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Organic Reactivity and Through-Space Effects

James J. Brown

Thesis presented for the degree of
Doctor of Philosophy
The University of Edinburgh
2014
Declaration

This thesis is the original work of the author except where specific reference is made to other sources. The work was performed in the School of Chemistry at the University of Edinburgh. This thesis has not been submitted in whole, or in part for any other degree.

James J. Brown
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Last, but by no means least, thanks to my family for their continued support.
Abstract

Chapter 1 presents a mini-review of the prominent theoretical models which are employed in the prediction of the outcome of organic chemical reactions. The chapter covers the most widely used empirical and semi-empirical models, as well as some more recently developed models. Most have a common theme in that they were developed using electrophilic aromatic substitution as a model reaction.

Chapter 2 describes the development of a predictive model based on the average local ionisation energy. The model is shown to be of use in predicting both the regioselectivity and relative reactivity of a wide range of molecules in electrophilic aromatic substitution reactions. An attempt is made to expand the model beyond electrophilic aromatic substitution to various other electrophilic reactions.

Chapter 3 details the investigation into the predicted enhancement of reactivity of aromatic rings. Calculations of electrostatic surface potential surfaces show that the proximity of an electron rich atom to an aromatic ring increases the electron density of the ring. Analysis of the local ionisation energy surfaces of these molecules suggests that the reactivity of these rings towards electrophiles is also increased. Preliminary studies on model systems using NMR spectroscopy aim to determine whether this effect can be observed experimentally.

Chapter 4 introduces a method for applying the average local ionisation energy to nucleophilic reactions. The ability of the model to predict the regiochemical outcome and relative reaction rates of various molecules is examined in a variety of reaction types, including nucleophilic aromatic substitution.

Chapter 5 reports studies into the polarisation-induced cooperative effects that exist between hydrogen bonding groups. The cooperative effect has been measured quantitatively in some simple hydroxybenzene derivatives. An improved understanding of this effect, developed using small molecule models, should lead to an improved ability to predict the extent of this effect in larger systems.
Lay Summary

Chapter 1 presents a review of the prominent theoretical models employed in the prediction of the outcome of chemical reactions. The chapter covers the most widely used models, as well as some more recently developed models. Most have a common theme in that they were developed using the same type of reaction, known as electrophilic aromatic substitution, as a model reaction.

Chapter 2 describes the development of a predictive computational model based on a property called the average local ionisation energy, which is a measure of the energy required to remove an electron from a molecule. The model is shown to be of use in predicting the outcome of a wide range of reactions.

The local ionisation energy model discussed in chapter 2 predicts that the rate of reaction of some molecules can be enhanced under specific conditions. Chapter 3 details the investigation into this predicted enhancement of reaction rate, using practical methods to determine whether this effect can be observed experimentally.

Chapter 4 introduces a method for applying the average local ionisation energy to a different reaction type, known as nucleophilic substitution. The ability of the model to predict the outcome and rate a reaction of various molecules is examined.

When two alcohol groups are present on a single molecule, interaction between the two groups can affect the strength of the interaction of one of the groups with another molecule. Chapter 5 details studies into the extent of this effect in simple alcohol molecules. An improved understanding of this effect, developed with small molecules, should give a greater understanding of its importance in larger, more complex systems.
List of Publications

Parts of this thesis have contributed to the following publications:

Chapter 2
Aromatic Reactivity Revealed: Beyond Resonance Theory and Frontier Orbitals
*Chem. Sci.* 2013, 4, 1772 - 1780
Brown, J. J., Cockroft, S. L.

Chapter 5
Co-operativity in Hydrogen Bonding Networks
In Preparation
Brown, J. J., Dominelli-Whitely, N., Paterson, H., Cockroft S. L.

Effects of Hydrogen Bond Geometry on Cooperative Effects in Networks of Hydrogen Bonds
In Preparation
Brown, J. J., Dominelli-Whitely, N., Cockroft S. L.
## Abbreviations

<table>
<thead>
<tr>
<th>Symbol</th>
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<tbody>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>σ</td>
<td>Hammett Substituent Constant</td>
</tr>
<tr>
<td>ρ</td>
<td>Hammett Reaction Constant</td>
</tr>
<tr>
<td>B3LYP</td>
<td>Becke, three-parameter, Lee Yang Parr</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>d</td>
<td>deuterated</td>
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<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
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<tr>
<td>E</td>
<td>Electrophilicity Parameter</td>
</tr>
<tr>
<td>E_a</td>
<td>Electrophile Affinity</td>
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<tr>
<td>EAS</td>
<td>Electrophilic Aromatic Substitution</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron Donating Group</td>
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<tr>
<td>ESP</td>
<td>Electrostatic Surface Potential</td>
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<tr>
<td>EWG</td>
<td>Electron Withdrawing Group</td>
</tr>
<tr>
<td>eV</td>
<td>electronvolts</td>
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<tr>
<td>F</td>
<td>Field Substituent Constant</td>
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<tr>
<td>FMO</td>
<td>Frontier Molecular Orbital</td>
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<tr>
<td>HF</td>
<td>Hartree-Fock</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>IE</td>
<td>Ionisation Energy</td>
</tr>
<tr>
<td>I_{S,min}</td>
<td>Minimum Local Ionisation Energy Value</td>
</tr>
<tr>
<td>J</td>
<td>Coupling Constant</td>
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<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperbenzoic Acid</td>
</tr>
<tr>
<td>N</td>
<td>Nucleophilicity Parameter</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
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<tr>
<td>NCS</td>
<td>N-Chlorosuccinimide</td>
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<tr>
<td>NIS</td>
<td>N-Iodosuccinimide</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PAH</td>
<td>Polycyclic Aromatic Hydrocarbon</td>
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<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R</td>
<td>Resonance Substituent Constant</td>
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<tr>
<td>s</td>
<td>singlet</td>
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<tr>
<td>t</td>
<td>triplet</td>
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5.5 Computational Studies
5.6 Binding Studies
5.7 Conclusions and Future Work
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Chapter 1

Models of Organic Reactivity

Abstract

One of the primary driving forces in the field of physical organic chemistry is the desire to explain and predict the outcome of chemical reactions based on a mechanistic understanding. Many theories and models have been proposed to account for the diverse reactivity observed in organic chemistry. This chapter presents a non-exhaustive review of some of the most widely used simple models that are used in rationalising the outcome of organic reactions. In addition, some recently proposed reactivity models are covered.

