmetry53 and undergoes ring inversions37 that are
rapid relative to the rate of the decomplexation process.128 We shall
describe this lock as a g+g+g+g+ system. (ii) The di-cis isomers (72)
and (73) of dicyclohexano-18-crown-6 can both attain "ideal" complexing
conformations for their 18-membered rings. However, they are "flexible"
systems in which the macrorings are constrained119 to invert at rates
approximating to those of the decomplexation processes because of the need
for both 6-membered rings to invert as well. These locks will be described
as g+g+g+g+ systems. (iii) Although the 18-membered
rings in the trans-cisoid-trans isomer (74) of dicyclohexano-18-crown-6,
and in the carbohydrate derivatives α-Đ-(63), β-Đ-(63), α-Đ-(65), β-Đ-(65),
and α-Đ-(67), can attain "ideal" complexing conformations, they are "rigid"
systems and so cannot undergo macroring inversion. We shall describe these
locks as g+g+g+g+ systems. (iv) Not only can the 18-membered ring of
the trans-transoid-trans isomer (75) of dicyclohexano-18-crown-6 not undergo
inversion but it is also denied attaining the "ideal" complexing conformation.
Since this lock is a racemic modification we shall describe it as a
\[ \begin{array}{cccccccccccc}
\circ & \circ & \circ & \circ & \circ & \circ & \circ & \circ & \circ & \circ & \circ & \circ
\end{array} \] system. It is clear that a rough qualitative correlation (see Figure 19) exists between the magnitude of the \( \Delta \Delta G \) values in Tables 4 and 5 and the stereochemical classification developed above under headings (i) to (iv). The fact that the correlation exists for both metal and \( \text{Me}_3\text{CNH}_2^+ (6) \cdot \text{H}^+ \) cations suggests that it is the highly directional nature of electrostatic interactions which is the important feature in this stereochemical analysis. At this stage in our analysis, we can differentiate between (i) fine stereochemical differences involving conformational features only and (ii) gross stereochemical differences involving both configurational and conformational features. We propose that the fine stereochemical features emerge in the "ideal" complexing conformations because of small and different conformational perturbations to the 18-membered rings caused by 1,2-cis- and 1,2-trans-fusion of 6-membered rings. Although the torsional angles associated with bismethylenedioxy and substituted bismethylenedioxy units will vary according to the relative configurations at the ring junctions, a more precise description of the influence of fine stereochemical features upon \( \Delta \Delta G \) values is still not clear to us. By way of contrast, however, the influence of gross stereochemical features emerges very clearly. The denial to (75) of binding sites which act cooperatively provides an obvious explanation as to why it forms weaker complexes with metal cations (see Table 5) than does (74). Although we did not study the relative binding capacity of (74) and (75) towards \( \text{Me}_3\text{NH}_2^+ (6) \cdot \text{H}^+ \) ions in our earlier work, the availability of bis-\( \alpha \)-glycoside-18-crown-6 derivatives such as 2,3:2',3'-\( \alpha \)-DD-(83), 2,3:3',2'-\( \alpha \)-DD-(84), 2,3:2',3'-\( \alpha \)-DD-(85) and 2,3:3',2'-\( \alpha \)-DD-(86) with the trans-transoid-trans configuration provides.
an ideal opportunity to investigate gross stereochemical features.

It will be recalled that in metal cation templated syntheses a catalytic effect has been observed\textsuperscript{57} that relates rates of cyclisation with the complexing ability of crown ethers towards the cations used in their synthesis. In this context it is significant that only the trans-cisoid-trans isomer (74) of dicyclohexano-18-crown-6 was isolated after the attempted synthesis (see Scheme 4) of (74) and (75) by condensation of (\textsuperscript{\textpm}) trans-2,2'-(1,2-cyclohexyldiene)dioxyethanol (87) with its bistosylate (88) in benzene in the presence of Me\textsubscript{3}CO\textsuperscript{+}. The relative configurations of the products are established on formation of the first C-O bond in both of the intermediates in Scheme 4. The observed stereoselectivity is believed to ensue from the greater stabilisation through the templating action of the K\textsuperscript{+} ions on the transition state leading to (74) than on the transition state leading to (75). In the latter case, intermolecular reaction to give polymer is probably competing successfully with intramolecular cyclisation. If this explanation is correct, then the directional characteristics of noncovalent bonds can and will influence the diastereoisomeric ratios obtained during cation-templated syntheses of crown ethers. Faster and more efficient cyclisations will result when binding sites in the transition state act cooperatively in a stereochemical sense to lower the free energy of activation for the reaction. Thus, gross stereochemical features find kinetic as well as thermodynamic expression.

It is now evident that small conformational differences lead to large differences in (i) free energies of complexation by 18-crown-6 derivatives towards the same ion and (ii) free energies of activation for
cyclisation of open-chain precursors to 18-crown-6 derivatives templated by the same ion. Undoubtedly, the highly directional characteristics of noncovalent bonds is responsible for this particular phenomenon and we believe that a general principle is also established whereby it should be possible to build highly structured complexes by exercising appropriate constitutional and stereochemical control upon the lock in relation to the key.

During three decades now conformational analysis has been practised largely and traditionally at an intramolecular level. I predict that we are about to witness the development and growth of a relatively new and exciting area\textsuperscript{135} in stereochemistry, that of \textit{intermolecular conformational analysis} if you like!

6: Dreamland Revisited.

Our journey from carbohydrates to enzyme analogues has only just begun. The lessons that we have learnt while taking our first steps include the following: (i) Constitution, configuration, and conformation define the structures of noncovalently bonded species in much the same way as they define the structures of covalently bonded species. Noncovalent bonds are highly directional! (ii) By utilising secondary stabilising interactions, keys can locate the heterotopic faces of certain chiral asymmetric locks with high selectivity (> 1.4 kcal mol\textsuperscript{-1}). (iii) Reorganisation of the noncovalent bonding pattern within complexes is generally fast. The key spins in the lock! (iv) Some chiral symmetrical locks show modest enantiomeric differentiation (0.3 - 0.5 kcal mol\textsuperscript{-1}) towards racemic keys. (v) Complexes seek all opportunities (the counterion or additional binding sites) to become destructured. (vi) Carbohydrates are a convenient source of chiral locks.
Our principal objectives at the moment are to (i) construct highly structured complexes in which the locks will show high chiral recognition towards racemic keys, and (ii) construct highly structured complexes in which the locks will catalyse reactions that show high regioselectivity and stereoselectivity towards heterotopic and enantiotopic ligands and faces in appropriate keys. In short, our task is to build enzyme analogues.\textsuperscript{136,137} In principle, many chemical reactions are amenable to this kind of investigation—the challenges are both scientific and artistic in so far as our understanding of reaction mechanisms and stereochemistry is fast approaching the point where rapidly advancing synthetic skills can be put to the test in the design and preparation of man-made catalysts exhibiting the characteristics of enzymes. Some thoughts of Prelog's lend encouragement to those of us engaged in these challenges. He has said:\textsuperscript{138}

Chemistry takes a unique position among the natural sciences for it deals not only with material from natural sources but creates the major part of its objects by synthesis. In this respect,\ldots the potential of its creativity is terrifying.

Armed with a challenge and the potential to meet it we are entitled to go on dreaming in this case that one day we shall indeed be able to go "From Carbohydrates to Enzyme Analogues."

The account I have presented in this lecture was given life and substance through the supreme efforts of Howard F. Beckford, Geoffrey D. Beresford, Ian J. Burden, Andrew C. Coxon, W. David Curtis, Anthony J. Haslegrave, Dale A. Laidler, Janet C. Metcalfe, Roger B. Pettman, and John B. Wolstenholme. To them, I owe a lot including my thanks.
References and Notes


2. Plagiarised from the Address by Martin Luther King from the Washington Monument, August 1963; see, for example C.S. King, "My Life with Martin Luther King Jr.," Holt, Rinehart, and Winston, New York, 1969.


23. In the plane projection representation of the "all-gauche OCH₂CH₂O" conformation of the 18-membered ring in the complex (5)-(6).HSCN, the "up" oxygens are denoted by a dot and the "down" oxygens by a circle. Although previously (W.D. Curtis, D.A. Laidler, J.F. Stoddart, and G.H. Jones, *J. Chem. Soc.*, Perkin I, 1977, **1756**) the hydrogen bonds have been associated formally with the "down" oxygens in conformational representations, X-ray crystallographic evidence (D.J. Cram, personal communication, February 1978; I. Goldberg, *Acta Cryst.*, 1975, **B31**, 2592) on complexes of 18-crown-6 derivatives with Me₃CNH₃⁺SCN⁻ (6).HSCN indicates that "up" oxygens are always involved in hydrogen bonding in the solid state. On this basis alone, a choice between the two stereochemically distinguishable three-point binding models has been made in (5)-(6).HSCN. See also, the crystal structure (O. Nagano, A. Kobayashi, and Y. Sasaki, *Bull. Soc. Chem. Japan*, 1978, **51**, 790) of the ammonium bromide dihydrate complex of 18-crown-6.

24. This method has been employed previously to represent an "all-planar" conformation for the 18-membered ring in the cationic complex (5)-(7)⁺.H⁺.


32. The $K_a$ values quoted for (S)-(17) and (SS)-(18) have been corrected on the basis of a revised value for $Me_3CNH^+SCN^- \cdot (5)$. HSCN between CDCl$_3$ and D$_2$O. Since they were also measured on "scale C" they have been "corrected" (cf. ref. 21) by dividing the experimentally determined values by 2.


53. To our knowledge a top view or bird's eye perspective drawing was used (J.F. Stoddart and W.A. Szarek, Canad. J. Chem., 1968, 46, 3061) for the first time in 1968 to represent the conformation of di-β-D-ribo-furanose 1,5′:1′,5-dianhydride. Subsequently, this mode of representing the conformations of medium-sized and large-sized rings has been adopted (Acta Chem. Scand., 1973, 27, 1115) and popularised (Topics Stereochem., 1976, 9, 199) by Dale.


59. It has also been suggested⁴² that a decrease in the enthalpy of activation for the reaction contributes to lowering the free energy of activation through ion-pair separation leading to an increase in the nucleophilicity of the alkoxide ion. However, it is difficult to reconcile this suggestion with the intermediate ion-pair (31) in Equation 4.


61. It is intriguing to reflect on the fact that from a knowledge of only the molecular formula (C₆H₁₂O₆) of D-glucose, we could put an upper limit of six on the number of possible chiral centres. In fact, five of these are chiral centres in the cyclic forms (pyranose and furanose) of D-glucose! In general terms, the problem is to translate this numerical advantage of carbohydrates into steric and electronic expressions of chirality.

62. Unfortunately, it must be conceded that more often than not only one enantiomer enjoys attribute (vii).


I thank Dr. R.A. Wall (University of Edinburgh) for drawing my attention to this fact in a personal communication, May, 1977.


83. E. Fischer, Ber., 1894, 27, 2985.
85. Where enantiomeric differentiations towards \((\text{RS})-(\text{S}) \cdot \text{HPF}_6\) have been determined the \((\text{R}):\text{(S)}\) ratios are quoted inside the formulae of the chiral locks.
88. Key-to-lock ratios in excess of 1.0, indicating some 2:1 complex formation, are probably partly responsible for this observation.
89. In contrast, \(\text{DD}-(\text{S})\) does not show chiral recognition towards \((\text{RS})-(\text{S}) \cdot \text{HCIO}_4\).
93. The \(\text{D}-(\text{R})-(\text{S})\) isomer could be considered to be topologically similar to the achiral \((\text{RS})\text{-bisbinaphthyl-22-crown-6} \) \((\text{RS})-(\text{S})\).
97. A "blank" experiment on D-(58) uncomplexed did not reveal any temperature dependence of the \(^1\)H n.m.r. spectrum recorded in CD\(_2\)Cl\(_2\).


103. The locks α- and β-DD-(64), α- and β-DD-(66), and α-DD-(68) also comprise a 1,2:5,6-di-O-isopropylidene-α-D-mannitol D-(35) residue.

104. The asymmetric locks α-DD-(64) and α-DD-(68) were prepared in analogous fashion. The asymmetric locks α-D-(62), β-D-(63), α-D-(65), β-D-(65), α-D-(67), and α-D-(69) have been prepared by (i) condensing the methyl 4,6-O-benzylidene-D-glycosides with Ts(OCH\(_2\)CH\(_2\))\(_3\)OTs and (ii) condensing the derived "half-crown" diols, e.g. D-(71), with Ts(OCH\(_2\)CH\(_2\))\(_3\)OTs.

105. The C\(_2\) symmetry of the "half-crown" ditosylate ensures that only one 18-crown-6 derivative, i.e. α-DD-(66), can be formed in this condensation.


107. IUPAC have recommended (Pure App. Chem., 1976, 45, 13) that \(\sigma^+\) be replaced by (P) (for plus) and \(\sigma^-\) be replaced by (M) (for minus).

108. In relation to these chiral asymmetric locks, we shall refer to complexes involving the α- and β-faces as α- and β-complexes, respectively.


111. Although, in the case of the α-DD-(68)-(6).HSCN complex, an unambiguous assignment of major and minor complexes to α- and β-complexes is not possible, we tend to favour associating the major complex with the α-face for steric reasons.

As a result of changes in ion-pairing phenomena and displacement of solvent molecules from cations and crown ethers, approximately uniform increases in translational and rotational entropy are anticipated to operate on formation of both organic and metal cationic complexes. However, the most important entropic contribution to complexation is probably the decrease in the rotational freedom component about bonds that accompany adoption of the "all-gauche-OC(CH₂)₂O" conformation in the complex. Indeed, significant decreases in entropy have been observed (R.M. Izatt, J.D. Lamb, G.E. Maas, R.E. Asay, J.S. Bradshaw, and J.J. Christensen, J. Amer. Chem. Soc., 1977, 99, 2365; R.M. Izatt, J.D. Lamb, R.E. Asay, G.E. Maas, J.S. Bradshaw, J.J. Christensen, and S.S. Moore, ibid., p. 6134; R.M. Izatt, N.E. Iout, B.E. Rossiter, J.J. Christensen, and B.L. Haymore, Science, 1978, 199, 994) by calorimetry.
in MeOH at 25°C on complexation by 18-crown-6 (6) of Me$_3$CNH$_3$$^+$ (6).HI
($\log K_a = 2.90; \Delta G = -4.00$ kcal mol$^{-1}; \Delta H = -7.76$ kcal mol$^{-1}$;
$\Delta S = -3.8$ kcal mol$^{-1}$) and of Na$^+$Cl$^-$ (log $K = 4.36; \Delta G = -6.0$ kcal mol$^{-1}$;
$\Delta H = -8.4$ kcal mol$^{-1}; \Delta S = 2.2$ kcal mol$^{-1}$) and of K$^+$Cl$^-$ (log $K_a = 6.05$;
$\Delta G = -8.2$ kcal mol$^{-1}, \Delta H = -13.4$ kcal mol$^{-1}; \Delta S = -5.2$ kcal mol$^{-1}$).

121. J.F. Stoddart, Proceedings of an International Conference on "Enzymic


126. Hydrogen bonding to "up" oxygens is also characteristic of the crystal
structures of the ammonium bromide dihydrate complex of 18-crown-6 (5)
51, 790) and the hydronium chloride complex of monoaza-18-crown-6

127. Undoubtedly, the energy of complexation is maximised by the complex
(i) seeking the best hydrogen bonding geometry at the expense of (ii)
not being able to optimise its pole-dipole stabilisation because of
(iii) conformational constraints - mainly torsional - imposed by the
18-membered ring (cf. ref. 121).

128. F. de Jong, D.N. Reinhoudt, C.J. Smit, and R. Huis, Tet. Letters,
1976, 4783.

129. C. Romers, C. Altona, H.R. Buys, and E. Havinga, Topics Stereochem.,
1969, 4, 39.

130. Our earlier observation (A.C. Coxon and J.F. Stoddart, J.C.S. Perkin 1,
1977, 767) that 20-crown-6 derivatives and synthetically related
macrobicyclic polyethers with bridgehead carbon atoms form extremely
weak complexes with Na$^+$, K$^+$, Rb$^+$, and Cs$^+$ chlorides in MeOH can also
be explained by lack of cooperativity of binding sites.

625.
In giving these bis-α-D-glycoside-18-crown-6 derivatives formula descriptors, I have chosen to differentiate isomers as having 2,3:2',3' or 2,3:3',2' constitutions depending upon the nature of the two ring junctions with respect to the numbering of the pyranosidic rings proceeding in an anticlockwise fashion around the macroring.

Since this lecture was delivered, we have completed a preliminary investigation (D.A. Laidler, J.F. Stoddart, and J.B. Wolstenholme, Tet. Letters, submitted) of these bis-α-glycoside-18-crown-6 derivatives. The constitutionally isomeric glucosides 2,3:2',3'-α-D-D-(83) and 2,3:3',2'-α-D-D-(84) and galactosides 2,3:2',3'-α-D-D-(85) and 2,3:3',2'-α-D-D-(86) have all been prepared and their constitutions have been assigned on the basis of dynamic $^1$H n.m.r. spectroscopy on suitable complexes. The $K_a$ values for complexing of 2,3:2',3'-α-D-D-(83), 2,3:3',2'-α-D-D-(84), 2,3:2',3'-α-D-D-(85), and 2,3:3',2'-α-D-D-(86) by Me$_3$CNH$_3^+$SCN$^-$ (6).HSCN in CDCl$_3$ were estimated to be <50, <50, 4650, and 5750 M$^{-1}$, respectively. Comparison of these values with those of 2000 and 201,000 M$^{-1}$ for complexing of α-D-(63) and α-D-(65) respectively with (6).HSCN in CDCl$_3$ illustrate the importance of gross stereochemical features in stabilising complexes.

Examples which illustrate the importance of intermolecular stereochemistry abound in the field of natural polymers, e.g. nucleic acids, proteins, and polysaccharides, but are relatively few and far between in the small molecule domain. There are, however, instances where rather severe geometrical restraints govern the approach of reactant centres in reactions e.g. $S_N^2$ displacements (L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, Helv. Chim. Acta., 1970, 53, 2059) and carbonyl additions (H.B. Burgi, J.D. Dunitz, J.M. Lehn, and G. Wipff, Tetrahedron, 1974, 30, 1563), and hence demonstrate the general significance and importance of intermolecular conformational analysis.

The term enzyme analogue has connotations that the term enzyme model lacks (see ref. 121). Whereas an enzyme model seeks to mimic a known enzyme in its catalytic function, an enzyme analogue is merely a practical expression of the lessons learnt from Nature.

Captions to Figures

Figure 1 View of the cationic complex (5) - (7).H⁺ formed between 18-crown-6 (5) and the MeNH₃⁺ cation (7).H⁺ from the front (I) and from the back (II)

Figure 2 Some examples of the gauche effect. Gauche and anti conformations about C-C bonds are indicated by g and a, respectively. The helicities of the gauche conformations are denoted by plus and minus signs (see later for a definition in absolute terms)

Figure 3 Selected carbohydrate precursors with C₂ symmetry. "Chiral ethyleneglycol" and "chiral diethyleneglycol" units are represented by thickened bonds

Figure 4 Selected asymmetric carbohydrate precursors. "Chiral ethyleneglycol" and "chiral diethyleneglycol" units are represented by thickened bonds

Figure 5 The broad-band decoupled ¹³C n.m.r. spectrum of the equilibrated complexes DD-(48)-(R)-(49).HPF₆ and DD-(48)-(S).HPF₆ in CDCl₃; L indicates lock and K indicates key signals. Key signals are assigned from low field to high as (a) substituted carbons in the (R) and (S) phenyl rings, meta- and para-carbons in the phenyl rings, and ortho-carbons in the (S) and (R) phenyl rings, (b) (R) and (S) methine carbons, and (c) (R) and (S) methyl carbons

Figure 6 The degenerate equilibration process of keys between the homotopic faces of C₂ symmetrical locks

Figure 7 The ¹H n.m.r. spectrum recorded at 220 MHz of lock D-(58) in CD₂Cl₂. The temperature dependent ¹H n.m.r. spectra - (b) and (c) - of the 1:1 complex formed with (60).HClO₄

Figure 8 The designation of absolute conformation in gauche 1,2-disubstituted ethanes

Figure 9 Change in chemical shifts of the indicated protons with change in key : lock ratio. Oxygen atoms believed to be involved in hydrogen bonding and/or electrostatic stabilisation with the ammonium hydrogens of the Me₃CNH⁺ ions in the anisometric complexes α-D-(65)-β-(6).HSCN and α-D-(65)-α-(6).HSCN are indicated by means of arrows (→)
Figure 10  Change in chemical shifts of the indicated protons with change in key : lock ratio. Oxygen atoms believed to be involved in hydrogen bonding and/or electrostatic stabilisation with the ammonium hydrogens of the Me_3CNH_3^+ ions in the anisometric complexes α-DD-(64)-β-(6).HSCN and α-DD-(64)-α-(6).HSCN are indicated by means of arrows (→).

Figure 11  The equilibration process of keys between the heterotopic faces of chiral asymmetric locks.

Figure 12  The ^1^H n.m.r. spectrum (220 MHz) of lock α-D-(65) in CD_2Cl_2. The temperature dependent ^1^H n.m.r. spectra - (b) and (c) - of the 1:1 complex formed with (60).HSCN.

Figure 13  The ^1^H n.m.r. spectrum (220 MHz) of lock α-DD-(64) in CD_2Cl_2. The temperature dependent ^1^H n.m.r. spectra - (b) and (c) - of the 1:1 complex formed with (S)-(49).HSCN.

Figure 14  The ^1^H n.m.r. spectrum (220 MHz) of lock α-D-(67) in CD_2Cl_2. The temperature dependent ^1^H n.m.r. spectra - (b) and (c) - of the 1:1 complex formed with (60).HSCN.

Figure 15  The ^1^H n.m.r. spectrum (220 MHz) of lock β-D-(65) in CD_2Cl_2. The temperature dependent ^1^H n.m.r. spectra - (b) and (c) - of the 1:1 complex formed with (60).HSCN.

Figure 16  The ^1^H n.m.r. spectrum (220 MHz) of lock β-D-(63) in CD_2Cl_2. The temperature dependent ^1^H n.m.r. spectra - (b) and (c) - of the 1:1 complex formed with (60).HClO_4.

Figure 17  The free energy profile diagram for equilibration of anisometric complexes.

Figure 18  The designation of conformational behaviour in complexes of (5), (72) to (75), and α-D-(63).

Figure 19  The qualitative correlation between complex strength and stereochemistry.
Figure 1

(1)

(II)
Figure 2

(24a) 43-61%  (24b) 39-57%

(25a) 51%  (25b) 49%

(26a)  (26b)

(27)
Figure 3

\[ L-(33) \]

\[ L-(34) \]

\[ D-(35) \]

\[ L-(36) \]

\[ D-(37) \]

\[ L-(38) \]
Figure 4

\[ \text{PhCH}_2\text{OH}_2\text{C} - \text{H} \]

\( \alpha-D-\text{(39)} \)

\[ \text{Ph} \]

\[ \text{O} \]

\[ \text{HO} \]

\( \beta-D-\text{(39)} \)

\[ \alpha-D-\text{(40)} \]

\( R^1 = \text{OMe}; R^2 = \text{H} \)

\( \beta-D-\text{(40)} \)

\( R^1 = \text{H}; R^2 = \text{OMe} \)

\( \alpha-D-\text{(41)} \)

\( R^1 = \text{OMe}; R^2 = \text{H} \)

\( \beta-D-\text{(41)} \)

\( R^1 = \text{H}; R^2 = \text{OMe} \)

\[ \alpha-D-\text{(42)} \]

\( R^1 = \text{OMe}; R^2 = \text{H} \)

\( \beta-D-\text{(42)} \)

\( R^1 = \text{H}; R^2 = \text{OMe} \)

\[ \alpha-D-\text{(43)} \]

\[ \text{Ph} \]

\[ \text{O} \]

\[ \text{HO} \]

\( \beta-D-\text{(43)} \)

\( \text{Ph} \)

\[ \text{O} \]

\[ \text{HO} \]

\[ \text{OMe} \]

\[ \alpha-D-\text{(44)} \]

\[ \text{Ph} \]

\[ \text{O} \]

\[ \text{HO} \]

\[ \text{CO}_2\text{CH}_2\text{Ph} \]
Figure 5

$K = (RS)-\text{PhCHMeNH}_3^+\text{PF}_6^-$
Homotopic hydrogens

Homotopic faces

Figure 6

(Slow) CD $\rightarrow$ $C_2$ (Fast)

Identical complexes
Figure 7

(a) Lock = D-(58)

(b) +30°

(c) -80°

Key: \( \text{PhCH}_2\text{NH}_3^+\text{ClO}_4^- \)

Absent in the complex with D-(58)-d₄
Figure 8
Figure 9

Chemical shift

CD$_2$Cl$_2$

Molar ratio 0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0

Key: Lock

β-Complex

α-Complex

α-δ-(65)-β-(6).HSCN

α-δ-(65)-α-(6).HSCN
Figure 10

Molar ratio  Key:Lock

β-Complex

α-Complex

α-\(\text{DD}-(6\_4)\-\beta-(6)\).HSCN

α-\(\text{DD}-(6\_4)\-\alpha-(6)\).HSCN
Figure 11

Heterotopic faces

(Slow) CD $\rightarrow$ C$_2$ (Fast)

Anisometric complexes
Figure 12

(a) 

Lock ≡ α-D- (65) 

(b) 

Fast

α-Complex

β-Complex

(c) 

Slow

α-Complex

β-Complex

Key = PhCH₂NH⁺SCN⁻
Figure 13

(a) Complex

Key = (S)-PhCHMeNH\textsubscript{3}+SCN\textsuperscript{-}

(b) Complex

(c) Complex?

R = \begin{align*}
& \text{Me} \\
& \text{H} \\
& \text{Me}
\end{align*}

δ  8  7  6  5  4  3  2  1
Key: $\text{PhCH}_2\text{NH}_3^+\text{SCN}^-$

(a) $\text{Lock} \equiv \alpha-D-(67)$

(b) $\alpha$-Complex: Fast

(c) $\alpha$-Complex: Slow
MeO
0 H
Key PhCH2NH3+SCN-

(a) Lock = β-D-(65) PhCH
-30°

α-Complex

β-Complex

Fast

(b) +30°

α-Complex

β-Complex

Slow

-90°

δ

7 6 5 4 3 2
Figure 16

(a) Lock = β-D-(63)

+30°

α-Complex

Fast

β-Complex

(b)

α-Complex

Slow

β-Complex

(c) H-3 (α-Complex)

Key: PhCH<sub>2</sub>NH<sub>3</sub><sup>+</sup>CIO<sub>4</sub><sup>-</sup>
Figure 17.

Complexation-decomplexation

G

Major Complex

Lock + Key

Minor Complex

$\Delta G_d$
Figure 19

Increasing complex strength

\[ g^+ g^- g^+ g^- g^+ g^- g^+ > g^- g^+ g^- g^+ g^- g^+ \]

Gross stereochemical differences

Fine stereochemical differences
Scheme 1

D- (35)

MeCOMe

ZnCl₂

H₂O

Me

H

H

H

H

(47) OTs

NaH / DMSO

(R): (S) = 52:38

(< 98; > -2.71)

DD- (48)

Homotopic faces
Reagents: 
i, CH₂=CHCH₂Br, KOH, toluene; ii, O₃, MeOH; iii, NaBH₄, MeOH; iv, TsCl, pyridine; 
v, NaH, MeSOMe

SCHEME 2
**Scheme 3**

Diastereotopic

\[ \text{Reagents: i, } \text{Ac}_2\text{O, pyridine; ii, } \text{MeSOMe, NBS; iii, } \text{NaOMe, MeOH; iv, } \text{TsOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OTs, NaH, MeSOMe, MeOCH}_2\text{CH}_2\text{OMe; v, } \text{H}^+, \text{H}_2\text{O} \]
Scheme 4

Polymer?
Equations

(28) \[ \text{BF}_3(\text{gas})/\text{HF} \rightarrow \text{Di oxan} \]

(29) \[ \text{0} \]

(30) \[ \text{0} \]

(31) \[ \text{0} \]

(32) \[ \text{0} \]
Equation

(4) \[ \text{H}_2 (70 \text{ atm}) \]
\[ \text{Ru-Al}_2\text{O}_3 \]
\[ \text{C}_4\text{H}_9\text{OH} \]
\[ 100^\circ\text{C} \]

\[ \rightarrow \]

(72) + (73)

(5)
Formulae

(1)

(2)

(3)

(4)

(5)
Formulae

(5)-(6)·HSCN

(8) (130; -2.88)
(9) (1650; -4.38)
(10) (3300; -4.78)
(11) (55000; -6.50)
(12) (615000; -7.88)
(13) (209000; -7.24)
(14) (4180000; -9.01)
(15) (5800000; -9.20)
(16) (1830000; -8.52)
Formulae

(< 1540; > -4.33)

(S)-(17)

(< 150; > -2.96)

(SS)-(18)

DD-(48)-(R)-(49).HPF₆

DD-(48)-(S)-(49).HPF₆
Formulae

(5)-(54)

D-(56)

D-(58)

DD-(57)
87.

Formulae

\[ \text{Formulae} \]

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]

\[ \text{(62)} \]

\[
\begin{align*}
\text{H} & \quad \text{R} \\
\text{H} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\end{align*}
\]

\[ \text{Me} \quad \text{O} \\
\text{Me} \quad \text{O} \\
\text{Me} \quad \text{O} \\
\]

\[ \text{D}-(58)-\text{PhCHR}^1\text{NH}_3^+ \]

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[ \text{(6140; -3.81)} \]

\[ \alpha - \text{D}-(63) \]

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{O} \\
\end{align*}
\]

\[ \text{(640; -3.81)} \]

\[ \alpha - \text{DD}-(64) \]

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{O} \\
\end{align*}
\]

\[ \text{(6200; -4.49)} \]

\[ \alpha - \text{D}-(63) \]

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{O} \\
\text{MeO} & \quad \text{O} \\
\end{align*}
\]

\[ \text{(1300; -4.23)} \]

\[ \beta - \text{D}-(63) \]
Formulae

\[ \text{(1000; -4.08)} \]
\[ \beta - \text{DD- (64)} \]

\[ \text{(201000; -7.21)} \]
\[ \alpha - \text{D- (65)} \]

\[ \text{(5800; -5.11)} \]
\[ \beta - \text{D- (65)} \]

\[ \text{(7800; -5.29)} \]
\[ \alpha - \text{DD- (66)} \]
Formulae

\( \alpha-D\,(-64) - \beta-(S) - (49).HSCN \)

\( \alpha-D\,(-64) - \beta-(R) - (49).HSCN \)

\( \alpha-D\,(-67) - \beta-(69).HSCN \)
$\beta - D-(63)-\alpha-(60).HClO_4$

$\beta - D-(63)-\alpha-(60).HClO_4$

$\beta - D-(65)-\alpha-(60).HSCN$
2,3:2',3'-α-δδ-(82)

2,3:2',3'-αα-δδ-(83)

2,3:3',2'-αα-δδ-(84)
Formulae

2,3:2',3'-$\alpha$-$\text{DD}$-(85)

2,3:3',2'-$\alpha$-$\text{DD}$-(86)
CHAPTER 1

SYNTHESIS OF CROWN ETHERS AND ANALOGS

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I. HISTORICAL BACKGROUND

It is interesting to reflect upon the fact that, although linear compounds containing sequential ether linkages\(^1-^3\) have occupied an important position in chemistry for many years, it is only during the last decade or so that macrocyclic polyethers and their analogs have made their major impact upon the scientific community. Alas, the fascinating complexing properties of macrocyclic polyethers was not anticipated from the comparatively mundane chemical behavior of cyclic ethers containing up to seven atoms in their rings.\(^4,^5\) Indeed, as often happens in science, serendipity played\(^6\) an important role in the discovery of the so-called crown ethers and the appreciation of their somewhat intriguing characteristics. Although the early literature was not devoid of reports on the synthesis of macrocyclic polyethers, their value and potential was not realised by those involved. It is easy to feel with hind-sight that it should have been; it is difficult to envisage how it could have been!

The first macrocyclic polyethers were reported by Lüttringhaus\(^7\) in 1937 as part of an investigation of medium- and large-sized rings. For example, he obtained the 20-membered ring compound (1) in low yield after reaction of the monosubstituted resorcinol derivative (2) with potassium carbonate in pentan-1-ol. Later, the tetrafuranyl derivative (3) was isolated\(^8\) after acid-catalysed condensation of furan with acetone and the cyclic tetramers (4) and (5) of ethylene\(^9\) and propylene\(^10\) oxides, respectively, were reported.

[Formulae (1)-(5) here]
Several acyclic polyethers, as well as compound (5), were found to dissolve small quantities of potassium metal and sodium-potassium alloy giving unstable blue solutions of solvated electrons and solvated cations. However, it was not until 1967 that Pedersen reported on the formation of stable complexes between macrocyclic polyethers and salts of alkali and alkaline earth metals. During an attempted preparation of the diphenol (6) from the dichloride (7) and the monoprotected catechol derivative (8), the presence of 10% of catechol (9) as an impurity led to the isolation (see Scheme 1) of the unexpected by-product which was identified as the macrocyclic polyether (10). Given the trivial name dibenzo-18-crown-6 by Pedersen, it was found to be insoluble in methanol by itself but became readily soluble on the addition of sodium salts. Furthermore, it was obtained in 45% yield when pure catechol (9) was employed in its synthesis. This amazingly high yield for a macrocycle obtained on condensation of four molecules raises questions of fundamental importance which will be discussed in Section II. Following upon his initial discoveries, Pedersen prepared more than sixty compounds in order to ascertain the optimum ring size and the preferred constitutional arrangement of oxygen atoms in the macrocycles for them to complex with a wide variety of cationic species. Those compounds which contain between five and ten oxygen atoms, each separated from its nearest neighbor by two carbon bridges, were found to be the most effective complexing agents. These observations have led to the synthesis of many crown
ethers and analogs. This Chapter is devoted to a review of the general principles and fundamental concepts governing this kind of macrocyclic ring formation as well as to a summary of the methodology and reaction types employed in the synthesis of these macrocycles.

II. FACTORS INFLUENCING YIELDS IN SYNTHESIS

A. The Template Effect

The isolation of dibenzo-18-crown-6 (10) in 45% yield under the conditions given in Scheme 1 prompted Pedersen to observe that "the ring-closing step, either by a second molecule of catechol or a second molecule of bis(2-chloroethyl)ether, was facilitated by the sodium ion, which, by ion-dipole interaction 'wrapped' the three-molecule intermediates around itself in a three-quarter circle and disposed them to ring closure". The isolation of numerous other macrocyclic polyethers in synthetically attractive yields by Williamson ether syntheses, as well as by other approaches, has led to the recognition of a template effect involving the cationic species present in the reaction mixture. Such a phenomenon is, of course, not unique to the synthesis of macrocyclic polyethers. Transition metal template-controlled reactions have been used extensively in the synthesis of (a) porphyrins from suitably-substituted pyrroles, (b) corrin ring systems leading to vitamin B₁₂, and more recently (c) large ring lactones. Evidence for the operation of a template effect in crown ether syntheses comes from a consideration of the published procedures for the preparation of 18-crown-6. Somewhat surprisingly, base promoted cyclisation of hexaethyleneglycol monochloride (11) in MeOCH₂CH₂OMe using either Me₃COK or NaH as base led (equation 1) to very low (ca.2% in each case) isolated yields of (12) in the
first synthesis to be reported by Pedersen. Consequently,

\[ \text{Equation (1) here} \]

improved procedures were sought; these are summarised in Table 1. Depending upon the nature of the solvent, 18-crown-6 (12) can be obtained \(^{17,18}\) in 33-93% yields from reaction of triethyleneglycol (13) with its ditosylate (14) in the presence of Me\(_3\)CO\(_2\)K. By employing less expensive reagents, e.g. triethyleneglycol (13), its dichloride

\[ \text{Table 1 here} \]

(15), and KOH in aqueous tetrahydrofuran \(^{19}\) or tetraethyleneglycol (16), diethyleneglycol dichloride (7), and KOH in dry tetrahydrofuran \(^{20}\) yields of 30-60% can be attained. In all these synthetic approaches to 18-crown-6 (12), a template effect involving the K\(^+\) ion is an attractive proposition as, at least, a partial explanation for the high yields. In the reactions of (13) with (16) employing methods ii-iv in Table 1, a mechanism for cyclisation (see equation 2) involving formation of an intermediate acyclic complex is envisaged. \(^{18}\) The observations that (a) the macrocycle (12) can be isolated \(^{17,18}\) as its potassium tosylate complex (12)\(_{\text{KOTs}}\), (b) doubling the concentration of reactants in method iii resulted \(^{18}\) only in a decrease in the yield from 84 to 75%, and (c) when tetra-\(\eta\)-butylammonium hydroxide was used as the base the yield of (12) was reduced drastically, \(^{18}\) all support the operation of a template effect in the formation of
TABLE 1. 18-Crown-6 (12) syntheses.