1.0. Introduction

The prediction of reactivity is one of the cornerstones of synthetic chemistry. The intrinsic link between theory and experiment is fundamental to the development of more efficient synthetic methodology. Indeed, the development of many of the classic theories underpinning chemistry such as valence bond theory,\cite{1,2} substituent effects,\cite{3,4} resonance theory,\cite{5} and Frontier Molecular Orbital (FMO) theory,\cite{6,7} were developed in close alignment with experiment. These and other models have given insight into mechanistic processes of practical importance in the control of chemical reactions.\cite{8}

1.1. Aromatic Chemistry and its Role in Theoretical Developments

The chemistry of aromatic molecules has played a pivotal role in shaping foundational concepts such as valence bond theory,\cite{1,2} substituent effects,\cite{3,4} resonance theory,\cite{5} and Frontier Molecular Orbital (FMO) theory,\cite{6,7} as is discussed later in this chapter. Aromatic chemistry is a vast field of study which despite being one of the oldest branches of organic chemistry still has great significance in both industry and academia. Many natural products, which are of interest to synthetic chemists as target molecules, contain aromatic or heteroaromatic rings. Similarly, marketed oral drugs
contain a median of three rings.\textsuperscript{[9]} Indeed, the discovery of a diverse range of pharmaceuticals, agrochemicals and materials has depended upon methods for predicting and controlling the regiochemistry of aromatic functionalisation reactions.\textsuperscript{[10-17]}

Before considering the contributions that aromatic chemistry has made to the development of reactivity models, it is first important to be familiar with the characteristics of aromatic functionalisation reactions. The classic methods for the preparation and derivatisation of aromatic and heteroaromatic compounds are largely concerned with electrophilic substitution reactions,\textsuperscript{[18]} which typically proceed \textit{via} the same basic mechanism (Figure 1.1).

![Figure 1.1 – Reaction profile accompanying an electrophilic aromatic substitution mechanism.](image)

The first step of the reaction is usually rate-determining,\textsuperscript{[19]} since the addition of the electrophile to the aromatic ring to form the ‘Wheland intermediate’,\textsuperscript{[3]} also called the arenium ion,\textsuperscript{[20]} breaks the aromaticity of the benzene ring. Since the transition state for this step is closer in energy to the intermediate than the starting materials, the Hammond postulate\textsuperscript{[21]} infers that the structure of the transition state more closely resembles that of the intermediate. The second, much faster step involves removal of a proton from the arenium ion by a nucleophile, restoring the aromaticity of the ring and resulting in the substitution product. Since the nucleophile is removing a proton
from the arenium ion, it can be said to be acting as a Brønsted base.

Dewar first proposed that electrophilic aromatic substitution reactions involved the formation of a \( \pi \)-complex prior to arenium ion formation.\(^{[22]}\) These \( \pi \)-complexes can be observed during the course of the reaction because they are coloured, while some have been isolated by crystallisation.\(^{[23]}\) In addition, spectroscopic observations of arenium ions by NMR spectroscopy\(^{[24]}\) and by transient absorption spectroscopy\(^{[25]}\) provide strong evidence for a mechanism proceeding via an arenium ion intermediate.

![Scheme 1.1 – Reaction scheme of electrophilic aromatic substitution showing the formation of the \( \pi \)-complex prior to arenium ion formation as proposed by Dewar.\(^{[22]}\)](image)

Scheme 1.2 – Possible products of electrophilic aromatic substitution of mono-substituted benzenes.

In contrast to the relatively simple reaction mechanism, understanding the outcome of electrophilic aromatic substitution reactions can be quite complex; multiple reaction outcomes are possible even considering the simple case of mono-substitution reactions in mono-substituted benzenes. This is illustrated by the four possible products that can result from mono-electrophilic aromatic substitution of mono-substituted benzenes as shown in Scheme 1.2. The situation can be further complicated by the possibility that some products may be formed by rearrangement reactions of another product,\(^{[26-28]}\) particularly when it may be difficult to determine when rearrangement reactions have taken place.\(^{[29]}\)

Reaction conditions are also important in determining the outcome of the reaction. For example, the ortho/para-ratio observed in the chlorination of toluene can
vary from approximately 30:60 to 60:30 depending on the conditions used. The sulfonation of naphthalene gives two different products depending on the temperature of the reaction. At 80°C the system does not reach equilibrium and is therefore under kinetic control, resulting in the α-naphthalenesulfonic acid isomer,[30] while at 160°C equilibrium is reached and the thermodynamically more stable β-naphthalenesulfonic acid isomer is formed.[31]

The simplicity of the reaction mechanism combined with the numerous possible reaction products makes electrophilic aromatic substitution an attractive reaction to test the predictive power of a theoretical model, and accordingly many of the theories discussed in this chapter were first proposed due to their ability to predict the outcome of reactions of this type.

1.2. Empirical Models

Empirical models are those based on experimental observations, as opposed to those which are derived from mathematical relationships. Many of the earlier models of reactivity were developed empirically, being based on direct observation of experimental evidence rather than being deduced or derived from some theoretical assumptions. Some of the best-known empirical relationships include resonance theory[32] and the Hammett linear free energy relationship.[33]

1.3. Resonance Theory

The resonance effect (also known as the mesomeric effect) refers to the delocalisation of electrons in certain molecules, including aromatic compounds. Resonance theory in combination with the Hammond postulate allows the outcome of the reaction to be deduced as substituents are varied (Figure 1.2, page 15). The approach involves drawing the resonance structures of the arenium ion intermediates in the reaction while assuming that the transition state in the rate determining step is stabilised or destabilised by the same electronic factors that influence the stability of the intermediates.[5]
If X is an electron-donating group (EDG) then the canonical forms in the ortho and para-substitution pathways where the positive charge is located on the carbon bearing the X substituent are energetically favoured over those in the meta-substitution pathway since the positive charge is stabilised by donation of electrons into the aromatic ring by X. Resonance theory would therefore predict that when X is an electron-donating group, the reaction would predominantly give ortho/para-substituted products.