<table>
<thead>
<tr>
<th>Method</th>
<th>X</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>OTs</td>
<td>Me₃COK</td>
<td>Me₃COH/C₆H₆</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>ii</td>
<td>OTs</td>
<td>Me₃COK</td>
<td>THF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30-60</td>
<td>18</td>
</tr>
<tr>
<td>iii</td>
<td>OTs</td>
<td>Me₃COK</td>
<td>DMSO&lt;sup&gt;b&lt;/sup&gt;</td>
<td>84</td>
<td>18</td>
</tr>
<tr>
<td>iv</td>
<td>OTs</td>
<td>Me₃COK</td>
<td>DME&lt;sup&gt;c&lt;/sup&gt;</td>
<td>93</td>
<td>18</td>
</tr>
<tr>
<td>v</td>
<td>Cl</td>
<td>KOH</td>
<td>THF&lt;sup&gt;a&lt;/sup&gt;/H₂O</td>
<td>40-60</td>
<td>19</td>
</tr>
<tr>
<td>vi</td>
<td>Cl</td>
<td>KOH</td>
<td>THF&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

<sup>a</sup> Tetrahydrofuran  <sup>b</sup> Dimethyl sulfoxide  <sup>c</sup> 1,2-Dimethoxyethane
18-crown-6. The effect has generality. In reactions of ethylene-glycol (17) and diethyleneglycol (18) with (15) (equations 3 and 4, respectively), Li$^+$ and Na$^+$ ions have been shown$^{21}$ to template the formation of 12-crown-4 (4) and 15-crown-5 (19), respectively.

[Equations (3) and (4) here]

Interestingly, however, a better yield of (19) is reported$^{20}$ for condensation (equation 5) of the diol (13) with the dichloride (7) under the same conditions as those employed in equation (4). It would be unwise to read too much into situations of this kind;

[Equation (5) here]

isolated yields often reflect the skills of the experimentalist!

The optimisation of template effects is probably achieved when the diameter of the cation corresponds most closely to the cavity diameter of the macrocycle being formed. Thus, for simple crown-ethers, Li$^+$, Na$^+$, and K$^+$ ions are clearly suited to templating the syntheses of 12-crown-4 (4), 15-crown-5 (19), and 18-crown-6 (12), respectively. However, the effect is quite general. For example, in the acid-catalysed cyclic co-oligomerization of furan and acetone to form the 16-crown-4 derivative (3), the addition of LiClO$_4$ to the reaction mixture increased$^{22}$ the yield of (3) from 18-20 to 40-45%. Also, large variations in yields (see Table 2) of the cyclic monomers (25)-(31) were observed$^{23}$ in condensations between the dibromide (20) and the dipotassium salts of HO(CH$_2$CH$_2$O)$_n$H ($n = 2-8$). Significantly, the maximum yield (67%) occurred with the meta-xylyl-18-crown-5 derivative (27) and was virtually insensitive to variations in the rate of addition of the dibromide (20) to the glycolate derived from
TABLE 2. The dependence of isolated yields on ring size

![Chemical Reaction](image)

<table>
<thead>
<tr>
<th></th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(18) 2</td>
<td>2&lt;sup&gt;a&lt;/sup&gt; (25)</td>
</tr>
<tr>
<td>(13) 3</td>
<td>16&lt;sup&gt;b&lt;/sup&gt; (26)</td>
</tr>
<tr>
<td>(16) 4</td>
<td>67      (27)</td>
</tr>
<tr>
<td>(21) 5</td>
<td>49      (28)</td>
</tr>
<tr>
<td>(22) 6</td>
<td>18      (29)</td>
</tr>
<tr>
<td>(23) 7</td>
<td>21      (30)</td>
</tr>
<tr>
<td>(24) 8</td>
<td>21      (31)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The cyclic dimer was isolated in 30% yield.

<sup>b</sup> The cyclic dimer was isolated in 9% yield.
from tetraethyleneglycol (16). This latter observation suggests that during the second stage of the reaction, intramolecular displacement of bromide ion to give (27) is very much faster than the competing intermolecular reaction. A related investigation\textsuperscript{24} on the cyclization of 1,2-bis(bromomethyl)benzene (32) with polyethyleneglycolates revealed that the yields of cyclic monomers were not only dependent upon the chain length of the glycol but also on the nature of the cation present in the reaction mixture. For the 14-crown-4 (33), 17-crown-5 (34), and 20-crown-6 (35) derivatives, the optimum yields were obtained when Li\textsuperscript{+}, Na\textsuperscript{+}, and K\textsuperscript{+} ions, respectively, were present with the appropriate polyethyleneglycolate. If a template effect operates in these reactions, then the comparative yields of crown ethers will reflect the relative stabilities of the cationic transition states leading to them. Perhaps, it is not surprising that, in competitive experiments, comparative yields of crown ethers reflect\textsuperscript{24} their complexing ability towards the cation in question!

Kinetic evidence\textsuperscript{25} for a template effect has also been presented recently. The influence of added Group IA and IIA metal ions upon the rate of formation of benzo-18-crown-6 (36) from the crown's precursor (37) in aqueous solution at +50\textdegree was investigated with Et\textsubscript{4}N\textsuperscript{+} ions as the reference. The initial concentration (ca. 2 \times 10^{-4} M) of (37) was made sufficiently dilute to make any contribution from second order dimerization negligible. When the kinetics were followed spectrophotometrically by monitoring the disappearance of phenoxide ions,
first order behavior was observed in all cases. Although Li$^+$ ions had a negligible effect upon the cyclization rate, significant rate enhancements were observed when Na$^+$ and K$^+$ ions were present at concentrations between ca. 0.1 and 1.0 M. Most strikingly, there were dramatic increases in cyclization rates when Ba$^{2+}$ and Sr$^{2+}$ ions were present in low concentrations (<0.1 M) indicating the remarkable templating properties of these Group IIA metal ions. Thus, it would appear that rates of cyclization reflect a close correspondence between the catalytic effect and the relative complexing ability of crown ethers towards the cations used in their synthesis.

Organic cations can also act as templates for crown ether syntheses. The bases, Me$_3$COK, HN=C(NH$_2$)$_2$, and HN=C(NMe$_2$)$_2$ have all been examined$^{26,27}$ under similar reaction conditions for their comparative abilities to template the synthesis of benzo-27-crown-9 (38) from catechol (9) and octaethylene glycol ditosylate (39). Yields of (38) of 59, 23, and 2%, respectively, indicate that K$^+$ ion > H$_2$N=C(NH$_2$)$_2$ ion > H$_2$N=C(NMe$_2$)$_2$ ion in bringing together the reacting centers of the acyclic intermediate during the final cyclization step. In particular, the 10-fold difference in yields between the condensations employing HN=C(NH$_2$)$_2$ and HN=C(NMe$_2$)$_2$ as bases suggests that in the former case an intermediate acyclic complex (40) involving six hydrogen bonds might stabilise the transition state leading to the complex (38).H$_2$N=C(NH$_2$)$_2$OTs of benzo-27-crown-9 as shown in equation (6). The abilities of Me$_3$COK, HN=C(NH$_2$)$_2$, HN=C(NMe$_2$)$_2$,
and (MeCH₂CH₂CH₂)₄N⁺OH⁻ to produce benzo-9-crown-3 (41), dibenzo-18-
crown-6 (10), and tribenzo-27-crown-9 (42) from catechol and diethylene-
glycol ditosylate (43) were also compared.27 The results recorded in
Table 3 show that the large nontemplating H₂N=C(NMe₂)₂⁺ and

\[
\text{(MeCH₂CH₂CH₂)₄N⁺ ions favor the formation of (41) while K⁺ ion > H₂N=C(NH₂)₂⁺ ion > (MeCH₂CH₂CH₂)₄N⁺ ion > H₂N=C(NMe₂)₂⁺ ion in}
\]

assembling four molecules to produce (10) and six molecules to produce
(42). The ability of the H₂N=C(NH₂)₂⁺ ion to favor the formation of
(10) and (42) suggests that it acts as a template during the final
unimolecular reactions which produce dibenzo-18-crown-6 (10) and
tribenzo-27-crown-9 (42) although it does so less effectively than
K⁺ ion.

B. The Gauche Effect

There is overwhelming physical and chemical evidence²⁸-³¹ that
the C–C bond in -OCH₂CH₂O- units prefers to adopt the gauche confor-
mation. Infrared spectroscopy indicates³² that, although the simplest
model compound, 1,2-dimethoxyethane, comprises a range of conformational
isomers including both gauche (44a) and anti (44b) conformations in
the liquid phase at +25⁰, it adopts only the gauche conformation in
the crystal at -195⁰. (The descriptors g and a are employed here
beside formulae to denote gauche and anti torsional angles, respectively.
In addition, gauche torsional angles are described as g⁺ or g⁻
according as to whether they exhibit positive or negative helicities.)
In the crystal, polyoxyethylene adopts³³ only gauche conformations
TABLE 3. Effect of base on yields of crown ethers when catechol (9) was reacted with diethyleneglycol ditosylate (43) in tetrahydrofuran-Me₃COH under reflux.²⁷

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Base</th>
<th>(41) n = 1</th>
<th>(10) n = 2</th>
<th>(42) n = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₃COK</td>
<td>5</td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td>HN=C(NH₂)₂</td>
<td>4</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>HN=C(NMe₂)₂</td>
<td>11</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>(MeCH₂CH₂CH₂)₄N⁺OH⁻</td>
<td>15</td>
<td>23</td>
<td>5.5</td>
</tr>
</tbody>
</table>
about the C-C bonds with the expected anti preferences for the C-O bonds. A helical conformation (45) results. Comparisons between empirical and calculated physical properties indicate that this is also the preferred conformation in solution.

[Formulae (44a), (44b), and (45) here]

The gauche effect would appear to play a significant role in crown ether syntheses in appropriate situations. For example, even though it is not the most stable product thermodynamically, 12-crown-4 (4) is the major product formed from the cyclo-oligomerization of ethylene oxide (46) using BF$_3$ as catalyst and HF as co-catalyst. Crown ethers up to the undecamer (33-crown-11) have been separated and identified by gas-liquid chromatography. The product distribution recorded in Table 4 is not influenced markedly by changes in temperature or reactant concentrations. These observations suggest a mechanism for cyclo-oligomerization compatible with a helical shape for the growing oligo-oxyethylene chain (47), which brings the reactive centers, as shown in equation (7), into a good relative disposition for cyclization after addition of the fourth ethylene oxide residue.

[Table 4 here]

[Equation (7) here]

Template effects can operate in conjunction with the gauche effect. Thus, the presence of certain suspended metal salts during BF$_3$-catalysed cyclo-oligomerization of (46) leads to the exclusive production of 12-crown-4 (4), 15-crown-5 (19), and 18-crown-6 (12).
TABLE 4. Product distribution from the acid-catalysed oligomerisation of ethylene oxide (46).

\[
\begin{array}{cccccccccccc}
\text{n} & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11 & >11 \\
\text{Percentage yield} & 40 & 1 & 15 & 5 & 4 & 3 & 2 & 2 & 1 & 1 & 25 \\
\end{array}
\]
The product distribution depends (see Table 5) upon the nature of the cation. The experimental procedure, which now forms the basis of a successful commercial route to crown ethers, involves the addition of (46) to a cold suspension of the insoluble metal salt in dioxane containing the catalyst (e.g. BF₃, PF₅, or SbF₅). As the salt dissolves, the metal ion-crown complexes either precipitate or afford a separate liquid phase. The complexes may be separated without prior neutralisation leaving the mother liquors for use in further reactions. The crown ethers are most simply liberated from their complexes by pyrolysis under reduced pressure. The salt which remains behind may be reused without purification. The crown ethers are obtained pure (a) by fractional distillation, or alternatively (b) by fractional crystallisation of their complexes prior to pyrolysis. The results in Table 5 show that, for the Group IA and IIA metal ions at least, the relative yield of a particular crown ether is highest when its cavity diameter corresponds most closely to the ionic diameter of the metal ion present during its synthesis. The cation seems to mediate the reaction by promoting appropriate folding of the growing polymer chain prior to cyclization (i.e. the gauche and template effects are operating in unison) as well as by protecting the crown ethers which are formed from subsequent degradation. The positive charge on the metal in the complex prevents the formation of the oxonium salt which would initiate degradation.

So far, we have seen that the gauche and template effects can operate together to increase the rate of cyclization by raising the probabilities that molecules are in favorable conformations and
TABLE 5. The product distribution of crown ethers resulting from polymerization of ethylene oxide (46) by BF₃ as catalyst in 1,4-dioxane in the presence of suspended anhydrous salts.³⁶

<table>
<thead>
<tr>
<th>Salt</th>
<th>Ionic diameter of cation (Å)</th>
<th>12-Crown-4 (4) 1.2-1.4</th>
<th>15-Crown-5 (19) 1.7-2.2</th>
<th>18-Crown-6 (12) 2.6-3.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiBF₄</td>
<td>1.36</td>
<td>30</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>NaBF₄</td>
<td>1.94</td>
<td>25</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>KBF₄</td>
<td>2.66</td>
<td>0</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>KPF₆</td>
<td>2.66</td>
<td>20</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>KSBF₆</td>
<td>2.66</td>
<td>40</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>RbBF₄</td>
<td>2.94</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>CsBF₄</td>
<td>3.34</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Ca(BF₄)₂</td>
<td>1.98</td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Sr(BF₄)₂</td>
<td>2.24</td>
<td>10</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Ba(BF₄)₂</td>
<td>2.68</td>
<td>10</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>AgBF₄</td>
<td>2.52</td>
<td>35</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Hg(BF₄)₂</td>
<td>2.20</td>
<td>20</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>Ni(BF₄)₂</td>
<td>1.38</td>
<td>20</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Cu(BF₄)₂</td>
<td>1.44</td>
<td>5</td>
<td>90</td>
<td>5</td>
</tr>
<tr>
<td>Zn(BF₄)₂</td>
<td>1.48</td>
<td>5</td>
<td>90</td>
<td>5</td>
</tr>
</tbody>
</table>

- Estimated from Corey-Pauling-Koltun molecular models.
dispositions relative to each other to react. However, the implications of stereochemical control appear to go deeper than the gauche effect alone in the templated reactions of oligo-oxyethylene fragments to give crown ethers. The complete stereochemistry of the acyclic precursor can become important. In order to examine this claim, consider what is known about the structures of complexes of 18-crown-6 (12). There is evidence that they adopt the "all-gauche-OCH₂CH₂O" conformation (12a) with D₃d symmetry in solution as well as in the crystalline state. Moreover, the association constants

\[ K_a \] and the corresponding free energies of association (ΔG) for the 1:1 complexes formed between Na⁺Cl⁻ and K⁺Cl⁻ in MeOH and 18-crown-6 (12) are considerably greater (see Table 6) than the corresponding K_a and ΔG values for the isomeric dicyclohexano-18-crown-6 derivatives (48)-(51). Figure 1 shows that the cis-cisoid-cis (48a) and

\[ \text{cis-transoid-cis (49a)} \] isomers (a) can attain an "ideal" complexing conformation and (b) are "flexible" to the extent that the 18-membered ring can undergo inversion (\( g^+q^-q^+g^-g^+ \)). The trans-cisoid-trans (50a) and trans-transoid-trans (51a) isomers are "rigid" to the extent that the 18-membered ring cannot undergo inversion and, whilst (50) can attain an "ideal" \( g^+q^-q^+g^-g^+ \) conformation (50a), (51) is unable to adopt this "ideal" complexing conformation. In view of the fact that it is a racemic modification, it has a \( g^+q^-q^+g^-/g^-q^+g^-g^+ \) conformation (51a). It is clear from the results in Table 6 and the stereochemical features highlighted in
TABLE 6. The log $K_a$ (based on $K_a$ in M$^{-1}$) and $\Delta G$ values for the formation of 1:1 complexes with Na$^+\text{Cl}^-$ and K$^+\text{Cl}^-$ in MeOH.

<table>
<thead>
<tr>
<th>Crown ether</th>
<th>Na$^+$</th>
<th>K$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\log K_a^{b,c}$</td>
<td>$\Delta G^c$</td>
</tr>
<tr>
<td>18-Crown-6 (12)</td>
<td>4.3$^{d,e}$</td>
<td>-5.9$^e$</td>
</tr>
<tr>
<td>cis-cisoid-cis-DCH-18-C-6$^a$(48)</td>
<td>4.08$^d$</td>
<td>-5.5</td>
</tr>
<tr>
<td>cis-transoid-cis-DCH-18-C-6$^a$(49)</td>
<td>3.68$^d$</td>
<td>-5.0</td>
</tr>
<tr>
<td>trans-cisoid-trans-DCH-18-C-6$^a$(50)</td>
<td>2.99$^g$</td>
<td>-4.0</td>
</tr>
<tr>
<td>trans-transoid-trans-DCH-18-C-6$^a$(51)</td>
<td>2.52$^g$</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

$^a$ DCH-18-C-6 $\equiv$ Dicyclohexano-18-crown-6

$^b$ Obtained for the equilibrium, M$^+$MeOH + Crown $\rightleftharpoons$ M Crown$^+$ + MeOH, at 20$\pm$25$^\circ$ by potentiometry with ion selective electrodes.

$^c$ In kcal/mol. The $\Delta \Delta G$ values correspond to the differences in the $\Delta G$ values between the particular crown ether and 18-crown-6 (12).

$^d$ Values from ref. 42.

$^e$ Values for $\log K_a$, $\Delta G$, $\Delta H$ (kcal/mol), and $T\Delta S$ (kcal/mol) determined calorimetrically (ref. 44) at 25$^\circ$ are 4.36, -6.0, -8.4, and -2.4, respectively.

$^f$ Values for $\log K_a$, $\Delta G$, $\Delta H$, and $T\Delta S$ determined calorimetrically (ref. 44) at 25$^\circ$ are 6.05, -8.2, -13.4, and -5.2, respectively.

$^g$ Values from ref. 43.
Figure 1 that a qualitative correlation exists\textsuperscript{31,45,46} between the $\Delta\Delta G$ values and the conformation of the 18-crown-6 ring in (48)-(51). Fine stereochemical differences involving only conformational features and gross stereochemical differences involving both configurational and conformational features can be differentiated. An example of gross stereochemical control in synthesis appears to be operative during the attempted preparation\textsuperscript{47} as shown in Scheme 2 of (50).