If X is an electron-withdrawing group (EWG) then the canonical forms in the ortho and para-substitution pathways are destabilised since electrons are removed from the aryl ring which would otherwise stabilise the positive charge. In this case the meta-substituted isomers would be expected to be the major products because the intermediates in the ortho and para-pathways are less stable than those in the meta-pathway. EWGs are therefore known as meta-directing groups not because they stabilise this reaction pathway, but because the other pathways are more destabilised, making them even less favourable. It is widely accepted that in mono-substituted benzene compounds electron-donating groups activate the aromatic ring towards electrophilic substitution reactions, making it more reactive than benzene itself, while
electron-withdrawing groups deactivate the ring. In multiply-substituted benzenes the properties of the molecule are dominated by the strongest electron-donating group.

Resonance theory is widely used by organic chemists in a qualitative manner, but it can be used quantitatively,[34] while the resonance energy (the energy by which an aromatic molecule is stabilised compared to a system with the same number of isolated double bonds - for example, benzene is 152 kJ more stable than the hypothetical cyclohexatriene molecule[35]) can give an estimate of the degree of aromaticity of a compound.[36]

The advantage of resonance theory lies in the simplicity of its core concepts. It is easy to apply to benzene derivatives and is generally able to predict the outcome of reactions in many simple heterocycles. However, its simplicity and ease of application can quickly be lost on moving to slightly more complicated structures; even a relatively simple molecule such as isoquinoline has 24 resonance structures to consider.[37]

A further limitation of resonance theory is that it is unable to account for subtle differences in the ortho/para product ratio in some cases where inductive effects are not negligible. The phenoxide anion, for example, is correctly predicted to react in the ortho and para positions, however resonance theory predicts that 66% of the product will be the ortho isomer, whereas the observed yield of the ortho isomer is often more than 80%. Another example is provided by the halobenzenes, which are ortho/para-donating yet weakly deactivating.

Given the limitations of resonance theory, it is clear that other approaches are needed to accurately predict the outcome of electrophilic aromatic substitution reactions, particularly for more complex molecules with more than one aromatic ring. The Hammett linear free energy relationship[4] is one such approach which has been, and continues to be successfully employed in this regard. The Hammett relationship also has the advantage that it can be applied to polycyclic aromatics.[41]

1.4. Hammett Linear Free Energy Relationship

The Hammett linear free energy relationship is defined by equation 1.1 (hereafter called ‘the Hammett equation’). This was introduced in 1937 and provides a measure of the effect of a substituent in the meta or para positions of a substituted aryl ring on
the rate of reaction or the position of an equilibrium.[4] The ionisation of benzoic acid at 25°C (Scheme 1.3) is used as a reference reaction.

\[
\log \frac{K}{K_0} = \sigma \rho
\]

Equation 1.1

Where \( K \) and \( K_0 \) are the equilibrium constants for a given reaction with substituent \( R \) and the equilibrium constant of the reference reaction where \( R \) is replaced by a hydrogen atom, respectively. The substituent constant \( \sigma \) quantifies the resonant contributions of the substituent in addition to field effects and inductive electron withdrawal and donation that is not taken into account using resonance structures. The reaction constant \( \rho \) describes the sensitivity of a given reaction to substituent effects relative to the ionisation of benzoic acid. An important consequence of the Hammett equation is the partitioning of the two constants; \( \sigma \) depends only on the substituent, while \( \rho \) depends only on the type of reaction. Rate constants \( k \) and \( k_0 \) can also be used in place of equilibrium constants. For multiply substituted benzenes, the effects of individual substituents on the \( pK_a \) of aromatic compounds is essentially additive.[42]

The application of the Hammett equation to polycyclic aromatic compounds was achieved[41] using calculated substituent constants.[43]

Scheme 1.3 – the ionisation of benzoic acid, used as the reference reaction in the definition of Hammett constants.

The standard Hammett substituent constant, \( \sigma \) does not distinguish between the field/inductive and resonance contributions to the electron-withdrawing or donating properties of a substituent. Substituted bicyclooctane carboxylic acids have been proposed to allow the elucidation of the inductive contribution of a substituent.[44] In these systems resonance is not possible through the saturated hydrocarbon framework separating the substituent from the acid (Figure 1.3), therefore any substituent effect
must be due to inductive donation or withdrawal of electrons. It follows that the resonance contribution to $\sigma$ is calculated by the difference between the substituent constant $\sigma$ and the inductive parameter, $I$. However, one limitation of this approach is that the contributions from field and inductive effects cannot be dissected, since both effects have similar influences on the ionisation of the carboxylic acid group.

![Figure 1.3 - The bicyclooctane carboxylic acid motif used to determine the inductive contribution of a substituent X.](image)

Hammett constants are commonly used to estimate how the reactivity of an aromatic ring is affected by substituents, and they have been shown to correlate well with $pK_a$ values,\cite{45} core electron binding energies,\cite{46} and electrostatic potential (ESP) minima.\cite{42} Calculated ESP surfaces have been used to determine the substituent constants in multiply substituted benzenes.\cite{42} A high-throughput method for the determination of Hammett constants using electrospray mass spectrometry was developed relatively recently.\cite{47}

The major drawback of the Hammett equation is that it cannot be applied to ortho-substituted compounds since steric and through-space field effects (which the equation does not consider) have a far greater influence here than they do in either meta or para-substituted compounds. Another initial shortcoming was that values of $\sigma$ for substituents that can conjugate with the aromatic ring gave poor correlations with experimental data.\cite{44} However this limitation was overcome by Brown and colleagues,\cite{48} who introduced the $\sigma^+$ constant which gave much better correlations.

Charged substituents also present a further difficulty. These groups are prone to solvent interactions with polar solvents, and as such the substituent constants in these molecules should be solvent-dependant.\cite{49} It should also be noted that while the Hammett equation often gives excellent predictions of reaction rates, it is less able to predict regioselectivity.