![Scheme 2 here]

and (51) by condensation of (\(\pm\))-trans-2,2'-(1,2-cyclohexyldiene)-dioxoethanol (52) with its ditosylate (53) in benzene in the presence of Me\textsubscript{3}COK. Only (50) was isolated with a comment\textsuperscript{47} about "the marked tendency for pairing of (\(\pm\)) with (\text{-}) in the cyclization to give the meso-form". On formation of the first C-O bond in both of the intermediates in Scheme 2, the relative configurations of the products are established. The observed stereoselectivity ensues from the greater stabilisation through efficient templating action of K\textsuperscript{+} ions on the transition state leading to (50) than on the transition state leading to (51). In the second instance, intermolecular reaction to give polymer is probably competing successfully with the intramolecular reaction. Thus, it would even seem to be possible to control diastereoisomeric ratios during cation-templated syntheses of chiral crown ethers. This possibility, which relates to the principle\textsuperscript{31,45} that noncovalent bonds are highly directional in character, is capable of considerable exploitation.

C. Other Effects

The synthesis of medium- and large-sized ring compounds is usually a highly inefficient process. As we have seen in Sections IIA
and IIB, success in crown ether syntheses depends strongly upon pre-organized reactants being brought together under some external influence and then the acyclic precursor having the "correct" stereochemical orientation in the final cyclization step. The operation of template and/or gauche effects helps to overcome unfavorable entropic factors which mitigate against the formation of highly ordered species. Rigid groups (e.g. benzo groups) can also increase the rate of cyclization by reducing the number of conformational possibilities for the reactants and providing favorable stereochemistries for both inter- and intra-molecular reactions. Historically, reactions to form macrocyclic compounds have often been performed under high dilution conditions. This meant that all reactions including cyclizations had to be fast in order to maintain very low concentrations of reactants and so suppress the formation of acyclic oligomers with respect to cyclic products. Although it is seldom possible to employ fast reactions to prepare crown ethers because C-O bond formation is relatively slow, it often proves worthwhile to use high dilution conditions in the syntheses of aza- and thia-crown ethers. The case of forming C-N and C-S bonds relative to forming C-O bonds makes the use of high dilution technology attractive from the point of view of obtaining higher yields for these derivatives than could be obtained by conventional means.

In this Section on factors influencing yields in synthesis we have tried to highlight those areas which have particular relevance to crown ether syntheses. It is obvious that other factors such as (a) the nature of the leaving group in displacement reactions, (b) the solvent in which the reaction is conducted, (c) the temperature of the
reaction mixture etc. will all have a bearing on the outcome of a particular synthetic step. Also, particular reaction conditions often pertain to the more specialised approaches to crown ether synthesis. These will be discussed as and when necessary in Section IV on synthesis exemplified.

III. DESIGN AND STRATEGY

The well-known receptor properties of crown ethers and their analogs (see Chapters 2-4) provide one of the main incentives for their synthesis. Indeed, the design of receptor molecules for appropriate substrates is becoming more of a science than an art every day. During the embryonic phase of development of this science, the use of space-filling molecular models has become an indispensable adjunct and activity in the design stage and has generated a lot of new synthetic strategies and goals in different laboratories around the world. Nonetheless, it should be pointed out that, as far as molecular models are concerned, the framework variety have an important role to play in highlighting subtle stereochemical features such as those discussed in Section IIB. However, there is little doubt that design and strategy is going to rely more and more in future upon model building with the aid of high speed electronic computers.

The design of synthetic receptor molecules which complex with (a) metal and other inorganic (e.g. $\text{H}^+$, $\text{NH}_4^+$, and $\text{H}_3\text{O}^+$ ions) cations and (b) inorganic anions (e.g. $\text{Cl}^-$, $\text{Br}^-$, and $\text{N}_3^-$) has been extensively reviewed by Lehn. Recommended strategies to be adopted in synthesis have also been outlined in considerable detail. In
several reviews,\textsuperscript{52-55} Cram has discussed the design of achiral and chiral crown ethers which complex with organic cations (e.g. \(\text{RNH}_3^+\), \(\text{RN}_2^+\), and \(\text{H}_2\text{N}==\text{C(NH}_2\text{)}_2^+\) ions). He has appealed to axial chirality in the shape of resolved binaphthyl units in the elaboration of chiral crown ethers as synthetic analogs to Nature's enzymes and other receptor molecules. The attractions of utilizing natural products—and particularly carbohydrates—as sources of inexpensive chirality is one that the present authors\textsuperscript{31,45,56} have championed.

IV. SYNTHESIS EXEMPLIFIED

In this Section, we shall deal with synthetic methods for preparing achiral crown compounds, chiral crown compounds, and macro-bi-, -tri-, and -poly-cyclic ligands. We shall also include a brief mention of "acyclic crown compounds". Our treatment overall will be far from exhaustive! Portuititously, a number of lengthy reviews\textsuperscript{57-60} have appeared which are highly comprehensive in their coverage of the literature.

A. Monocyclic Multidentate Ligands

Equations (8)-(11) illustrate the most common approaches (cf. ref. 48) employed in the preparation of monocyclic multidentate ligands. Experimentally, the approaches illustrated in equations (8)

[Equations (8)-(11) here]

and (9) represent the most facile "one-pot" methods. Depending upon the nature of \(X-X\) and \(Y-Y\), two-molecule (equation 8) and four molecule condensations may compete. The approach indicated in equation (10) suffers from the disadvantage that the intermediate \(X-Z-Y\) may undergo intramolecular cyclization as well as intermolecular cyclization. The
stepwise approach outlined in equation (11) is a versatile one and usually affords good yields of macrocyclic ligands. Despite the low yields in general, the approaches depicted in equations (8) and (9) are preferable for the synthesis of "simple" monocyclic multidentate ligands. The approaches depicted in equations (10) and (11) are important in preparing macrocyclic ligands incorporating a variety of different structural features.

1. All oxygen systems

The general method for preparing macrocyclic polyethers is the Williamson ether synthesis\textsuperscript{61} which involves the displacement of halide ions from a dihaloalkane by the dianion derived from a diol. Common adaptations of this reaction utilise sulfonate esters — usually toluene-\textsubscript{p}-sulfonates — as leaving groups. Equations (8)-(11) illustrate (where \( - \) = a carbon chain, \( X \) = a leaving group, \( Y \) = OH, \( Z \) = a heteroatom and \( P \) = a base-stable protecting group) the general approaches employed in the assembly of macrocyclic compounds. The base employed is typically NaH, NaOH, KOH, or Me\textsubscript{3}COK. The solvent is typically Me(CH\textsubscript{2})\textsubscript{3}OH, Me\textsubscript{3}COH, MeOCH\textsubscript{2}CH\textsubscript{2}OMe, Me\textsubscript{2}SO, or tetrahydrofuran. Reactions are usually conducted at room temperature or just above. The synthesis of 12-crown-4 \( (4) \), 15-crown-5 \( (19) \) and 18-crown-6 \( (12) \) have been discussed in considerable detail already in Section IIA. 21-Crown-7 \( (54) \) was obtained\textsuperscript{17} in 26\% yield when triethyleneglycol \( (13) \) was reacted with the ditosylate of tetraethyleneglycol \( (16) \) and Me\textsubscript{3}COK in benzene. Using similar conditions, 24-crown-8 \( (55) \) was isolated\textsuperscript{17} in 15\% yield from condensation of tetraethyleneglycol \( (16) \) with its ditosylate.

[Formulae \( (54) \) and \( (55) \) here]
and triethyleneglycol ditosylate (14) in the presence of Me₃COK gave¹⁸ (54) in 18% yield. Substituents can, of course, be introduced into the polyether ring with little difficulty. For example, the long-chain alkyl-substituted 18-crown-6 derivatives (56)-(58) can be obtained in four steps from the corresponding alkenes as depicted in equation (12). This reaction sequence illustrates one method of preparing substituted "half-crown" diols for use in crown ether syntheses. Double bonds can also be introduced into polyether rings. The stilbenediol dianion can be generated by reaction of benzoin with NaOH in water under phase-transfer conditions. Subsequent reaction of the dianion with difunctional alkylating reagents gives cyclic derivatives in which the double bonds have (Z) configurations. The 18-crown-6 derivative (59) has been prepared (equation 13) in 19.5% yield by reaction of benzoin (60), NaOH, and diethyleneglycol ditosylate (43) in a C₆H₆-H₂O two phase system using (MeCH₂CH₂CH₂)₄N⁺Br⁻ as a phase-transfer catalyst. The accessibility of the unsaturated 18-crown-6 derivative (59) and the possibility of chemical modification of the prochiral C=C double bonds could prove valuable in the synthesis of substituted 18-crown-6 derivatives.

Although alkylation to give macrocyclic polyethers provide the most important synthetic routes to the compounds, other approaches are available. As we have seen already in Section IIB, the acid-catalysed cyclo-oligomerization of ethylene oxide (46) is important.⁵₅,⁶₆
from a commercial angle. One report of a photochemically generated, Li⁺ ion locked 12-crown-4 derivative is intriguing. Irradiation of the bisanthracene (61) in benzene in the presence of Li⁺ClO₄⁻ yields the complex (62), LiClO₄ which is thermally stable but dissociates easily on addition of MeCN (equation 14). Finally, a method of synthesising macrocyclic polyethers by acid-catalysed insertion of an olefin into cyclic acetals in a one step process lacks wide appeal because of (a) the mixtures of compounds which can result, and (b) the presence of three carbon units—which is generally detrimental to good complexing ability—in the products.

2. All nitrogen systems

A wide variety of cyclic polyamines have been synthesised and listings of those prepared up to mid-1975 have been produced. Several reviews have been published describing their synthesis and the distinctive coordination chemistry and biological significance of their complexes. Since cyclic polyamines are only distantly related to crown ethers, a detailed discussion is outside the scope of this review. A few examples will be cited, however. The tetra-aza-12-crown-4 derivative (63) can be isolated (see equation 15) in 96% yield from the reaction between N-benzylaziridine (64) and toluene-p-sulfonic acid in refluxing aqueous ethanol. It appears to be a unique reaction for (64) as aziridine itself and other N-substituted derivatives give only high molecular weight polymers. Chiral
1-benzyl-2-(R)-ethylaziridine (65) ring opens in the presence of BF₃-Et₂O at room temperature to give (66). As a result of ring opening exclusively at the primary center only one constitutional isomer is produced (equation 15) in which the configurations at the chiral centers are preserved. A more general method of preparing aza-analogs of crown ethers has appeared. The compounds (67)-(70) were synthesized by condensation of α,ω-ditosylates with the pre-formed sodium salts of appropriate α,ω-bis-sulfonamides in HCONMe₂ as shown in equation (16).

The free amines can be obtained by acid-catalysed hydrolysis of the cyclic sulfonamides, followed by treatment of the salts with base. It does not appear that Na⁺ ions act as templates since their replacement with Me₄N⁺ ions did not lead to a significant decrease in the yield of the cyclic tetramer. Macrocyclic polyamines can be obtained as shown in equation (17) by reduction of bislactam precursors which are readily available from the condensations of α,ω-diamines with diesters. For example, reaction of (71) with diethyl malonate (72) in ethanol under reflux gave (73) (30%) the cyclic bislactam which afforded the tetra-aza-14-crown-4 derivative (74) on diborane reduction.

3. All sulfur systems

The synthesis of polythiaethers is of interest in many areas of chemistry and has been the subject of an extensive review. The first perthia crown compounds were described over 40 years ago, some 30 years before the preparation of the oxygen analogs by Pedersen. The synthesis
of trithia-9-crown-3 \((75)\) as shown in equation (18) from \(\text{BrCH}_2\text{CH}_2\text{Br} \ (76)\) and alcoholic \(\text{KSH} \) saturated with \(\text{H}_2\text{S} \) was described\(^7_3\) in 1920. The isolation of hexathia-18-crown-6 \((77)\) in very low yield (<2%) from the reaction (see equation 19) between the dimercaptan \((78)\) and \(\text{BrCH}_2\text{CH}_2\text{Br} \ (76)\) in the presence of \(\text{KSH} \) was reported\(^7_4\) in 1934. More recently, \((77)\), as well as tetrathia-12-crown-4 \((79)\) and pentathia-15-crown-5 \((80)\) were prepared\(^7_5\) by reaction of the appropriate \(\alpha,\omega\)-dimercaptans with \(\alpha,\omega\)-dihalopolythyiaethers in yields of 25-35, ca. 6, and 11%, respectively. Yields can be improved\(^7_6\) by resorting to the use of high dilution techniques.

4. Oxygen and nitrogen systems

The variety and number of mixed heteroatom macrocycles that have been synthesized to date is immense. Fortunately, lists of mixed heteroatom macrocycles reported in the literature up to mid-1977 have been compiled.\(^5_7,5_9\) These reviews also serve as excellent reference sources for their syntheses and properties. Macrocyclic aza-polyethers have been prepared in good yields under high dilution conditions by condensation of \(\alpha,\omega\)-diamines with \(\alpha,\omega\)-diacid dichlorides followed by hydride or diborane reduction of the key macrocyclic bislactam intermediates. The method has been exploited \textit{par excellence} by Lehn\(^4_8,5_0,5_1\) in the synthesis of macrobicyclic systems with nitrogen bridgeheads (see Section IVG). An efficient flow synthesis of macrocyclic bislactams has also been developed.\(^7_7\) However, a convenient synthesis of the aza-polyethers \((81)-(84)\) by cyclization of the readily
available dimethyl esters of the \(\alpha,\omega\)-dicarboxylic acids (85) and (86) with the commercially available polyethylenepolyamines (87)-(89) in refluxing ethanol followed by reduction of the resulting cyclic amides (90)-(93) has been reported\(^{78}\) which requires neither high dilution techniques nor protection of the secondary amine functions in the starting polyethylenepolyamines. Although the yields recorded in equation (20) are lower than those obtained using high dilution techniques, the method is much more convenient experimentally. Other researchers have prepared macrocyclic aza-polyethers by alkylation. For example, reaction between \(N\)-benzyldiethanolamine (94) and tetraethyleneglycol ditosylate (95), followed by hydrogenolysis of the resulting \(N\)-benzylazacrown (96) gives\(^{79}\) monoaza-18-crown-6 (97) as shown in equation (21). The diaza-12-crown-4 (98) and 18-crown-6 (99) derivatives have been prepared\(^{70}\) in 80% yields by reaction of the (100) and (101) dianions derived from the appropriate \(\alpha,\omega\)-bis-sulfonamides with diethyleneglycol ditosylate (43) and triethyleneglycol ditosylate (14), respectively, in HCONMe\(_2\). The corresponding free amines (102) and (103) were obtained (see equation 22) by acid-catalysed hydrolysis of the cyclic bis-sulfonamides followed by treatment of the salts with base. The diaza-18-crown-6 (103) was obtained\(^{80}\) (see equation 23) in much lower yield by (a) reacting triethyleneglycol ditosylate (14) with the dianion derived from the
\( \alpha, \omega \)-bis-trifluoroacetamide (104) followed by alkaline hydrolysis of the trifluoroacetyl groups and (b) reacting the \( \alpha, \omega \)-dichloride (15) with excess of \( \text{NH}_3 \).

\[ \text{Equation (23) here} \]

5. Oxygen and sulfur systems

Since the early reports\(^{73,74} \) of macrocyclic compounds containing oxygen and sulfur atoms, a large number of simple thia-polyethers have been synthesized.\(^ {76,81-84} \) Those reported in the literature up to mid-1975 have been the subject of two extensive reviews.\(^ {59,72} \) The most convenient method of synthesizing thia-crown ethers involves reaction of an appropriate \( \alpha, \omega \)-oligoethyleneglycol dichloride with either an \( \alpha, \omega \)-dimercaptan or sodium sulfide. These methods are illustrated by the preparations\(^ {83} \) of (a) 1,4,7-trithia-15-crown-5 (105) from the \( \alpha, \omega \)-dichloride (15) and the dithiol (106) (see equation 24), (b) 1,4,10-trithia-15-crown-5 (107) from the \( \alpha, \omega \)-dichloride (108) and ethanodithiol (109) (see equation 25), and (c) thia-18-crown-6 (110) from the \( \alpha, \omega \)-dichloride (111) and sodium sulfide (see equation 26).

\[ \text{Equations (24)-(26) here} \]

6. Nitrogen and sulfur systems

Approaches involving both (a) alkylation and (b) acylation, followed by amide reduction, have been employed to obtain this series of crown compounds. The diazatetrathia-18-crown-6 derivative (112) has been isolated\(^ {85} \) from the reaction shown in equation (27)
between the dibromide (113) and ethanedithiol (109) in ethanol under high dilution conditions. More recently, however, an acylation-reduction sequence has afforded better overall yields of (112)\textsuperscript{86} and related crown compounds.\textsuperscript{78,87}

[Equation (27) here]

7. Oxygen, nitrogen, and sulfur systems

Systems such as (114)-(116) have been synthesized using (a) the alkylation approach\textsuperscript{85} and (b) the acylation-reduction sequence.\textsuperscript{86,87}

[Formulae (114)-(116) here]

B. Crown Compounds Incorporating Aromatic Residues

1. Systems fused to benzene rings

Subsequent to his report of the accidental synthesis of dibenzo-18-crown-6 (10) in 1967, Pedersen\textsuperscript{11,12} described the preparation of numerous other crown ethers, e.g (117) and (118), incorporating ortho-disubstituted benzene rings with both symmetrical and asymmetrical deployments around the polyether ring and with up to four aromatic rings fused to the macrocycle. More recently, the synthesis of hexabenzo-

[Formulae (117) and (118) here]

18-crown-6 (119) has been described.\textsuperscript{88} A series of Ullmann-type condensations and de-\textsuperscript{O}-methyllations starting from 2,2'-oxydiphenol and \textsuperscript{O}-bromoanisole afforded the diphenol (120) which was condensed with \textsuperscript{O}-dibromobenzene (121) to give (119) (see equation 28). Alas, it does not complex with Group IA and IIA metal ions! Benzo-crown

[Equation (28) here]
ethers incorporating 4-methyl\textsuperscript{89} and 4-t-butyl\textsuperscript{12} substituents have been reported. 4-Vinyl-benzo-18-crown-6 (122) and -15-crown-5 (123) have been obtained\textsuperscript{90} by cyclization of 3,4-dihydroxybenzaldehyde with the appropriate \( \alpha, \omega \)-dichloropolyethyleneglycol followed by reaction of the formyl group with a methyl Grignard reagent and dehydration of the resulting alcohol. The vinyl benzo-crown ethers

[Formulae (122) and (123) here]

serve as important intermediates in the synthesis of polymer supported crown ethers. A series of 4,4'-disubstituted dibenzo-crown ethers have been prepared\textsuperscript{91} from the constitutionally isomeric 4,4'-diamino-dibenzo-18-crown-6 derivatives by condensation with aldehydes and isothiocyanates. A diamino-dibenzo crown ether was obtained by nitration of dibenzo-18-crown-6 (10) followed by reduction of the aromatic nitro groups to amino groups. Other interesting benzo-crown ethers in which the aromatic ring carries functionality have been prepared. The 15-crown-5 derivatives (124) and (125) of adrenaline and apomorphine, respectively, were obtained\textsuperscript{92} in one step from their physiologically active precursors. The bis-15-crown-5 derivative (126) incorporating a fully de-0-methylated papaverine residue has been reported.\textsuperscript{93} Nitrogen atoms have been incorporated