With the exception of the complicated data for ortho-substituted compounds,
these limitations are relatively minor and hence Hammett constants have found widespread use in the study of organic reactions. The fact that the equation is still in use more than sixty years after its introduction speaks of its great utility. It is limited to aromatic systems however, and more recent research has attempted to define standard scales of nucleophilicity and electrophilicity which are more broadly applicable.\textsuperscript{50}

1.5. The Mayr-Patz Equation

The establishment of a standard method for the quantification of nucleophilicity has been a long-standing aim in physical organic chemistry. While the concept of nucleophilicity was already established in the 1920s,\textsuperscript{51} Swain and Scott were the first to attempt to quantify nucleophilicity in 1953.\textsuperscript{52} Since this study, there have been many subsequent attempts to quantitatively define nucleophilicity\textsuperscript{53},\textsuperscript{54} with one study proposing seventeen factors which must be considered,\textsuperscript{55} while another concluded in 1968 that quantitative prediction of the rate of nucleophilic attack was not possible.\textsuperscript{56} Ritchie\textsuperscript{57} subsequently simplified matters somewhat when he proposed the “constant selectivity relationship” (Equation 1.2), referred to as such because the relative rate of reaction of two nucleophiles is independent of the reactivity of the electrophile. It was later discovered that equation 1.2 is only strictly valid when different classes of electrophiles are treated separately.\textsuperscript{58}

\[ \text{Equation 1.2} \quad \log \frac{k}{k_0} = N_+ \]

Building on this earlier work, Mayr and colleagues have made great progress towards the establishment of a standard scale of nucleophilicity applicable to a wide range of substrates and reaction conditions.\textsuperscript{50} By measuring the rate of reaction of various nucleophiles with different electrophiles, graphs can be plotted similar to that depicted in Figure 1.7. The logarithm of the rate constant for the reaction of a given electrophile/nucleophile pair is plotted on the Y axis, while the parameter $E$ is plotted on the X axis. The $E$ parameter is defined as the rate of reaction of a given electrophile with 2-methyl-1-pentene (Scheme 1.4, page 20).
Three parameters can be extracted from these graphs: $E$, $N$ and $s$. The electrophilicity parameter $E$ for any given electrophile is defined as the rate constant for the reaction shown in Scheme 1.4. The nucleophilicity parameter $N$ is equal to $-E$ at the point where the rate constant for the reaction of the nucleophile with an electrophile equals 1 ($\log k = 0$). This can be obtained from the graph by taking the negative value of $E$ at the point where the line (or the extrapolated line) crosses the 0 line at $\log k = 0$. The $s$ parameter is the slope parameter which reflects the sensitivity of the reaction towards changes in the electrophile. This is specific to each nucleophile and is obtained from the gradient of the line.

Mayr derived equation 1.3 from these graphs, which allows the rate of reaction between a given nucleophile and electrophile to be calculated (and therefore predicted), provided that $N$, $E$ and $s$ are known.
Equation 1.3

$$log_{20^\circ C} k = s_N(N + E)$$

In a later adaptation of this method, Mayr introduced a series of diarylcarbenium ions as reference electrophiles (Figure 1.5).\cite{59} These compounds have the advantage that the steric environment around the reactive carbocation centre remains constant while the electronic properties of the molecule can be adjusted by varying the substituents $X$ and $Y$. The introduction of reference electrophiles allows the relative reactivity of an enormous range of molecules to be measured on a single reactivity scale, allowing for a much easier comparison of the reactivities of disparate types of substrates.

Figure 1.5 – Carbenium ion used in Mayr's work, where $X$ and $Y$ represent electron donating and withdrawing groups.

The Mayr-Patz equation does not include steric effects, as the error introduced was considered to be negligible compared to the range of reactivity covered by the scale, which spans many orders of magnitude. The most prominent caveat of Mayr’s method is that the reactivity parameters are strictly only comparable when the reactions being compared are performed in the same solvent.\cite{60}

A very large number of $N$, $E$ and $s$ parameters have been published,\cite{61,72} and have also been collected in an online database.\cite{73}

1.6 Semi-Empirical Models

Semi-empirical models tend to be more recently developed as advances in computing power and theoretical methods\cite{80,81} have allowed more complex calculations to be performed in a reasonable amount of time. Desktop computers are now able to run computational chemistry software such as Spartan\cite{82} and Gaussian\cite{83} with relative ease, making computational chemistry more accessible to the experimental chemist.

The remainder of this chapter will discuss some of these semi-empirical
models, from the simple yet successful FMO theory,\textsuperscript{[7]} which can be calculated by pen-and-paper methods, to more complex ideas such as electrophile affinity,\textsuperscript{[84]} which involves rigorously modelling the structure of various species present at different stages along the reaction coordinate.

1.7. Electrostatic Potential Energy Surfaces

The electrons and nuclei of a molecule create an electrostatic potential around the molecule.\textsuperscript{[85]} Electrostatic potential energy surfaces (ESPs or ESP surfaces) were introduced by Scrocco and Tomasi\textsuperscript{[86],[87]} and were one of the first methods of visually representing the outcome of quantum chemical calculations. The electrostatic potential is defined by equation 1.4 where $Z_A$ is the charge on nucleus A at the point $R_A$ and $\rho(r)$ is the electron density.

Equation 1.4

$$V(r) = \sum_A \frac{Z_A}{|R_A-r|} - \int \frac{\rho(r')dr'}{|r'-r|}$$

If the outcome of equation 1.4 is plotted on the molecular surface, the resulting ESP surface can be used as a measure of the charge distribution within a given molecule (Figure 1.6, page 23). The areas of lowest electrostatic potential are indicated by the red colour on the surface, while dark blue represents areas of highest electrostatic potential. While sometimes these types of plots are interpreted in terms of electron density, such an interpretation can be imprecise since the observed ESP is the result of the sum total effects of the positively charged nuclei and the charge associated with electron density at a given point. The ESP surface of nitrobenzene clearly shows the increased electrostatic potential over the aromatic ring compared to benzene, due to the strong field effect and resonant electron-withdrawing properties of the nitro group. The electron-donating properties of the methyl group via hyperconjugation in toluene is less visually apparent, however examination of the minimum $V(r)$ values confirms that the aryl ring must have a higher electron density than benzene.
Figure 1.6 - ESP surfaces of benzene, nitrobenzene and toluene showing the regions of negative (red) and positive (blue) electrostatic potential. Minimum $V(r)$ values are given in kJ mol$^{-1}$. The global minimum of nitrobenzene corresponds to the oxygen lone pairs.