[Formulae (124)-(126) here]

into the polyether rings of benzo- and dibenzo-crown ethers by employing (a) \( \alpha \)-aminophenol\textsuperscript{94,95} (b) \( \alpha \)-amino-aniline,\textsuperscript{94,95} and (c) \( \alpha \)-nitrophenol\textsuperscript{95} as readily available precursors. The syntheses\textsuperscript{24} and detailed mass spectral analyses\textsuperscript{96} of numerous crown ethers, e.g.
(127), containing one or two ortho-xylyl residues have been reported. The derivatives were obtained by reaction of o-xylylene dibromide with polyethyleneglycols in the presence of Me₃COK or NaH as base. Ortho-xylyl-dithia-crown ethers, e.g. (128), are also known.⁹⁷,⁹⁸

[Formulae (127) and (128) here]

We have already discussed the synthesis of meta-xylyl crown ethers, i.e. (25)-(31), in Section II.A. In addition to these investigations by Reinhoudt and his collaborators,²³ Cram and his associates⁹⁹ have prepared numerous meta-xylyl-18-crown-6 derivatives with substituents at C(2) and C(5). Recently, phenolic crown ethers, such as (129) have been obtained¹⁰⁰ in greater than 90% yield by de-O-methylation of the corresponding methyl ethers upon exposure to anhydrous LiI in dry C₅H₅N at 100⁰C for 10 h. followed by acidification. The success of these de-etherifications has been attributed to intramolecular crown ether catalysis as neither anisole

[Formula (129) here]

nor 2,6-dimethylanisole furnish the corresponding phenol when subjected to similar treatment. Meta-xylyl-diaza-15-crown-5 derivatives have been synthesised¹⁰¹ by reaction of m-xylylene dibromide with dianions generated from α,ω-bisurethanes on treatment with base. For example, when the α,ω-bis-N-benzyloxycarbonyl derivative (130) was treated with NaH in Me₂SO and m-xylyl dibromide (20) added, the macrocyclic bisurethane (131) was obtained as shown in equation (29). Removal

[Equation (29) here]

of the benzyloxycarbonyl protecting groups affords the free amine
which is a useful synthetic intermediate. Meta-xylyl-18-
crown-5 derivatives containing sulfur atoms have also been reported.\textsuperscript{97,98}

Para-phenylene units have been incorporated into a wide range
of crown compounds. Standard synthetic approaches have led to the
preparation of (a) \textsuperscript{(133)} and \textsuperscript{(134)} from p-hydroquinone and the
appropriate polyethylene glycol ditosylate,\textsuperscript{102} (b) \textsuperscript{(135)} and \textsuperscript{(136)}
from p-xylylene dibromide and the appropriate diol\textsuperscript{23} or dithiol\textsuperscript{98},
and (c) \textsuperscript{(137)} from p-phenylene-\(\beta,\beta'\)-diethylamine and triethylene
glycol ditosylate.\textsuperscript{103} Recently, the synthesis of some anion

\textsuperscript{[Formulae (133)-(137) here]}

receptor molecules incorporating para-phenylene units and guanidinium
groups has been described.\textsuperscript{104} For example, reaction of the diamine
\textsuperscript{(138)} with the bisisothiocyanate \textsuperscript{(139)} affords the macrocyclic
bis-thiourea \textsuperscript{(140)}, which can be converted (see equation 30) into
the bis-guanidinium bromide \textsuperscript{(141)}.\textsuperscript{2Br} by treatment with EtBr in
EtOH followed by reaction of the bis-S-ethyl thiononium derivative
with NH\textsubscript{3} in EtOH.

\textsuperscript{[Equation (30) here]}

Polycyclic compounds which incorporate (a) aryl groups
of the [2.2]-paracyclophane nucleus\textsuperscript{102} and (b) naphthalene-1,5, -1,8,
and -2,3-dimethyl\textsuperscript{105} units into crown-6 macrocycles have also been
reported. Finally, biphenyl residues have been included\textsuperscript{106} as
aromatic subunits—exhibiting both 2,2' and 3,3' substitution patterns—in various macrocyclic compounds.
2. Systems fused to furan rings

Furan-2,4- and -3,4-dimethylyl units have been incorporated\textsuperscript{23,24} into crown ethers by at least two groups of investigators. A series of 18-crown-6 derivatives, e.g. (142)-(144), containing one, two,

[Formulae (142)-(144) here]

and three furano residues deployed around the macrocyclic ring have been reported.\textsuperscript{107} The key starting material in their synthesis is 5-hydroxymethyl-2-furaldehyde which can be obtained\textsuperscript{108} from sucrose. This hydroxyaldehyde (145) can be converted into the diol (146), the dichloride (147), the extended diol (148) and chloroalcohol (149), and the bisfuran diol (150) and dichloride (151) by conventional methods. The compounds can then be employed as immediate precursors to (142)-(144) and other furan-containing cycles. Since furan rings lend themselves to chemical modification, macrocycles containing them have the potential to serve as precursors in the synthesis of receptor molecules whose perimeters are lined with a variety of shaping and binding residues. The monoterahydrofuranyl-18-crown-6 derivative, (152), for example, is obtained on catalytic hydrogenation of (142) (see equation 31). When Pd on C was used as catalyst, (152) was obtained as a 1:1 mixture of cis- and trans-isomers; however, in the presence of Raney nickel as catalyst, only the cis-isomer was isolated.

[Equation (31) here]

When (142) was heated in refluxing toluene with an excess of MeO\textsubscript{2}CC≡CCO\textsubscript{2}Me, the [4 + 2] cycloaddition product (153) was obtained
(see equation 31) in virtually quantitative yield. In addition to forming an adduct with MeO₂CC≡CCO₂Me, the monofuranyl-17-crown-6 derivative (154) incorporating a furan-3,4-dimethyl unit undergoes 34, 96 a Diels-Alder reaction with N-phenylmaleimide to form the adduct (155) as shown in equation (32).

\[
\text{[Equation (32) here]}
\]

3. Systems fused to pyridine rings

The pyridine-2,5-dimethyl unit is another one which has been widely employed as a heterocyclic subunit in crown compounds. In this work, the key starting material has been 2,6-bis(bromomethyl) pyridine. In 1973, Newkome and Robinson 109 isolated 22-, 33-, 44-, and 55-membered ring compounds after reaction of this dibromide with 1,2-di(hydroxymethyl)benzene in MeOCH₂CH₂OMe with NaH as base. An example of the smallest kind of macrocycle is provided by (156). A series of crown compounds, e.g. (157)-(159), containing between 12 and 24 atoms in the macroring and incorporating between 1 and 4 pyridine-2,6-dimethyl units have been synthesized 110 by conventional means. Diaza, e.g. (160), and dithia, e.g. (161), derivatives have also been reported, 97, 98, 111 and, in some cases, e.g. (161), the preparation of the N-oxide has been accomplished. The pyridine ring

\[
\text{[Formulae (156)-(161) here]}
\]

is found in other guises in a few macrocycles reported in the literature. Base promoted reaction of 2,6-bisbromopyridine with the appropriate polyethyleneglycol has yielded 112 (162) and (163),
for example, whilst incorporation of the 2,2'-bipyridyl unit into heteroatom containing macrocycles through its 3,3' and 6,6' positions has been achieved.\textsuperscript{58,113}

\[ \text{[Formulae (162) and (163) here]} \]

4. Systems fused to thiophene rings

Both thiophene-2,5- and -3,4-dimethyl units have been incorporated\textsuperscript{24,96,97,111} into crown compounds.

C. Macrocyclic Diester, Dithioester, and Diamide Compounds

Macrocyclic diesters have been synthesized by condensation of \( \alpha,\omega \)-dicarboxylic dichlorides and polyethyleneglycols in benzene using high dilution techniques. Using this simple procedure without the addition of any base, macrocycles containing between 4 and 6 ether oxygen atoms and incorporating 1 or 2 residues derived from oxalic,\textsuperscript{114} malonic,\textsuperscript{115-118} succinic,\textsuperscript{116,117,119} glutaric,\textsuperscript{114,117} and adipic\textsuperscript{117} acids have been prepared in good yields according to equation (33). Several methyl, phenyl, and perfluoro substituted

\[ \text{[Equation (33) here]} \]

diester crown compounds have also been reported\textsuperscript{117} as well as macrocycles incorporating fumaric\textsuperscript{117} and maleic\textsuperscript{119} acids. The syntheses of several macrocyclic thiapolyether diesters,\textsuperscript{114,116} e.g. (164), azapolyether diesters\textsuperscript{119} e.g. (165), polyether dithioesters\textsuperscript{114,116} e.g. (166), and thiapolyether dithioesters\textsuperscript{114} e.g. (167) derived from oxalyl, malonyl, succinyl, and glutaryl dichlorides have also been described. In addition, a series of macrocyclic

\[ \text{[Formulae (164)-(167) here]} \]
diesters have been synthesized,\textsuperscript{118,120,121} as shown in equation (34), by the condensation of }\alpha,\omega\text{-diglycolic acid dichloride and }\alpha,\omega\text{-thiodiglycolic acid dichloride with various polyethyleneglycols.}

\begin{equation}
\text{[Equation (34) here]}
\end{equation}

Macrocyclic diesters, e.g. (168)-(171), incorporating aromatic diacids have also been prepared.\textsuperscript{122,123} In particular, 2,6- and 3,5-pyridine dicarboxylate residues have been introduced\textsuperscript{123-125} into a variety of macrocyclic compounds, e.g. (172) and (173), by reaction of the diacid dichlorides derived from the pyridine dicarboxylates with polyethyleneglycols. In the case of (172), a high yield (78\%) was obtained from the reaction despite the absence of metal ions. It has been suggested\textsuperscript{124} that the high yield could arise from protonation of the nitrogen atom by HCl and the consequent ability of the pyridinium ion to act as a template for ring closure.

Several new crown ethers, e.g. (174) containing the 3,5-di(alkoxy-carbonyl) pyridine ring system have been prepared\textsuperscript{126} by an approach which is novel to crown ether synthesis. It relies upon a Hantzsch-type condensation of the }\alpha,\omega\text{-bis(acetoacetic ester) (175) of tetraethyleneglycol with HCHO and an excess of (NH}_4\textsuperscript{)}_2\text{CO}_3\text{ in an aqueous medium followed by dehydrogenation of the intermediate 1,4-dihydropyridine derivative (176) as shown in equation (35). The macrocyclic}

\begin{equation}
\text{[Equation (35) here]}
\end{equation}
and heterocyclic rings are thought to be generated simultaneously during the course of this reaction. The pyridyl derivative (174) can be converted into the N-methylhydropyridine derivative (177) by methylation to afford the pyridinium salt (178) followed by reduction with Na₂S₂O₄. The potential of (177) as a model for NAD(P)H has been demonstrated by its ability to transfer hydride readily to sulfonium salts. Attempts to extend this type of synthesis to systems other than (174) have met with only limited success and alternative procedures have been sought. Reaction of the dicesium salts of 3,5-pyridine dicarboxylic acid (179) (R=H or Me) with α,ω-polyethyleneglycol dibromides in HCONMe₂ gives (see equation 36)

\[
(\text{Equation (36) here})
\]

cyclic 3,5-di(alkoxycarbonyl)pyridine derivatives (180) (R=H or Me) in yields of between 20 and 90% depending upon the chain length of the glycol. Cs⁺ ions play a virtually irreplaceable role in the formation of (180) (R=H, n=3) since the yield of the macrocycle decreases drastically when Cs⁺ ions are replaced by Rb⁺, K⁺, or Na⁺ ions. It has been suggested that the Cs⁺ ion acts as a template during the early stages of the reaction.

Several groups of investigators have prepared macrocyclic compounds incorporating the ubiquitous amide functional group. For example, macrocyclic peptides have been synthesized and investigated for their cationic binding properties. In addition, macrocyclic diamides prepared by the approaches outlined in Section IV.A.4 have served as important intermediates in the synthesis of macrobicyclic diazapolyethers (see Section IV.G). The preparation of several macrocyclic diamides incorporating 2,6-disubstituted pyridine bridges
Benzimidazolone has been reacted\textsuperscript{129} with α,ω-polyethyleneglycol dichlorides in HCONMe\textsubscript{2} in the presence of LiH or NaH to afford a series of novel monomeric and dimeric derivatives, e.g. (181) and (182). Interestingly, benzimidazolethione undergoes\textsuperscript{129} alkylation firstly at sulfur and then at nitrogen to yield nitrogen-sulfur bridged compounds, e.g. (183). Quinoxaldione and 5-methyluracil have also been incorporated\textsuperscript{129} into macrocyclic polyethers.

D. Crown Compounds Containing Carbonyl Groups

1. Oxo crown ethers

The carbonyl group has been introduced into crown ethers both as a direct replacement for an ether oxygen atom and as a formal insertion into an OCH\textsubscript{2}CH\textsubscript{2}O fragment. The oxo-18-crown-5 derivative (184) has been prepared\textsuperscript{130} by base-promoted condensation of the dithiane (185) with tetraethyleneglycol ditosylate (95) followed by regeneration of the masked carbonyl group from the spiro intermediate as shown in equation (37). Reaction of tetraethyleneglycol (16) with NaH and 1,1-bis(chloromethyl)ethylene (186) gave\textsuperscript{131} the methylene-16-crown-5 derivative (187), which, on ozonolysis and decomposition of the ozonide, afforded (see equation 38) the oxo-16-crown-5 derivative (188) in nearly quantitative yield. Oxo-crown ethers promise to be valuable
synthetic intermediates. The novel dioxo-dithia-18-crown-6 derivative (189) has been obtained recently from reaction of 1,9-dichloroanthraquinone with the appropriate polyethyleneglycol dithiol.

2. Crown ethers incorporating β-diketone residues

Since enolisable β-diketonates, such as acetylacetone, form stable complexes with both metal ions and non-metallic elements; it is of interest to incorporate them into macrocyclic polyethers. Macrocyclic polyethers, e.g. (190)-(192), which contain 1, 2, and 3 β-diketone units in the ring have been made from reaction of the key starting material (193) with NaH and (a) pentaethyleneglycol ditosylate — to give the β-diketone (190) after regeneration of the carbonyl groups — or (b) diethyleneglycol ditosylate — to give a mixture of the bis(β-diketone) (191) and the tris(β-diketone) (192) after regeneration of the carbonyl groups. The templated syntheses of acyclic and cyclic acetylacetone derivatives have been investigated as well. The macrocycle (194) was produced in 13% yield from the reaction of the magnesium salt — but not the calcium salt — of (195) with bis(bromomethyl)benzene (20) under similar reaction conditions (see equation 39).

In addition, the disodium salt of (195) was noted to give only polymer when cyclization with the dibromide (20) was attempted. These experimental observations demonstrate that the cyclizations are templated selectively by metal ions.
E. Crown Compounds Incorporating Imine and Oxime Functions

1. Macrocycles from Schiff-base condensations

The Schiff-base condensation between a CO and an NH$_2$ group to form a C=N linkage forms the basis of many successful macrocyclic ligand syntheses. The use of alkaline earth and transition metal ions to control cyclizations and form in situ Schiff base complexes is well established. Two types of template effect have been recognized in this area. According as to whether the metal ion lowers the free energy of (a) the transition state in an irreversible reaction or (b) the product in a reversible reaction, a "kinetic" or "thermodynamic" template effect is operative. Although a "kinetic" template effect clearly operates (see Section II.A) during the irreversible crown ether syntheses, many of the templated reactions involving the formation of imine functions probably rely upon a "thermodynamic" template effect.

The 2,6-di-iminopyridyl moiety has enjoyed popular application in the in situ synthesis of metal complexes of both macrocyclic polyamines and azapolyethers. The isolation of crystalline iron (III) complexes of the pentadentate 15-membered ring (196) and hexadentate 18-membered ring (197) compounds after Schiff-base condensation of 2,6-diacetylpyridine with the appropriate polyamine in the presence of iron (II) salts has been reported. Other investigators have prepared similar types of complexes in situ. They have varied the nature of the coordinated metal ion, the size of the macrocycle and the nature (O, N, and S) of the heteroatoms in the rings. In some instances, benzene rings have also been fused on to the macrocycle.
In view of the relatively high abundance of Mg\textsuperscript{2+} ions in Nature—and particularly their occurrence in chlorophylls—the effectiveness of Mg\textsuperscript{2+} as a templating ion in the synthesis of planar nitrogen-donor macrocycles is of considerable biological interest. The Mg\textsuperscript{2+} ion templated syntheses of the macrocycles (198) and (199) and their isolation as hydrated MgCl\textsubscript{2} complexes has been reported.\textsuperscript{143} More recently, the magnesium (II) complexes of the 2,6-di-iminopyridyl polyethers (200) and (201) have been prepared.\textsuperscript{144} A Group IVB cation has been utilised\textsuperscript{145} in the templated Schiff-base condensation of 2,6-pyridinedicarbonyl derivatives with \(\alpha,\omega\)-diamines and lead (II) thiocyanate complexes of the macrocyclic iminopolyethers (202) and (203) have been isolated.

Recently, the first reported syntheses of alkaline earth metal complexes of macrocycles containing 2,5-di-iminofuranyl units have appeared\textsuperscript{146} in the literature. Schiff-base condensation of furan-2,5-dicarboxaldehyde with the appropriate \(\alpha,\omega\)-diamino polyethers in the presence of either Ca, Sr, or Ba thiocyanates as templates led to the isolation of the metal ion thiocyanate complexes of (204) and (205).

2. Oxime linkages in macrocycles

Oxime functions have recently been incorporated into multi-heteromacrocyclic structures. The syntheses of the dioximes (206) and (207) and the tetraoximes (208) and (209) have been accomplished\textsuperscript{147}
by reaction of diacetyldioxime with either the appropriate polyethylene glycol ditosylate, 2,6-bis(bromomethyl)pyridine, or 1,3-bis(bromomethyl)-benzene in anhydrous HCONMe₂. In addition, the cyclic oxime (210) was prepared in ca. 28% yield from salicylaldoxime and pentaethyleneglycol dibromide. In all these macrocycles, the oxime linkage has the (E)-configuration. Novel multiheteromacrocycles e.g. (211), have been isolated by polymerization of acetonitrile oxide in the presence of nucleophilic catalysts. Several of the compounds, including (211), form crystalline complexes with KSCN.