ESP surfaces are considered to be a “well established” and “effective tool” in the prediction of the regiochemical outcome of organic reactions$^{[88]}$ and are commonly found in undergraduate level textbooks. This does make intuitive sense, since electrophiles would be expected to be attracted to the regions of higher electron density, while nucleophiles gravitate towards regions of low electron density. However, “reactivity” is not a ground state property, and as mentioned above ESPs are not purely representative of the electron density at a particular site. ESPs have also found utility in a wide range of areas, including studies of solvation,$^{[89]}$ analysis of crystal surfaces and cavities, electrostatic effects in proteins$^{[90]}$ and structure-activity relationships.$^{[90]}$ They are also useful for quantifying substituent effects$^{[91],[92]}$ and in determining the electronegativity of substituents.$^{[93]}$

1.8. Frontier Molecular Orbital Theory

Kenichi Fukui first introduced the concept of frontier molecular orbitals (FMOs) in 1952.$^{[7]}$ According to FMO theory, the largest lobe of the HOMO (i.e. the position on the molecule where the highest energy electrons are most likely to be located) should indicate the most reactive position in a given molecule. The orbital lobes represent the distribution of frontier electron density around the molecule. Fukui and colleagues found that by considering the highest occupied $\pi$-orbital to be distinct from the other
lower lying orbitals, and making the assumption that this orbital played the most significant role in a given reaction, they were able to identify the most reactive position in a series of 15 polycyclic aromatic compounds (Figure 1.7).

![Molecules studied by Fukui in his 1952 paper. The most reactive positions are indicated by the position of the largest lobes. Both degenerate orbitals are shown for benzene and triphenylene.](image)

**Figure 1.7** – Molecules studied by Fukui in his 1952 paper. The most reactive positions are indicated by the position of the largest lobes. Both degenerate orbitals are shown for benzene and triphenylene.

All of the carbon atoms in benzene were correctly predicted to be equally reactive, as were those in triphenylene and coronene. A “perfect agreement” was found between the predictions of FMO theory and experimentally observed reactivity in all cases except for 3,4-benzopyrene. The predicted reactive site in this case is very sterically hindered, so the electrophile is substituted at the position of the second largest lobe.

FMO theory has since been widely employed to rationalise the reactive behaviour of many compounds, and its influence is such that Fukui shared the Nobel Prize with Hoffman for his work in this area.
Although widely acknowledged to be one of the leading theories of reactivity, FMO theory has been criticised because it fails “unpredictably”. Even when applied to very simple reactions, it is not possible to predict the cases where FMO theory should work and where it would be expected to fail. It has been claimed that FMO theory correctly predicts the reactivity of substrates that undergo “frontier-controlled” reactions, but fails in cases where reactions are charge-controlled.

1.9. The Fukui Function

The Fukui function was derived by Parr and Yang, who demonstrated that “the frontier-electron theory of chemical reactivity can be rationalized from the density functional theory of the electronic structure of materials.” It is formally defined by equation 1.5, where \( \mu \) is the chemical potential, \( v(r) \) is the external potential and the derivative is taken at a constant number of electrons, \( N \).

\[
\int^\alpha_r = \left( \frac{\delta \mu}{\delta v(r)} \right)_N = \left( \frac{\delta \rho(r)}{\delta N} \right)_v(r)
\]

Since \( \alpha \) can be positive, negative or zero, three types of Fukui function are possible. These are denoted \( f^- \), \( f^+ \) and \( f^0 \), and they measure the electrophilic, nucleophilic and radical reactivity respectively. The three functions are defined in equations 1.6, 1.7 and 1.8.

\[
\begin{align*}
\text{Equation 1.6} & \quad f^-(r) = [\rho_N(r) - \rho_{N-1}(r)] \\
\text{Equation 1.7} & \quad f^+(r) = [\rho_{N+1}(r) - \rho_N(r)] \\
\text{Equation 1.8} & \quad f^0(r) = \frac{[\rho_{N+1}(r) - \rho_{N-1}(r)]}{2}
\end{align*}
\]

According to FMO theory, the most favourable site for a chemical reaction to occur is the site of maximal Fukui function (i.e. the softest site). It was later claimed that the Fukui function describes soft-soft interactions well, while hard-hard interactions are best modelled by the molecular electrostatic potential. Another study concluded...
that chemical reactivity is determined by global hardness, while chemical selectivity is determined by the Fukui function.\textsuperscript{[102]}

A Fukui function overlap method was proposed for predicting reactivity in methylation reactions of benzene derivatives.\textsuperscript{[104]} This method was found to be “especially strong” in predicting steric effects because the force field calculations used allow a large number of possible configurations to be considered, with higher accuracy calculations used only in configurations that have a significant influence on reactivity.\textsuperscript{[104]}

The “atom-condensed indexes” are widely employed to obtain information about the susceptibility of an atom $x$ to undergo electrophilic, nucleophilic or radical attack.\textsuperscript{[105]} These indexes are defined by equations 1.9, 1.10 and 1.11, where $q_x(N)$ is the atomic charge associated with atom $x$ in an $N$-electron species.

\begin{equation}
\text{Equation 1.9} \quad f_x^- = [q_x(N) - q_x(N - 1)]
\end{equation}

\begin{equation}
\text{Equation 1.10} \quad f_x^- = [q_x(N + 1) - q_x(N)]
\end{equation}

\begin{equation}
\text{Equation 1.11} \quad f_x^+ = \frac{[q_x(N + 1) - q_x(N - 1)]}{2}
\end{equation}

These indexes have been shown to be reliable when calculated using basis sets which omit diffuse functions,\textsuperscript{[105]} however diffuse functions are generally required to accurately determine nucleophilic susceptibilities, which affects the reliability of the method.

\subsection*{1.10. Activation Hardness}

Zhou and Parr introduced the concept of “activation hardness” and showed that it can be used to predict the “orientation of electrophilic aromatic substitution”.\textsuperscript{[106]} The activation hardness is derived from density functional theory and is defined as

\begin{equation}
\text{Equation 1.12} \quad \Delta E^* = -2(\eta_{N-2} - \eta_N) = 2\Delta \eta^*
\end{equation}

where $\Delta \eta^*$ is the activation hardness, and $\eta_N$ and $\eta_{N-2}$ are the absolute hardness of the
ground and transition states. The absolute hardness is defined as being proportional to the second derivative of the total energy of a chemical system with respect to changes in the number of electrons at a fixed nuclear environment.\textsuperscript{107} The activation hardness is defined in such a way that the smaller its value, the faster the reaction – i.e. the reactive site within a molecule is predicted by the position of the smallest value of the activation hardness.

The activation hardness concept makes the assumption that the sum of the chemical potentials of the ground and transition states is equal to the total energy of the molecule:

\[
\mu_N + \mu_{N-2} = E
\]

This is argued to be a reasonable assumption based on the idea that the reactants and the transition state are in equilibrium. Activation hardness was found to accurately predict the reactive sites in a series of 31 aromatic compounds. The authors also found a good correlation with Hammett $\sigma^+$ constants, although there seems to be no correlation coefficient quoted in the paper.\textsuperscript{106} Activation hardness appears to be a very successful theory, however like most other models presented in this chapter steric effects and the influence of the electrophile are not taken into account.

1.11. \textit{Ab initio} Methods

1.11.1. Electrophile Affinity

Galabov and colleagues introduced a new concept in 2009 that they called the ‘electrophile affinity’.\textsuperscript{84} This is defined as “the energy change associated with formation of an arenium ion $\sigma$-complex from the initial arene and electrophile at the reacting carbon centre”, and was envisioned as a means to characterise the regioselectivity in aromatic molecules.\textsuperscript{84,108} It is defined mathematically by equation 1.14, where $E_a$ is the electrophile affinity.

\[
E_a = [E_{\text{arene}} + E_{\text{electrophile}}] - E_{\text{arenium ion}}
\]

Excellent correlations were found between calculated electrophile affinities and partial
rate factors in a series of methylbenzene derivatives for a variety of reactions, including chlorination,\textsuperscript{84} benzylation\textsuperscript{84} and bromination.\textsuperscript{108}

Although the electrophile affinity method produces good results, it is a very time consuming method since at least five calculations must be performed (one each to determine the energies of the arene and electrophile, and one for each of the ortho, meta and para-substituted arenium ions) before any predictions can be made (see Scheme 1.2 for one example). The large basis set (6-311+G(2d,2p)) used in Galabov’s study\textsuperscript{84} also adds to the computational cost. Additionally, the computational expertise required to perform the calculations and interpret the results is likely to limit the use of this method by synthetic chemists.

\textbf{Figure 1.8} – Models of the ground state and transition state calculated using the electrophile affinity model.\textsuperscript{108}

\section*{1.11.2 Average Local Ionisation Energy}

The average local ionisation energy, introduced by Politzer in 1990 as a “guide” to the reactivity of aromatic systems,\textsuperscript{109} is a relatively simple model compared to the electrophile affinity, which is defined by equation 1.15.

\textbf{Equation 1.15} \[ I(r) = \sum |\frac{\rho_i(r)|\varepsilon_i|}{\rho(r)} \]

Where $\rho_i(r)$ is the electronic density of the $i^{th}$ molecular orbital at the point $r$ on the molecular surface, $\varepsilon_i$ is the energy of the $i^{th}$ orbital and $\rho(r)$ is the total electron density.
of the molecule. This property was introduced after Politzer and colleagues recognised that previous descriptors based on electrostatic surface potentials do not take into account donor-acceptor interactions.\[110]\n
In Politzer’s original study, the local ionisation energies were calculated for a series of substituted benzenes (Figure 1.9) and the values of the local ionisation energy (local IE) were lowest over the ortho, para or meta positions in agreement with the experimentally determined directing effects of the substituent. Hence it was reasoned that local IE could be used to predict the regioselectivity of electrophilic aromatic substitution reactions.

![Figure 1.9 – Aromatic compounds studied by Politzer and colleagues.](image)

The local IE has also been found to correlate with pK\textsubscript{a} values of azines and azoles,\[111]\nHammett \(\sigma\) constants of substituted anilines,\[112]\natomic electronegativity and hardness,\[113]\nlocal polarisability,\[33]\nthe Fukui function,\[114]\nand has also been used to examine the bond character in a series of aromatic hydrocarbons.\[115]\nIt has been suggested that the local IE should be used in combination with other calculated molecular properties, including ESPs,\[116]\nand local hardness,\[110]\nto obtain a more complete description of molecular reactivity.

The advantages of this method will be discussed more fully in Chapter 2, but can be summarised as being the ease with which the model can be employed and the simplicity of interpreting the results.


For much of the history of organic chemistry, advances in synthetic methodology have largely been due to the expertise and imagination of individual chemists or a group of collaborators. Under these circumstances a diverse range of methodologies have been developed largely independently. In 2005 Grzybowski and colleagues analysed the Beilstein database and were able to identify several “statistical laws” describing how
organic molecules are synthesised and converted.\textsuperscript{74}

They represent the results of their statistical analysis as a directed graph, or network (Figure 1.10).\textsuperscript{74} Each point (node) in the network represents an organic molecule, while the connecting arrows represent the conversions between them (i.e. reactions of the molecule). The connectivity of any given node is given by the number of incoming and outgoing arrows, $k_{in}$ and $k_{out}$.\textsuperscript{74} Connectivity can also reveal trends in reactivity.\textsuperscript{75,76}

A number of structures and functional groups with high connectivity were identified as being most useful in organic synthesis due to the large number of reactions in which they participate.\textsuperscript{77} The network can be subdivided into the “core” and the “periphery”. The core refers to the set of chemically diverse compounds with high connectivity, while the periphery represents the molecules that can be synthesised from the core molecules. The majority of known organic compounds are therefore in the periphery of the network, while there are some isolated groups of compounds not connected to either subset.\textsuperscript{77} These islands are often comprised of complex natural products or non-naturally occurring isotopes.

\textbf{Figure 1.10} – Nodes representing about 1\% of the ‘network of organic chemistry’.\textsuperscript{78}

An algorithm was recently developed which was able to independently devise one-pot syntheses which were then successfully performed experimentally.\textsuperscript{78} By using an algorithm that considers the cost of production (cost of reagents and labour), this approach was able to decrease the costs of a chemical company by ~50\% through the optimisation of synthetic strategies, for example decreasing the number of steps, or
devising convergent synthetic strategies.[79]

One limitation of the Network of Organic Chemistry is that the discovery of new synthetic routes is dependent on the target molecule being linked through the network to known starting materials. If a novel molecule exists in an isolated “island” with no links to the rest of the network, no synthetic route to that molecule can be determined. This means that the network may be of little use in the discovery of novel compounds or methodologies, which are unrelated to known structures or reactions in the network.