F. Acyclic Crown Compounds

The solvating power of polyethyleneglycol ethers (glymes) toward alkali metals and their salts was first recognized by Wilkinson and his collaborators in 1959. They investigated the solubility of sodium and its potassium alloy in various glymes and observed that the intensities of the blue colored metal solutions increased with the number of oxygen atoms in the glyme. Since Pedersen's discovery of cyclic crown compounds in 1967, there have been numerous reports of "acyclic crown compounds". We shall limit our brief discussion of these compounds to those examples where the \(-\text{OCH}_2\text{CH}_2\text{O}^{-}\) repeating unit is the predominant constitutional feature. For the most part, they have been synthesized by alkylations involving mono-protected polyethyleneglycol derivatives. The terminal residues in these so-called "octopus" molecules may be introduced in the form of the original blocking group or they may be inserted in the final step
of the synthesis with the penultimate step involving the removal of a temporary protecting group. Examples (a) based on polyethylene-glycol chains, e.g. (212)-(216), (b) emanating from aromatic rings, e.g. (217)-(221), and (c) emanating from nitrogen atoms, e.g. (222)-(224), have been reported$^{149}$ in the literature. The triethanolamine tripod ligands can be viewed as analogs of the diazamacrobicyclic polyethers (see Section IV.E).

G. Macrobicyclic, Macrotricyclic and Macropolycyclic Ligands

1. Systems with nitrogen bridgeheads

The inspired association by Lehn and his collaborators$^{48,50,51,150}$ of the synthetic accomplishments of Pedersen$^{6,11,12}$ on crown ethers and Simmons and Park$^{151}$ on macrobicyclic diamines led to the realization of diazamacrobicyclic polyethers in 1969. These ligands which can encapsulate metal cations in spherical holes usually form very strong complexes. A generalized scheme of reactions employed$^{150}$ in the synthesis of the macrobicyclic ligands (225)-(231) is portrayed in Scheme 3. Reaction of an $\alpha,\omega$-diaminopolyether with an $\alpha,\omega$-diacid dichloride ($\text{l=}_m$ or $\text{l\neq}_m$) under high dilution conditions (cf. Section IV.A4) gives a macrocyclic diamide which can be reduced to the corresponding diamine. Condensation of this macrocycle with the same (i.e. $m=n$) or a different (i.e. $m\neq n$) $\alpha,\omega$-diacid dichloride under high dilution conditions gives a bicyclic diamide which can be reduced with $\text{B}_2\text{H}_6$ to afford the corresponding bis(borane-amine). Acid-catalysed hydrolysis followed by passage of the bishydrochloride salts through an anion exchange resin affords the diazamacrobicyclic
polyethers. As part of an investigation into the factors that control the selectivity of macrobicyclic ligands toward binding of various metal ions, the Strasbourg group have synthesized compounds, e.g. (232)-(237), in which (a) ortho disubstituted benzene rings have been incorporated and (b) the ether oxygen atoms have been replaced progressively either by secondary and tertiary amine groups or by sulfur atoms. More recently, meta-xylyl, pyridyl, and 1,1'-bipyridyl residues have been introduced into the side-arms. Finally, macrobicyclic polyethers have also been covalently bound to a polystyrene support. Macrotricyclic ligands can assume at least two types of topology—identified by (i) and (ii) in Figure 2—which are distinct. Type (i) ligands may be considered to be cylindrical and are formed when two monocycles are linked by two bridges. A synthetic approach—involving the established routine of sequential condensations and reductions—which allows construction of cylindrical macrotricyclic ligands, e.g. (238)-(242) with the same or different sizes of monocycles and the same or different lengths of bridges between them is based upon the following three stage strategy: (a) the synthesis of a monocyclic diaza crown ether which is then monoprotected at nitrogen before (b) forming a bis(monocyclic) crown ether and removing the protecting groups on the nitrogens and (c) inserting the second bridge to afford the macrotricyclic ligand. If the bridging units are chosen to incorporate nitrogen atoms, then a third bridge can be
introduced$^{156}$ to give a macrotetracyclic ligand with the topology represented under type (iii) in Figure 2. Returning to macrotricyclic ligands, the spheroidal topology belonging to type (ii) in Figure 2 has also been realised$^{157}$ (see Scheme 4) in the shape of [Scheme 4 here] (243) with four identical faces. The use of the protected tosylamides is the key to this elegant synthesis conceived and accomplished by Graf and Lehn.$^{157}$

2. Systems with carbon bridgeheads

In principle, any atom of valency three or higher can occupy the bridgehead positions. Macrobicyclic polyethers with bridgehead carbon atoms have been synthesized$^{158}$ in a number of different ways from diethylene glycol ditosylate (43) and either pentaerythritol or 1,1,1-tris(hydroxymethyl)ethane. For example, pentaerythritol can be converted$^{158}$ into the oxetane-diol (244) by known reaction procedures. [Formulae (244) and (245) here]

Reaction of (244) with NaH and (43) in Me$_2$SO afforded the dispiro-20-crown-6 derivative$^{159}$ (245) as shown in equation (40). The diastereoisomeric diols (246), obtained on reductive ring opening of the oxetane rings in (245), gave the macrobicyclic polyether (247) on reaction with NaH and (43) in MeOCH$_2$CH$_2$OMe. This ligand forms [Equation (40) here] extremely weak complexes with alkali metal cations! More recently, 1,3-dichloropropan-2-ol has been employed$^{160}$ as the source of bridgehead...
carbon atoms in a four step synthesis of the macrobicyclic polyethers (248) and (249). These derivatives of glycerol preserve the \(-O-C-C-O-\) unit throughout their constitution and hence it is not surprising that they bind Group IA metal cations strongly.

[Formulae (248) and (249) here]

3. A system with nitrogen and carbon bridgeheads

A novel macrobicyclic polyether diamide (250) containing both nitrogen and carbon bridgehead atoms has been prepared\(^{161}\) from the spiro compound (251) by opening of the oxetane ring with NH\(_3\) to give the amino alcohol (252) which was then condensed with diglycolyl dichloride as shown in equation (41).

[Equation (41) here]

H. Chiral Crown Ethers

1. Meso compounds and racemic modifications

Four—namely (48)-(51)—of the five possible configurational diastereoisomers of dicyclohexano-18-crown-6 are known. The two di-cis isomers (48) and (49) and the trans-cisoid-trans isomer (50) are meso compounds; the trans-transoid-trans isomer (51) belongs to a chiral point group \((\mathbb{D}_2)\) and so can be obtained optically active or as a racemic modification. Pedersen\(^{12,162,163}\) isolated two crystalline isomers of dicyclohexano-18-crown-6 after hydrogenation of dibenzo-18-crown-6 (10) over a ruthenium on alumina catalyst followed by chromatographic separation on alumina.\(^{42,163,164}\) They were designated\(^{42,163,164}\) as Isomer A (m.p. 61-62°) and Isomer B (m.p. 69-70°). After a period of some confusion in the literature (cf. ref. 43), Isomer A was identified as the cis-cisoid-cis isomer (48) on
the basis of an X-ray crystal structure analysis\textsuperscript{165} of its barium thiocyanate complex. Similarly, an X-ray crystal structure determination of the sodium bromide dihydrate complex of Isomer B established\textsuperscript{166} that it is the cis-transoid-cis isomer (49). More recently, X-ray crystallographic data on the uncomplexed ligand has confirmed that Isomer A is the cis-cisoid-cis isomer (48). Isomer B exists\textsuperscript{164} in a second crystalline form, Isomer $B'$, with m.p. 83-84$^\circ$. In solution, the two forms are identical. A ready separation of Isomer $B'$ from Isomer A takes\textsuperscript{168} advantage of the large differences in solubility in water between the lead and oxonium perchlorate complexes of the two isomers. X-ray crystallography has revealed\textsuperscript{167} that Isomer $B'$ like Isomer B has the cis-transoid-cis configuration. Whilst it is generally believed\textsuperscript{164} that Isomers B and $B'$ in the crystalline states are polymorphs, it is possible (cf. ref. 43) that they are conformational isomers differing in the relative conformations of the cyclohexane rings fused to the 18-membered ring. The stereospecific synthesis of the trans-cisoid-trans (50) and trans-transoid-trans (51) isomers from the methylenedioxydicyclohexanols\textsuperscript{169} has been achieved.\textsuperscript{43,170} Scheme 5 illustrates the synthetic route employed. Treatment of (253)

\textbf{[Scheme 5 here]}

and (254) in turn with diethyleneglycol ditosylate (43) under basic conditions gave the cyclic acetals (255) and (256), respectively. Acid-catalysed hydrolysis afforded diols, which following further base promoted condensations with (43) gave the two di-trans isomers (50) and (51) stereospecifically. A one-step synthesis of (50) and (51) from (+)-cyclohexane-trans-1,2-diol was accompanied by the formation of some (†)-trans-cyclohexano-9-crown-3.
The formal location of four constitutionally equivalent chiral centers at either \( C_{(6)} \), \( C_{(10)} \), \( C_{(17)} \), and \( C_{(21)} \) or \( C_{(7)} \), \( C_{(9)} \), \( C_{(18)} \), and \( C_{(20)} \) on the macrocyclic framework of dibenzo-18-crown-6 (10) generates five possible diastereoisomers in each series. The synthesis and separation of all ten configurational isomers of the constitutionally symmetrical tetramethyl-dibenzo-18-crown-6 derivatives have been described.\(^{171}\) On the basis of stereochemically-controlled reactions and X-ray crystal structure analyses relative configurations have been assigned\(^{171,172}\) to four of them. Scheme 6 outlines the preparation of the five diastereoisomers of the 6,10,17,21-tetramethyl derivative. A mixture of meso- and (\( \dagger \))-1,1'-oxydipropan-2-ol was prepared by reacting propylene oxide with (\( \dagger \))-propan-1,2-diol. The meso-isomer can be fractionally crystallised from the (\( \dagger \))-isomer. Tosylation of both the meso- and (\( \dagger \))-diols in turn afforded the meso-(257) and (\( \dagger \)-(258) ditosylates. Base promoted condensation of (257) with catechol (9) gave a mixture of diastereoisomers (259) and (260), which were separated by fractional crystallisation. Similarly, reaction of the racemic ditosylate (258) with catechol (9) under basic conditions led to the isolation of a pair of diastereoisomers (261) and (262) which were separated by solvent extraction. The final diastereoisomer (265) was obtained by a three stage procedure. The monobenzyl ether of catechol was condensed with (257) to give the dibenzyl ether (263). After removal of the protecting groups to afford the diol (264) condensation with (258) led to ring closure and isolation of (265). The configuration of (265) follows from its mode of synthesis. The relative configurations of (259) and (260), and
Catalytic hydrogenation of macrocyclic polyethers containing furan residues has led to mixtures of diastereoisomers which have not been separated.

2. Optically-active crown ethers from natural products

The first crowns incorporating optically-active residues were described by Wudl and Gaeta in 1972. L-Proline was introduced into the macrocyclic diaza-polyether LL-(266) by the procedure outlined in Scheme 7. D-ephedrine was incorporated into DD-(267) by a similar approach. In principle, a whole range of natural products including alkaloids, amino acids, carbohydrates, steroids, and terpenes can be viewed as chiral precursors. In practice, carbohydrates lend themselves to the most detailed exploitation. For example, treatment of the bis(N,N'-dimethylamide) L-(268) of L-tartaric acid with two equivalents of thallium (I) ethoxide in anhydrous OHCNMe₂, followed by an excess of diethyleneglycol diiodide (269) in a modification of the Williamson ether synthesis, afforded (see equation 42) the tetracarboxamide 18-crown-6 derivative LL-(270).

This compound can be hydrolysed to the tetracarboxylate which can be converted into the tetraacid chloride, a key compound in the preparation of derivatives with a whole range of side chains where the functionality has catalytic potential. The synthesis of LL-(270) illustrates the attractions of employing chiral sources with C₂
symmetry. Two such residues are incorporated into one macrocycle which has \(D_2\) symmetry. The same principle was relied upon in the synthesis of chiral 18-crown-6 derivatives, e.g. \(\text{LL-(271)}\), \(\text{LL-(272)}\), \(\text{DD-(273)}\), and \(\text{DD-(274)}\), incorporating \(L\)-threitol,\(^{178}\) \(L\)-iditol,\(^{179}\)

and \(D\)-mannitol,\(^{178}\), all of which have \(C_2\) symmetry. The key diols employed in these preparations were 1,4-di-O-benzyl-\(L\)-threitol and the 1,2:5,6-di-O-isopropylidene derivatives of \(L\)-iditol and \(D\)-mannitol. More recently, 1,3:4,6-di-O-methylene-\(D\)-mannitol has been incorporated\(^{181}\) into a 20-crown-6 derivative \(\text{D-(275)}\).

Chiral asymmetric 18-crown-6 derivatives, e.g. \(\text{D-(276)}\) and \(\text{DD-(277)}\) have also been synthesised with \(D\)-glucose,\(^{182}\) \(D\)-galactose,\(^{182}\) \(D\)-mannose,\(^{183}\) and \(D\)-altrose\(^{183}\) as the sources of asymmetry. In these cases, chain extensions to give "half-crown" diols through the sequence\(^{47}\) of reactions, (a) allylation, (b) ozonolysis, and (c) reduction, on the 4,6-O-benzylidene derivatives of the methyl glycosides proved invaluable. Although only one compound results from condensations involving two chiral precursors, one with \(C_1\) and the other with \(C_2\) symmetry, two constitutional isomers, e.g. \(\text{DD-(278)}\) and \(\text{DD-(279)}\) result\(^{184,185}\) when two asymmetric residues are incorporated into an 18-crown-6 derivative.

[Formulae \(\text{DD-(278)}\) and \(\text{DD-(279)}\) here]
Finally, 2,3-O-isopropylidene-D-glycerol has been utilised\textsuperscript{186} in an elegant synthesis of the chiral macrobicyclic polyethers DD-(280) and DD-(281). One of the novelties of the preparative route is that it affords a stereospecific synthesis of in-out isomers of bicyclic systems.

3. Optically active crown ethers from resolved precursors

The syntheses of (+)-(SSSS)-trans-transoid-trans-dicyclohexano-18-crown-6 as well as (+)-(SS)-trans-cyclohexano-15-crown-5 and (+)-(SS)-trans-cyclohexano-18-crown-6 have been reported\textsuperscript{47} starting from optically pure (+)-(1S, 2S)-cyclohexane-trans-1,2-diol resolved via the strychnine salts of the hemisulfate diester. However, it is the 1,1'-binaphthyl residue with axial chirality which has been utilized so elegantly by Cram and his associates\textsuperscript{52-55,106,187-189} that has found its way into a whole host of optically active crown ethers! 2,2'-Dihydroxy-1,1'-binaphthyl is the key starting material in the syntheses. The fact that this diol is easily accessible from 2-naphthol and can then be resolved readily through either its monomenthoxyacetic ester or through the cinchonine salt of its phosphate ester to give, for example, (-)-(S)-(282) with C\textsubscript{2} symmetry accounts for its unique status. A range of macrocycles incorporating one, e.g. (-)-(S)-(282) here and two, e.g. (-)-(SS)-(288) and (-)-(SS)-(289), and three, e.g. (-)-(RSS)-(290), binaphthyl moieties have been synthesized.
by reactions involving base-promoted substitutions on RCl, RBr, or
ROTs. Substituents, some containing functional groups have been
incorporated at positions 3, 3', 6, and 6', and other residues and
heteroatoms have been built into the macrocyclic ring. 'Resolution'
of the 1,1'-binaphthyl unit has also been achieved by employing
(RS)binaphthol (RS)-(282) and 1,2:5,6-di-O-isopropylidene-D-mannitol
in the syntheses of the diastereoisomeric macrocyclic polyethers
(R)-D-(291) and (S)-D-(292). Finally, it should be mentioned

[Formulae (R)-D-(291) and (S)-D-(292) here]

that (S)-(282) has been incorporated into the chiral macropoly-
cyclic ligand (S)-(293).

[Formula (S)-(293)]

V. TOXICITY AND HAZARDS

Despite the large number of crown compounds synthesized during
the past decade, comparatively little information is available in
the open literature relating to their physiological properties.
In his early papers, Pedersen reported that dicyclohexano-
18-crown-6 is toxic towards rats. The lethal dose for injection of
this crown ether was found to be approximately 300 mg./kg. of
body weight. In 10-day subacute oral tests, the compound did not
exhibit any cumulative toxicity when administered to male rats at
a dose level of 60 mg./kg./day. Dicyclohexano-18-crown-6 was also
found to be a skin irritant and generalized corneal injury, some
iritic injury, and conjunctivitis occurred when it was introduced
into the eyes of rats as a 10% solution in propylene glycol. Leong
and his associates\textsuperscript{192} have published toxicological data for 12-crown-4 (4) and other simple crown ethers. Rats exposed to (4) at concentrations between 1.2 and 63.8 p.p.m. in air suffered loss of body weight. They also developed anorexia, asthenia, hindquarter incoordination, testicular atrophy, auditory hypersensitivity, tremors, convulsions, and moribund conditions. Oral administration of (4) to rats in a single dose of 100 mg./kg. of body weight produces effects upon the central nervous system in addition to causing testicular atrophy. Acute oral toxicity investigations on 15-crown-5 (19), 18-crown-6 (12), and 21-crown-7 (54) revealed that these compounds also produce effects upon the central nervous system of rats although higher dosages were needed than those required with (4). It is clear that crown ethers should be handled with caution and respect!

There has been a report\textsuperscript{193} of an explosion during one particular experimental manipulation\textsuperscript{19} to obtain pure 18-crown-6 (12) from a reaction mixture. In one step of the isolation procedure, it is necessary to decompose thermally under reduced pressure the 18-crown-6-KCl complex formed during the reaction. However, at the temperatures of 100-200\degree C necessary to decompose the complex, decomposition may occur at the distillation head with the production of 1,4-dioxane. Breaking of the vacuum at >100\degree C can lead to autoignition of air-1,4-dioxane mixtures and hence explosions. Experimental procedures have been suggested\textsuperscript{194} to reduce the risk of these as a result of distilling 18-crown-6 (12) from its KCl complex at high temperatures. Constant vigilence is essential!
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Captions to Figures

Figure 1. The designations of conformational types for the di-cis (48a) and (49a) and di-trans (50a) and (51a) isomers of dicyclohexano-18-crown-6.

Figure 2. Topological representations of (i) cylindrical macrotricyclic, (ii) spheroidal macrotricyclic, and (iii) cylindrical macrotetracyclic ligands.
Figure 1

(48a)

(49a)

(50a)

(51a)
Figure 2
Scheme 1

Reagents: i, BuOH, NaOH; ii, H^+, H_2O
Scheme 2

(1) - (52) + (1) - (53) → Polymer?
Reagents and conditions:  

i, C₆H₆, high dilution;  
ii, LiAlH₄;  
iii, B₂H₆;  
iv, HCl;  
v, OH⁻
Reagents: 
i, NaCN, HCONMe2; ii, Ba(OH)$_2$, H$_2$O then HCl; iii, (COCl)$_2$, C$_6$H$_5$;
iv, H$_2$NCH$_2$CH$_2$OCH$_2$CH$_2$NH$_2$, C$_6$H$_6$; v, B$_2$H$_6$; vi, TsN(CH$_2$CH$_2$OCH$_2$COCl)$_2$, C$_6$H$_6$;
vii, LiAlH$_4$; viii, ClCOCH$_2$OCH$_2$COCl, C$_6$H$_6$.

Scheme 4
Reagents: i, TsOCH$_2$CH$_2$OCH$_2$CH$_2$OTs, NaH, Me$_2$SO/(MeOCH$_2$)$_2$; ii, H$^+$/H$_2$O

Scheme 5
Reagents:  

i, $\text{o-C}_6\text{H}_4(\text{OH})_2$ (9), NaOH, Me(CH$_2$)$_3$OH;  
ii, $\text{o-PhCH}_2\text{OC}_6\text{H}_4\text{OH}$,  
NaOH, Me(CH$_2$)$_3$OH;  
iii, H$_2$Pd;  
iv, (258), NaOH, Me(CH$_2$)$_3$OH

Scheme 6
Reagents:  

- i, LiAlH₄;  
- ii o-C₆H₄(CH₂Br)₂ (32), NaH, Me₂SO

Scheme 7
(1) Me₃COK or NaH

(2) MeOCH₂CH₂OMe

(12) OTs

(13) OH

(14) Me₂SO

(15) OH

(16) OH

(17) OH

(18) Me₃COK or NaH

MeOCH₂CH₂OMe

(14) Solvent

(12).KOTs

NaOH, LiClO₄

Me₂SO

(13%)
(18) + (15) \xrightarrow{\text{NaOH, 1,4-Dioxane}} (19) (14\%) (4)

(13) + (7) \xrightarrow{\text{NaOH, 1,4-Dioxane}} (19) (38\%) (5)
\[
\text{FTOc;} \quad \text{BF}_3(\text{gas})/\text{HF} \quad \text{Dioxane}
\]
\[
\text{TsO(CH}_2\text{CH}_2\text{O)}_8\text{Ts}
\]
\[
\begin{align*}
\text{HN=C(NH}_2\text{)}_2 & \quad \text{Me}_3\text{COH} \\
\text{Re flux} & \quad \text{OTs}^-
\end{align*}
\]
2 Mol base

(8)

(9)

(10)

(11)
\[ \text{CH}_2 + \text{H}_2\text{O}_2 \rightarrow \text{CH}_2\text{CHOH} \]

\[ \text{CH}_2\text{CHOH} \rightarrow \text{CH}_2\text{CH}_2\text{CO}_2\text{H} \]

\[ \text{LiAlH}_4 \rightarrow \text{HOCH}_2\text{CH}_2\text{CO}_2\text{H} \]

\[ \text{KOH} \rightarrow \text{HOCH}_2\text{CH}_2\text{CO}_2\text{H} \]

\[ \text{PhCH}_2\text{COOH} + \text{Ts}_2\text{O} \rightarrow \text{PhCH}_2\text{COO}^+ \text{Ts}^- \]

\[ \text{NaOH} \rightarrow \text{PhCH}_2\text{COO}^+ \text{Ts}^- \]

\[ \text{C}_6\text{H}_6 - \text{H}_2\text{O} \rightarrow \text{PhCH}_2\text{COO}^+ \text{Ts}^- \]
(61) \[ \text{(OCH}_2\text{CH}_2\text{)}_{23} \text{O-} \]

\[ \text{hv, C}_6\text{H}_6, \text{LiClO}_4 \]

\[ \text{MeCN} \]

(62) \[ \text{LiClO}_4 \]

(63) \[ \text{R = H} \]

(64) \[ \text{R = H} \]

(65) \[ \text{R = Et} \]

(66) \[ \text{R = Et} \]
LiAlH₄

or B₂H₆

\[ \text{Me}_1 = 1 \]

\[ \text{H}_2 \]

7,1

H₂L

\[ \text{EtOH} \]

![Chemical Diagram](image)

**Yield (%)**

<table>
<thead>
<tr>
<th>( n )</th>
<th>( m )</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td>2</td>
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<td>(91)</td>
<td>1</td>
<td>3</td>
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<tr>
<td>(92)</td>
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<td>1</td>
</tr>
<tr>
<td>(93)</td>
<td>2</td>
<td>2</td>
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</table>

| \( \text{LiAlH}_4 \) or \( \text{B}_2\text{H}_6 \) |

**Yield (%)**

<table>
<thead>
<tr>
<th>( n )</th>
<th>( m )</th>
<th>Yield (%)</th>
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<td>(82)</td>
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<tr>
<td>(83)</td>
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<tr>
<td>(84)</td>
<td>2</td>
<td>2</td>
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</table>
\[
\begin{align*}
\text{CF}_3\text{CONH} & \quad \text{HNCOCF}_3 \\
\text{OTs} & \quad \text{TsO}
\end{align*}
\]

(104) + (14) \xrightarrow{i, \text{NaH}} \xrightarrow{ii, \text{H}_2\text{O}, \text{OH}^-} \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow \rightarrow 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\right}
\[
\text{SH} \quad + \quad \text{Cl}_2\text{O}_2\text{H}_2 \quad \xrightarrow{\text{NaOEt, EtOH}} \quad \text{Cl}_2\text{O}_2\text{H}_2 \quad \xrightarrow{\text{NaOEt, EtOH}} \quad \text{Cl}_2\text{O}_2\text{H}_2
\]

(24)

\[
\text{Cl}_2\text{O}_2\text{H}_2 \quad + \quad \text{HS}_2 \quad \xrightarrow{\text{NaOEt, EtOH}} \quad \text{Cl}_2\text{O}_2\text{H}_2
\]

(25)

\[
\text{Cl}_2\text{O}_2\text{H}_2 \quad + \quad \text{HS}_2 \quad \xrightarrow{\text{NaOEt, EtOH}} \quad \text{Cl}_2\text{O}_2\text{H}_2
\]

(26)
(113) + (109) → EtOH → (112)

(120) + (121) → i, NaNMe, C₆H₆, ii, Cu₂Cl₂, C₅H₅N → (119)
A. \[ \text{PhCH}_2\text{OCONH} + \text{HNCOCH}_2\text{Ph} \rightarrow \text{PhCH}_2\text{CON}_{2}\text{CH}_2\text{Ph} \]

\[ \text{PhCH}_2\text{CON}_{2}\text{CH}_2\text{Ph} \rightarrow \text{H}_2, \text{Pd/C} \]

B.

\[ \text{PhCH}_2\text{OCONH} + \text{HNCOCH}_2\text{Ph} \rightarrow \text{PhCH}_2\text{CON}_{2}\text{CH}_2\text{Ph} \]

\[ \text{PhCH}_2\text{CON}_{2}\text{CH}_2\text{Ph} \rightarrow \text{H}_2, \text{Pd/C} \]

C.

\[ \text{PhCH}_2\text{OCONH} + \text{HNCOCH}_2\text{Ph} \rightarrow \text{PhCH}_2\text{CON}_{2}\text{CH}_2\text{Ph} \]

\[ \text{PhCH}_2\text{CON}_{2}\text{CH}_2\text{Ph} \rightarrow \text{H}_2, \text{Pd/C} \]
\( \text{H}_2 \text{Pd/C or Raney Ni} \)

\[ (152) \]

\[ (142) \] to \[ (153) \] via \[ \text{MeO}_2 \text{C} \!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\!=\!\= \]

\[ (154) \]

\[ (155) \] via \[ \text{Ph-} \text{N-} \text{Ph} \]
\[
\text{R = H or Me}
\]

(179)  

(180)  

(181)  

(182)  

(183)  

(184)  

(185)  

(186)  

(187)  

(188)
(195) \[ \overset{i, \text{Mg}}{\longrightarrow} \]
(194)

\[ \overset{\text{ii, } \text{LiN(CHMe}_2)_2}{\longrightarrow} \]

(244) \[ \overset{\text{NaH, } \text{Me}_2\text{SO}}{\longrightarrow} \]
(245) \[ \overset{\text{LiAlH}_4}{\longrightarrow} \]
(246)

(247) \[ \overset{\text{NaH, MeOCH}_2\text{CH}_2\text{OMe}}{\longrightarrow} \]
\[
\begin{align*}
\text{NH}_3, \text{H}_2\text{O} & \\
& \xrightarrow{200^\circ} \text{(252)} \\
\text{CH}_2\text{Cl}_2, \text{C}_6\text{H}_6 & \text{Et}_3\text{N} \rightarrow \text{(250)}
\end{align*}
\]
(1) 

(2) 

(3) 

(4) \(R = H\) 

(5) \(R = Me\) 

(32) 

(33) \(n = 1\) 

(34) \(n = 2\) 

(35) \(n = 3\)
\[(12a) \quad \text{[Diagram of a molecular structure]} \quad g^+ g^- g^+ g^- g^+ g^- \]

\[
\begin{align*}
(48) & \quad \text{[Diagram of another molecular structure]} \\
(49) & \quad \text{[Diagram of another molecular structure]} \\
(50) & \quad \text{[Diagram of another molecular structure]} \\
(51) & \quad \text{[Diagram of another molecular structure]} \\
(54) & \quad \text{[Diagram of another molecular structure]} \\
(55) & \quad \text{[Diagram of another molecular structure]} 
\end{align*}
\]
\[ n = 1 \]
\[ n = 2 \]

(114) \hspace{1cm} (115) \hspace{1cm} (116)

(117) \hspace{1cm} (118)

(122) \hspace{1cm} (123)
(145) \( R^1 = CH_2OH; R^2 = CHO \)
(146) \( R^1 = R^2 = CH_2OH \)
(147) \( R^1 = R^2 = CH_2Cl \)
(148) \( R^1 = R^2 = CH_2OCH_2CH_2OH \)
(149) \( R^1 = CH_2OH; R^2 = CH_2OCH_2CH_2Cl \)

(150) \( R = CH_2OH \)
(151) \( R = CH_2Cl \)

(156)

(157)

(158)

(159) \( X = O \)
(160) \( X = NTs \)
(161) \( X = S \)
(168)  

(169)  

(170)  

(171)  

(172)  X = CH; Y = N  

(173)  X = N; Y = CH
(196) \( n = 0 \)

(197) \( n = 1 \)

(198) \( \text{Me} - \text{NH}_2 \)

(199) \( \text{Me} - \text{NH}_3 \)

(200) \( \text{Me} - \text{O}_2 \)

(201) \( \text{H} - \text{O}_2 \)

(202) \( R = \text{H} \)

(203) \( R = \text{Me} \)

(204) \( \text{R} = \text{H} \)

(205) \( \text{R} = \text{Me} \)

(206) \( n = 1 \)

(207) \( n = 2 \)

(208) \( X = \text{N} \)
\[ R = \text{OMe} ; \quad n = 4 \]  
\[ R = \text{CONH}_2 ; \quad n = 5 \]  
\[ R = \text{CO}_2\text{Et} ; \quad n = 5 \]  
\[ R = -O - \text{Het} \quad n = 5 \]  
\[ R = -O - \text{Het} \quad n = 3 \]  
\[ X = \text{COMe} \]  
\[ X = \text{N} \]
(221) \( R = \text{Me}(\text{CH}_2)_3; \ n = 2 \)

(222) \( R = \text{Me} \)

(223) \( R = \text{Ph} \)

(224) \( R = \text{Naphthalene} \)

(232) \[ \begin{array}{c}
\text{(233)} \ V = \text{NMe} \\
\text{(234)} \ V = \text{NMe} \text{ NMe} \\
\text{(235)} \ V = \text{S} \\
\text{(236)} \ V = \text{S} \text{ S} \\
\text{(237)} \ V = \text{S} \text{ S} \text{ S} 
\end{array} \]
(238) $X = \text{O}; \ n = 1$

(239) $X = \text{O}; \ n = 2$

(240) $X = \text{NH}; \ n = 2$

(241) $X = \text{CH}_2; \ n = 2$

(242) $n = 3$

(248) $n = 2$

(249) $n = 3$

DD- (267)
(R) - D-(291) $R = \text{Me}$

(S) - D-(292) $R = \text{Me}$

(S) - (293)
THE SYNTHESIS OF A CHIRAL RECEPTOR MOLECULE CONTAINING THREE CARBOHYDRATE RESIDUES WITHIN A 20-CROWN-6 CONSTITUTION

David G. Andrews, Peter R. Ashton, Dale A. Laidler, J. Fraser Stoddart, and John B. Woistenholme

Department of Chemistry, The University, Sheffield S3 7HF

The rationale behind designing and the approach to synthesizing chiral crown ethers incorporating three trigonally-disposed carbohydrate residues is presented as a prelude to attaining chiral discrimination in the complexation of (R)- and (S)-α-phenylethylammonium perchlorate.

In our search for chiral receptor molecules which will differentiate between the enantiomers of racemic substrates, optically-active macrocyclic polyethers incorporating carbohydrate residues have been derived directly or formally from L-threitol, D-mannitol, D-iditol, D-glucose, D-galactose, D-mannose, and D-altrose. Previously, however, we have built only one, or at most two, carbohydrate residues into 18- or 20-crown-6 constitutions. Inspection of Corey-Pauling-Koltun (CPK) space-filling molecular models led us to the belief that chiral recognition of racemic primary alkylammonium salts such as (RS)-PhCHMeNH₃⁺ClO₄⁻ (RS)-(1).HClO₄ might conceivably be improved by including three carbohydrate residues—two the same and one different—into the 18-crown-6 constitution. The general design of such a molecular receptor containing C₂ symmetry with large (L'), medium (M'), and small (S') cavities on each of the homotopic faces to match sterically the large (L), medium (M), and small (S) ligands attached to the chiral centres of (R)-1.HClO₄ and (S)-1.HClO₄ suggested the 18-crown-6 derivative DDL-(2) incorporating two 1,2:5,6-di-O-isopropylidene-D-mannitol 6-O-(3) residues and one 1,4-di-O-benzyl-L-threitol 2,7-(4) residue as a possible synthetic goal. However, we felt that molecular receptor complexes embracing attractive electronic interactions of a dipole-induced dipole type between a 1,3-dioxan ring and a phenyl group might lead to them being more highly structured with a better

\[\text{DDL-2} \quad R¹ = \text{O>Me R CH₂OCH₂Ph} \]

\[\text{(R)-1.HClO₄} \quad \text{Me(M)} \quad \text{CIO₄}⁻ \]

\[\text{(S)-1.HClO₄} \quad \text{Me(M)} \quad \text{CIO₄}⁻ \]
chance consequentially of exhibiting good chiral recognition towards (RS)-1-HClO₄. In this communication, we describe the synthesis of a 20-crown-6 derivative DDD-5 incorporating two 1,2:5,6-di-O-isopropylidene-D-mannitol D-(3) and one 1,3:4,6-di-O-methylene-D-mannitol D-(6) residue and report on some preliminary observations regarding its complexing and chiral recognition properties.

Diacetone-D-mannitol D-(3) was converted² into a mixture of its mono- D-(7) and di- D-(8) allyl ethers which were separated by medium pressure liquid chromatography (m.p.l.c.)¹⁰ (light petroleum, b.p. 60–80°C:Et₂O, 6.7:1 – 1:1) on SiO₂. Both D-7 and D-8 were subjected to ozonolysis in MeOH followed by reduction with NaBH₄ in MeOH/H₂O to give the 'half-extended' diol D-(9), [α]₀ + 8° (c 2.3,
Table. Temperature dependent $^1$H n.m.r. spectral data and kinetic and thermodynamic parameters for the 1:1 complexes between (R)- and (S)-1.HClO$_4$, and $^{12}$D-5.$^a$

<table>
<thead>
<tr>
<th></th>
<th>δ-H$^b$</th>
<th>T$_c$$^c$</th>
<th>Δν(-90°C),$^2$</th>
<th>k$_c$</th>
<th>ΔG$_c$$^a$</th>
<th>ΔH$_c$$^a$</th>
<th>kcal mol$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R) - isomer</td>
<td>5.06</td>
<td>-59</td>
<td>28.9</td>
<td>64</td>
<td>-10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(S) - isomer</td>
<td>4.60</td>
<td>-64</td>
<td>19.6</td>
<td>44</td>
<td>11.5</td>
<td></td>
<td></td>
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</tbody>
</table>

$^a$ Spectra were recorded in CD$_2$Cl$_2$ at 220 MHz on a Perkin Elmer R34 spectrometer with Me$_4$Si as internal standard. Abbreviations used are: $T_c$, coalescence temperature; Δν, frequency separation for H of the OCH$_2$O protons at -90°C; k$_c$, exchange rate constant at $T_c$ calculated from the expression $k_c = Δν/2π$; ΔG$_c$, free energy of activation at $T_c$ calculated from the Eyring equation.

$^b$ Chemical shifts of the OCH$_2$O protons at +30°C.

$^c$ This signal separates out into two doublets centred on δ 5.09 and 5.18 at -90°C.

CHCl$_3$ as an oil and the "fully-extended" diol -9 (10), m.p. 76-77°C, [α]$_D$ + 14.2° (c 1.65, CHCl$_3$). Treatment (cf. ref. 12) of -9 in Me$_2$NCHO at 35°C with 1.0 molar equivs. of BuMe$_2$SiCl in the presence of Imidazole as base gave (88%) pure mono-t-butyldimethyilsilyl ether -11, [α]$_D$ + 3° (c 2.4, CHCl$_3$) without resort to chromatography. Partial silylation of -10 with 1.0 molar equivs. of BuMe$_2$SiCl afforded a mixture (46 and 15%, respectively) of the mono- -12, [α]$_D$ + 13.0° (c 3.0, CHCl$_3$) and di- -13, [α]$_D$ + 14.0° (c 1.8, CHCl$_3$) silyl ethers which were separated from each other and starting material by m.p.l.c. (light petroleum, b.p. 60-80°C : MeCO$_2$Et, 3:1) on SiO$_2$. After near quantitative (98%) conversion of -12 into its tosylate -14 (11), [α]$_D$ + 12.6° (c 1.8, CHCl$_3$), -14 was condensed with -15 in tetrahydrofuran in the presence of BuOK at 60°C to give the disilyl ether -15, [α]$_D$ + 19.7° (c 0.97, CHCl$_3$) in 23% yield after m.p.l.c. (CHCl$_3$ : MeCO$_2$Et, 9:1) on SiO$_2$. Treatment (cf. ref. 12) of -15 with BuMe$_2$SiF in tetrahydrofuran at 35°C afforded (77%) the diol -16 (16), [α]$_D$ + 23.8° (c 1.5, CHCl$_3$) after column chromatography (MeCO$_2$Et) on SiO$_2$. Conversion (80% isolated yield) of -16 into its pure ditosylate -17 (17), [α]$_D$ + 16.0° (c 0.88, CHCl$_3$) proceeded smoothly in the presence of 3.5 molar equivs. of TsCl in C$_2$H$_5$N below 0°C. Condensation (NaH/Me$_2$SO) of -6 with -17 at 60°C afforded in 42% yield—after column chromatography (Et$_2$O) on SiO$_2$—the 20-crown-6 derivative -18 (5), m.p. 50-55°C, [α]$_D$ - 1.6° (c 0.99, CHCl$_3$), $^1$H n.m.r. data: δ (CD$_2$Cl$_2$) 1.34 and 1.41 (2xs, 24H, 8xCH$_3$), 3.27-4.38 (m, 36H, all other protons other than OCH$_2$O protons), and 4.62 and 5.03 (4H, AB system, $^3$J$_{AB}$ = 6 Hz, OCH$_2$O).