Another limitation of this method is the database itself. In order for algorithms to perform their functions, the database needs to be kept up to date with data such as new synthetic strategies or changes in the cost of materials etc.[77] It is likely that such databases will become available in the near future as computational approaches to designing reactions become more prevalent. The future direction of organic synthesis and development of synthetic methodology is likely to rely more heavily on the combination of computational predictions and lab-based experiments to devise new and more efficient syntheses.

1.12. Conclusions
The plethora of theoretical models proposed for the understanding and prediction of chemical reactivity is testament to the difficulty in devising a theory which satisfies the requirements of being accurate, widely applicable, and easily calculated. The way forward may be to combine theoretical calculations with databases of empirical observations (such as the network of organic chemistry) to obtain a more complete understanding of reactivity and thus allow the development of more powerful predictive tools.
References

[82] I. I. Spartan’08 Wavefunction, CA


Chapter 2

Local Ionisation Energy as a Reactivity Descriptor

Abstract
One of the long-standing objectives of chemistry is the prediction of the outcome of chemical reactions. This chapter presents a systematic analysis of the predictive capacity of several prominent theories of organic reactivity. This analysis is based on reactivity patterns observed in aromatic molecules spanning 150 years of synthetic developments.

This study revealed several regioselectivities that were not predicted by resonance theory, electrostatic potentials or frontier molecular orbital theory. In contrast, calculated local ionisation energy surfaces are shown to consistently reveal the most nucleophilic sites in aromatic molecules even where established reactivity models fail. These local ionisation energy minima are also found to correlate with experimentally determined reactivity parameters. Attempts to extend the scope of the model beyond aromatic chemistry produced mixed results. Since ionisation energy surfaces are provided as standard in popular computational chemistry software and are simple to interpret, this approach serves as a readily accessible tool for visualising the fundamental factors governing the reactivity of aromatic molecules.

2.1. Introduction
The chemistry of aromatic molecules is typified by the reactions of their $\pi$-systems with electrophiles. Such reactions are often rationalised using empirical reactivity rules derived from resonance theory,[1] or calculated properties such as FMOs[2,3] and electrostatic potentials.[4-7] This chapter will show that none of these popular methods offer a comprehensive solution to the prediction of aromatic reactivity. Instead, our analysis of thousands of experimental observations of electrophilic substitution reactions has revealed average local ionisation energy (IE) surfaces as a more reliable, yet simple model for visualising the reactivity of aromatic molecules under kinetic control. Furthermore, correlations with experimentally determined reactivity
parameters show that the model can provide quantitative predictions of the relative nucleophilicities of aromatic molecules.

The average local ionisation energy was introduced by Politzer\textsuperscript{[8]} and is now included as a standard surface in popular off-the-shelf computational chemistry software. The theory of the method is discussed more fully in chapter 1. In the current work, the concept of the local IE has been expanded beyond the scope of Politzer’s original work to systematically investigate the breadth of the local IE as a reactivity descriptor beyond simple monosubstituted benzenes to include a wide range of heterocycles, polycyclic aromatics and some non-aromatic compounds. In addition, a hypothesis is presented explaining why the local IE should be a good descriptor of reactivity. To our knowledge this is the first mechanistic hypothesis explaining the predictive ability of the model.

The most significant difference between this work and Politzer’s previous study is that our calculations have used Density Functional Theory (DFT) methods, whereas equation 1.4 was defined within the framework of Hartree-Fock theory. Before explaining the reason for this change it is necessary to briefly describe the interpretation of local IE surfaces.

2.2. Interpretation of Ionisation Energy Surfaces

Minimised molecular geometries and molecular surfaces were calculated using \textit{Spartan ’08}, with DFT/B3LYP/6-311G*, unless otherwise stated. Ionisation energies and electrostatic potentials are plotted on the 0.002 electrons/bohr\textsuperscript{3} density surface. Ionisation energy surfaces emphasising minima are scaled from the average local ionisation energy minimum on the molecular surface, $\bar{I}_{S,\text{min}}$ (red) to $\bar{I}_{S,\text{min}} +0.4$ eV (blue) of each molecule. Based on the large-scale analysis of experimentally observed reactivity patterns presented in this chapter, this scale was found to be the most appropriate to show the location of the minimum value, while the numerical value can be read by placing the cursor at the appropriate point on the surface.
Figure 2.1 - Example showing the positions on the 0.002 electrons/bohr$^3$ average local ionisation energy surface corresponding to $I_{S,\text{meta}}$ and $I_{S,\text{para}}$ in the example of trifluoromethyl benzene.

Figure 2.1 shows the local IE surface of trifluoromethyl benzene as an example, with the meta and para positions indicated. It should be noted that the value at a particular position on a molecule is read over the centre of the carbon atom (the black dot) rather than the centre of the red area. In most aromatic molecules this is not an issue, however with alkenes and in cases where the bond has more alkene-like character and less aromatic character the two can sometimes differ (as is discussed below).

2.3. Determination of the Appropriate Level of Theory

We quickly established that average local ionisation energy calculations performed using Density Functional Theory (DFT) successfully rank the relative nucleophilicities of aromatic carbons and heteroatoms where previously used Hartree-Fock (HF) methods sometimes fail (Figure 2.2, page 38) $^{[8-9]}$. Indeed, average local ionisation energies calculated using DFT have been shown to be theoretically robust,$^{[8]}$ and were also employed in the most detailed assessment of local average ionisation energies prior to the present study (21 aromatic molecules).$^{[10]}$

2.3.1 Comparison of DFT with HF Methods

A series of ionisation energy calculations were performed with both DFT and HF methods using a variety of different basis sets. The results are summarised in Figure 2.2 (page 38). The experimental reactivity is shown by the shaded arrows. The black arrow indicates the most reactive nucleophilic position, while the grey and light grey arrows indicated secondary and tertiary nucleophilic sites, respectively.
Figure 2.2 - Experimental reactivity patterns for a range of aromatic substrates and corresponding average local ionisation energy surfaces and minimum values ($\bar{I}_{x,\text{max}}$) at the 0.002 electrons/bohr$^3$ surface calculated using the methods shown. Examples where the calculation correctly ranks the relative nucleophilicities of different reactive sites are highlighted with a green background. References for the observed reactivity patterns are given in the captions of other figures.