Variable temperature $^1$H n.m.r. spectroscopy in CD$_2$Cl$_2$ of the 1:1 complexes formed between (R)- and (S)-1.HClO$_4$, and $^{12}$D-5 resulted in each case in the separation of the A portion$^3$ of the AB system for the OCH$_2$O protons into two doublets at low temperatures (f.e. -90°C). This behaviour indicates that the phenyl groups are interacting electronically with the 1,3-dioxan rings and that both complexes are highly structured. The kinetic and thermodynamic data for these 1:1 complexes are summarized in the Table. The ΔG$_c$ values can be equated (cf. ref. 8) with the free energies of activation (ΔG$_a$) for dissociation of the
complexes in a process in which the cations are exchanging between the homotopic faces of DDD-5. On the assumption that the free energies of the transition states for dissociation of the complexes are characterized predominantly by the dissociated crown and enantiomeric cations, the difference of 0.9 kcal mol\(^{-1}\) in the \(\Delta^T\) values reflects (cf. ref. 8) the difference in the ground state free energies of the diastereoisomeric complexes. Thus, DDD-5 exhibits modest chiral recognition towards (RS)-\(\text{HClO}_4\) in favour of the (S)-isomer at low temperatures in \(\text{CD}_2\text{Cl}_2\). This observation is in accordance with the prediction gleaned from inspection of CPK space-filling molecular models. These show that the (S)-isomer of \(\text{HClO}_4\) experiences (see ref. 4) a better match electronically and sterically with DDD-5 than does the (R)-isomer. Clearly, chiral crown ethers containing three carbohydrate residues disposed trigonally have much more potential to discriminate between enantiomeric salts than do chiral crown ethers containing two carbohydrate residues disposed diagonally.

References and Footnotes
1. Address all correspondence to this author at the Corporate Laboratory, Imperial Chemical Industries Ltd., P.O. Box No. 11, The Heath, Runcorn, Cheshire WA7 14QE.
4. We have indicated by means of arrows and the symbols L', M', and S' the relative dispositions of the large, medium, and small cavities on the top face of the formula for DDL-2. If the 1,3-dioxan ring in DDD-5 underneath the circular area denoted by L' is assumed to interact attractively with a phenyl group, then the medium and small cavities on the top face have the relative dispositions defined by M' and S' respectively within the circular areas shown.
10. A detailed specification of our 'home-built' n.p.l.c. system will be supplied upon request.
11. The compositions of all new compounds were confirmed by elemental analyses. Structural assignments were based upon the results of mass spectrometry and \(^1\text{H}\) n.m.r. spectroscopic evidence.
13. In each case, the B portion was obscured by signals for other protons in the 1:1 complexes at low temperatures.
14. An attempt to assess the chiral recognition properties of DDD-5 towards (RS)-\(\text{PhCHMeNH}_3^+\text{PF}_6^-\), following equilibration of the diastereoisomeric complexes in the presence of excess of racemic salt and LiPF\(_6\) between CCl\(_3\) and D\(_2\)O (cf. ref. 2), was thwarted by lack of resolution in the \(^1\text{H}\) n.m.r. spectrum at 220 MHz of any of the \(^1\text{H}\) n.m.r. probes in the previously enantiomeric salts.
THE COMPLEXING PROPERTIES OF A CHIRAL 18-CROWN-6 DERIVATIVE INCORPORATING A 2,5-ANHYDRO-D-MANNITOL RESIDUE. A CONSTITUTIONAL AND STEREOCHEMICAL MEANS OF ENHANCING COMPLEXATION

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Measurements of both a thermodynamic and kinetic nature establish that an 18-crown-6 derivative incorporating a 'chiral diethylene glycol' unit in the shape of a 2,5-anhydro-D-mannitol residue forms extremely strong complexes with alkali metal, NH₄⁺, and R'NH₃⁺ ions.

Our appreciation that the stereochemistry of noncovalent interactions in metal and organic cationic complexes of crown compounds plays a crucial role in determining their stabilities has prompted us to try and optimise the complexing ability of chiral 18-crown-6 derivatives containing carbohydrate residues. Examination of framework molecular models indicates that incorporation of a constrained 'diethylene glycol' fragment in the form of either a cis- or trans-fused tetrahydrofuranyl-2,5-dimethyl unit into the 18-crown-6 constitution can lead to improved orientations of oxygen atoms with respect to the bound cation—metal or primary alkylammonium—compared with those observed for complexes of 18-crown-6. Indeed, there is evidence that tetrahydrofurano-18-crown-6 compounds containing one, two, and three fused 5-membered rings—usually obtained and evaluated as diastereoisomeric mixtures—form slightly stronger complexes with Bu⁴NH⁺SCN⁻ in CDCI₃ than does 18-crown-6 itself. Fortunately, there is a readily available source of a 'chiral diethylene glycol' unit in 2,5-anhydro-D-mannitol D-(1), which can be obtained in two steps from D-glucosamine hydrochloride. In this communication, we describe the preparation of the 18-crown-6 derivative D-(2) and report on (ii) a preliminary assessment of the binding properties of D-2 towards alkali metal, NH₄⁺, and RNH₃⁺ ions.

Treatment (cf. ref. 10) of D-3 in Me₂NCHO with 2.2 molar equivs. of Bu⁴Me₂SiCl in the presence of imidazole (5 molar equivs.) led to a good yield (62%) of the bis-2-butyldimethylsilyl ether D-(3), m.p. 40-42⁰, [α]B +19.0⁰ (c 0.4, CHCl₃) after medium pressure liquid chromatography (Et₂O:light petroleum, b.p. 60-80⁰, 2:1) on SiO₂. Methylation

\[ R^1 \quad R^2 \]
\[ D-1 \quad H \quad H \]
\[ D-2 \quad \text{SiMe₂Bu}^+ \quad H \]
\[ D-3 \quad \text{SiMe₂Bu}^+ \quad \text{Me} \]
\[ D-5 \quad H \quad \text{Me} \]
Table 1. The association constants \( K_a \) and derived free energies of complexation \( (\Delta G) \) for the formation of 1:1 complexes between \( \mathcal{D}-2 \) and some selected picrate salts in \( \text{CDCl}_3 \) at 25°C.

<table>
<thead>
<tr>
<th>Cation</th>
<th>Li⁺</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Rb⁺</th>
<th>NH₄⁺</th>
<th>MeNH₃⁺</th>
<th>Bu⁺NH₃⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_a \times 10^{-6} ) (M⁻¹)</td>
<td>0.075</td>
<td>1.30</td>
<td>110.0</td>
<td>4.90</td>
<td>12.0</td>
<td>1.60</td>
<td>0.25</td>
</tr>
<tr>
<td>( \Delta G ) (kcal mol⁻¹)</td>
<td>-6.6</td>
<td>-8.3</td>
<td>-11</td>
<td>-9.1</td>
<td>-9.7</td>
<td>-8.5</td>
<td>-7.4</td>
</tr>
</tbody>
</table>

The \( K_a \) values were determined by a u.v. spectroscopic method following extraction of aqueous picrate solutions with \( \text{CDCl}_3 \) solutions of \( \mathcal{D}-2 \) (see K.E. Koenig, R.C. Helgeson, and D.J. Cram, *J. Amer. Chem. Soc.*, 98, 4018 (1976) and S.S. Moore, T.L. Tarnowski, M. Newcomb, and D.J. Cram, ibid., 98, 6398 (1977)).

The association constants \( (K_a) \) for 1:1 complex formation between \( \mathcal{D}-2 \) and selected picrate salts are listed in Table 1. The derived free energies of complexation \( (\Delta G) \) indicate that, although the 'all-gauche-0-C-C-0' conformation is denied to the macrocyclic ring, \( \mathcal{D}-2 \) still forms very strong complexes with alkali metal, \( \text{NH}_4^+ \), and \( \text{RNH}_3^+ \) ions. At least two factors—one constitutional and the other stereochemical—probably contribute to this observation. They are (i) the increased basicity of tetrahydrofuranyl oxygen atoms over 'ordinary' crown ether oxygen atoms and (ii) the increased cooperativity of binding sites indicated from inspection of molecular models—brought about by incorporation of a trans-fused tetrahydrofuranyl residue into the 18-crown-6 constitution. The \( C_2 \) symmetry which characterises \( \mathcal{D}-2 \) means that dynamic \( ^1H \) n.m.r. spectroscopy can be employed to study the kinetics of exchange of \( \text{RNH}_3^+ \) cations between opposite faces of isometric 1:1 complexes. The results of these investigations, which rely upon the temperature dependent behaviour of the signals for \( \text{H}-2 \) and \( \text{H}-5 \)—and in some cases, for the \( \text{OMe} \) protons—of \( \mathcal{D}-2-\text{RNH}_3^+X^- \) complexes in \( \text{CD}_2\text{Cl}_2 \) are recorded in Table 2. Since the 18-membered ring of \( \mathcal{D}-2 \) cannot undergo ring inversion, the \( \Delta G \) values can be equated with the free energies of activation \( (\Delta G^\ddagger) \) for dissociation of the isometric complexes. Reference to the data listed in Tables 1 and 2 allows the following observations to be made: (i) The order of stabilities for the alkali metal cations as their picrate salts is \( K^+ > \text{Rb}^+ > \text{Na}^+ > \text{Li}^+ \) as expected for an 18-crown-6 derivative. (ii) The pircate salts of \( \text{RNH}_3^+ \) cations decrease in stability in the order for \( \text{R} \) of \( \text{H} > \text{Me} > \text{Bu}^+ \), a trend which probably reflects the decreasing stabiilisation of the complexes through pole pole interactions and hydrogen bonding with the anion as much as the increasing steric bulk of the \( \text{R} \) group across the series. (iii) The kinetic stabilities...
Table 2. Temperature dependent $^1$H n.m.r. spectral data and kinetic and thermodynamic parameters for the 1:1 complexes formed between selected RNH$_3^+$X salts and $\text{C}_{12}$

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>$^1$H n.m.r. probes (6 at 30°)</th>
<th>$T_c$[°C]</th>
<th>$\Delta_v$[Hz]</th>
<th>$k_c$[s$^{-1}$]</th>
<th>$\Delta G^\circ$[kcal mol$^{-1}$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me SCN</td>
<td>H-2,5</td>
<td>(4.12)</td>
<td>-80</td>
<td>59 (-95)</td>
<td>131</td>
<td>9.3</td>
</tr>
<tr>
<td>Me CIO$_4^-$</td>
<td>H-2,5</td>
<td>(4.10)</td>
<td>-82</td>
<td>58 (-95)</td>
<td>129</td>
<td>9.2</td>
</tr>
<tr>
<td>Et SCN</td>
<td>H-2,5</td>
<td>(4.11)</td>
<td>-59</td>
<td>54 (-90)</td>
<td>120</td>
<td>10.5</td>
</tr>
<tr>
<td>Pr SCN</td>
<td>2 x OMe</td>
<td>(3.33)</td>
<td>-75</td>
<td>8 (-85)</td>
<td>18</td>
<td>9.9</td>
</tr>
<tr>
<td>Pr CIO$_4^-$</td>
<td>H-2,5</td>
<td>(4.12)</td>
<td>0</td>
<td>40 (-28)</td>
<td>89</td>
<td>13.5</td>
</tr>
<tr>
<td>Bu SCN</td>
<td>H-2,5</td>
<td>(4.15)</td>
<td>-35</td>
<td>66 (-60)</td>
<td>147</td>
<td>11.5</td>
</tr>
<tr>
<td>Bu CIO$_4^-$</td>
<td>H-2,5</td>
<td>(4.15)</td>
<td>-15</td>
<td>61 (-70)</td>
<td>135</td>
<td>12.5</td>
</tr>
<tr>
<td>PhCH$_2$ SCN</td>
<td>H-2,5</td>
<td>(4.08)</td>
<td>-40</td>
<td>10 (-50)</td>
<td>22</td>
<td>12.1</td>
</tr>
<tr>
<td>PhCH$_2$ CIO$_4^-$</td>
<td>H-2,5</td>
<td>(4.08)</td>
<td>-50</td>
<td>81 (-80)</td>
<td>179</td>
<td>10.6</td>
</tr>
<tr>
<td>(R)-PhCHMe SCN</td>
<td>H-2,5</td>
<td>(4.10)</td>
<td>-50</td>
<td>66 (-80)</td>
<td>147</td>
<td>10.0</td>
</tr>
<tr>
<td>(R)-PhCHMe CIO$_4^-$</td>
<td>H-2,5</td>
<td>(4.10)</td>
<td>-54</td>
<td>62 (-80)</td>
<td>138</td>
<td>10.5</td>
</tr>
<tr>
<td>(S)-PhCHMe SCN</td>
<td>H-2,5</td>
<td>(4.08)</td>
<td>-54</td>
<td>57 (-70)</td>
<td>126</td>
<td>10.6</td>
</tr>
<tr>
<td>(S)-PhCHMe CIO$_4^-$</td>
<td>H-2,5</td>
<td>(4.05)</td>
<td>-55</td>
<td>61 (-90)</td>
<td>135</td>
<td>10.5</td>
</tr>
</tbody>
</table>

aAll spectra were recorded in CD$_2$Cl$_2$ at 220 MHz on a Perkin Elmer R34 spectrometer with Me$_4$Si as "lock" and internal standard.
bAbbreviations used are: $T_c$, coalescence temperature; $\Delta_v$, frequency separation of the appropriate $^1$H n.m.r. probe with the temperature at which it was measured indicated in parenthesis; $k_c$, exchange rate constant at $T_c$ calculated from the expression $k_c = \frac{\Delta v}{2}$; $\Delta G^\circ$, free energy of activation calculated from the Eyring equation.

of the SCN$^-$ and CIO$_4^-$ salts depend upon the nature of the cation and the sequence for R of Pr$^+$ > Bu$^+$ > PhCH$_2$ > (R)-PhCHMe ≅ (S)-PhCHMe ≥ Et > Me holds more or less in accordance with previous observations. (iv) Complexes involving CIO$_4^-$ salts are generally more stable kinetically than those involving SCN$^-$ salts, although MeNH$_3^+$X and (S)-PhCHMeNH$_3^+$X provide exceptions.

The following conclusions can be drawn: (i) Complexation of cations by 18-crown-6 derivatives can be enhanced by constitutional and stereochemical means. (ii) Differences in $\Delta G$ values are not necessarily reflected in differences in $\Delta G^\circ$ values, i.e. the free energies of association can vary depending upon the nature of the crown (cf. ref. 3) and the cation. (iii) The nature of the cation can influence the relative kinetic complexing strengths of complexes associated with different anions.

References and Footnotes

1. Address all correspondence to this author at the Corporate Laboratory, Imperial Chemical Industries Ltd., P.O. Box No. 11, The Heath, Runcorn, Cheshire WA7 4QE.
6. It has not escaped our attention that tetrahydrofuranyl units are encountered commonly in naturally-occurring ionophores.

7. Dr. R.A. Wall of Edinburgh University extolled the virtues of this source of chirality to us in April, 1977.

8. The 'chiral diethyleneglycol' unit in $\text{D-1}$ to $\text{D-5}$ is indicated by means of thickened bonds in the formulae.


11. *D-1* is most readily purified by converting (Ac$_2$O/pyridine) it to its tetraacetate, $[\alpha]_D + 33.0^\circ$ (c 1.12, CHCl$_3$) (R.U. Lemieux and B. Fraser-Reid, *Canad. J. Chem.*, 42, 547 (1964) report $[\alpha]_D = 27.3$ (c 4.2, CHCl$_3$)) and subjecting it to medium pressure liquid chromatography (light petroleum, b.p. 60-80°C : EtOAc, 3:1) on SI02 before regenerating (NaOMe/MeOH) $\text{D-1}$.

12. The compositions of all new compounds were confirmed by elemental analysis. Structural assignments were based upon the results of mass spectrometry and $^1$H n.m.r. spectroscopic evidence.

13. See footnote 9 in ref. 10.


15. By way of comparison, the $K_a \times 10^{-6}$ values for the 1:1 complexes formed between methyl 4,6-O-benzylidene-2,3-dideoxy-3-O-glucopyranosidol(2,3-b)[1,4,7,10,13,16]hexaoxaacyclo-octadecane (R.B. Pettman and J.F. Stoddart, *Tetrahedron Lett.*, 457 (1979)) and the picrates of Li$^+$, Na$^+$, K$^+$, Rb$^+$, NH$_3^+$, and Bu$_4$NH$^+$ in CDCl$_3$ are (R.B. Pettman and J.F. Stoddart, unpublished results) 0.073, 0.13, 0.53, 0.22, 0.24, 0.011, and 0.002 M$^{-1}$ respectively.


22. In the case of the $\text{D-2-MeNH}_2X^-$ complexes, it is conceivable that $X^-$ ions—can hydrogen bond to the acidic Me group rather than compete with the crown ether oxygens for hydrogen bonding to the NH$_3^+$ centre. Thus, we caution against any generality for the recent claim (see ref. 21) that 'the structure of the cation has little effect on the relative complex stabilities for different anions.'

23. Inspection of the relevant data in Tables 1 and 2 reveals that although the MeNH$_2^+$ cation forms a stronger complex with $\text{D-2}$ under equilibrium conditions than does the Bu$_4$NH$_3^+$ cation, the MeNH$_2^+$ cationic complexes are kinetically much less stable than the Bu$_4$NH$_3^+$ cationic complexes. Despite the fact that an anion effect cannot be discounted as the source of at least a partial explanation for this observation, it seems likely that the differences in $\Delta G$ values are not always reflected (cf. ref. 21) in differences in $\Delta H$ values when the cations are markedly different in constitution.