Figure 2.2 shows that HF fails to identify the correct regioselectivity in the majority of cases tested. In the case of aniline, only DFT correctly highlights the nitrogen lone pair, while in 1-methylcytosine the oxygen lone pair is missed by all HF methods. Chlorobenzene is an ortho/para-director, however mostly the para-substituted product is formed.$^{[11]}$ HF is more successful here than in the other examples, and compares favourably with the DFT method. 9-methylguanine is known to react through the lone pair of the nitrogen in the 7-position under electrophilic substitution conditions.$^{[12]}$ Alkylation at the 8-position has been observed, however the initial step of this mechanism is electrophilic substitution at the 7-position.$^{[13]}$
It was also found that HF overestimates the value of the minimum ionisation energy. For example, the experimentally measured ionisation energy of benzene is 9.24 eV.\(^8\) The value calculated by HF was much higher, at 12.04 eV, while that obtained with DFT calculations was 9.25 eV.

In addition, correlations of average local ionisation energy minima calculated using DFT and various basis sets against experimental reactivity parameters were also found to be better than corresponding calculations performed using HF (See bottom of Figure 2.3 and discussion below).

**2.3.2. Determination of Basis Set**

Having established that DFT gives more accurate predictions than HF, the optimal basis set was determined using a set of Mayr's data.\(^{14}\) Using a relatively small set of data, the results of a range of basis sets was plotted against the minimum ionisation energy value (\(I_{S,min}\)). The results are summarised in figure 2.3 (page 40).
Figure 2.3 – Correlations of experimental nucleophilicity parameters, $N$ with average local ionisation energy minima $\bar{I}_{S, \text{min}}$ calculated using the methods indicated at the 0.002 electrons/bohr$^3$ surface.

The correlation coefficients are all broadly similar ($\sim R^2 = 0.8$), so it was decided to use the 6-311G* basis set as it is sufficiently large to be capable of handling iodinated substrates, it has one of the highest correlation coefficients while being one of the most efficient methods in terms of calculation time.
2.4. A Comparison of Regioselectivity Predictions of Popular Theoretical Descriptors

The effects of substituents on the regioselectivity of electrophilic aromatic substitution reactions in benzene derivatives serve as an excellent test-bed for examining the predictive utility of IE surfaces. Figure 2.4 (page 42) compares the predictions of some well-established models with those of the IE calculations.

Resonance theory states that substituents that withdraw electron density via resonance direct attack to the meta-positions, while substituents that donate electron density through resonance or hyperconjugation are ortho/para-directing.\cite{15} Experimental data shows that chlorobenzene (Figure 2.4a) is more likely to react with electrophiles in the para position rather than the ortho position, despite there being two ortho-positions and only one para-position.\cite{11,16,17} In contrast, the phenoxide anion (Figure 2.4b) reacts primarily in the ortho position.\cite{16,18,19,20} Resonance theory is unable to differentiate between the reactivity of these two compounds, simply predicting both to be ortho/para-directing, however calculated average local ionisation energy surfaces correspond well with the observed reactive behaviour.

In halobenzenes, it can be hypothesised that both ortho and para positions are activated by resonant electron donation from the lone-pair electrons on the halogen substituent, but the competing inductive influence of the electronegative halogen reduces the nucleophilicity of the nearby ortho positions more than the para position. In the case of phenoxide similar resonant effects may come into play, but the ortho positions are more activated than the para position.
**Figure 2.4** – A comparison of regioselectivity in electrophilic aromatic substitution reactions vs. theoretical descriptors. The positions of the ionisation energy minima on the molecular surfaces ($I_{S,\text{min}}$, red) correspond with the experimentally determined nucleophilic sites, even where predictions based on resonance theory, FMO theory (HOMOs) and electrostatic potentials fail (red background shading). Blue regions of the ionisation energy (IE) surfaces represent all regions where the local IE is $> I_{S,\text{min}} + 0.4$ eV. The electrostatic potential surfaces are scaled from the lowest potential on each aromatic ring (red) to this value plus 15 kJ mol$^{-1}$ (blue). Values shown underneath the theoretical structures correspond to the ortho, meta and para positions as indicated. All molecular surfaces were calculated using Spartan ’08 with B3LYP/6-311G*. Percentage yields estimated from IE values were calculated using Equation 2.1 and are associated with an error of up to ±25% (Figure 2.7). References for the reactions shown: a$^{[11]}$, b$^{[16]}$, c$^{[21]}$, d$^{[18]}$, e$^{[19]}$, f$^{[22]}$, g$^{[23]}$, h$^{[24]}$. 
While electrostatic potentials (ESPs) might be expected to take resonant and inductive effects into account, Figure 2.4 shows that ESPs do not provide a useful indicator of reactivity since the electrostatic minima (red regions) are often located over unreactive substituents. In addition, ESP values taken over the *ortho*, *meta* and *para* positions of chlorobenzene do not vary in relation to their reactivities (Figure 2.4a).

In accord with predictions derived from resonance theory, benzonitrile reacts predominantly in the *meta* position (Figure 2.4c). However resonance theory fails to provide an explanation for the significant *ortho*-reactivity observed in this molecule.[22],[23],[17] This reactivity pattern is difficult rationalise, yet the IE surfaces correspond with this observation and show significant streaking of lower IE energies from the *meta* positions across the *ortho* positions (but much less so across the *para* position). At this point it is worth mentioning that the largest HOMO lobe lies over the *para* position in benzonitrile (Figure 2.4c). Thus, frontier molecular orbital (FMO) theory incorrectly predicts *para*-substitution in benzonitrile, despite the method serving as a powerful tool for predicting the outcome of many organic reactions, and pericyclic reactions in particular.[25]

### 2.5. Why Might the IE Method be so Successful in Predicting Aromatic Reactivity?

The question of why the local IE is so effective at describing the reactivity of aromatic systems must be addressed. The important point is that the outcome of electrophilic aromatic substitution reactions is governed by the initial rate-determining attack of the electrophile to form the cationic Wheland intermediate (Figure 2.5, page 44). The rate of the reaction will be determined by the size of the activation barrier, $\Delta G^\ddagger$, which depends on the identity of the aromatic substrate.
Figure 2.5 - The relationship between ionisation energies and the mechanism of electrophilic aromatic substitution. (a) Scheme showing the ionisation of benzene via the removal of a single electron. (b) Scheme showing a typical reaction mechanism for EAS and the corresponding reaction energy profile.

Average local ionisation energies encode the energy required to remove an electron from a particular point on the surface of the molecule (Figure 2.5a). The ground state for both the reaction and the ionisation energy calculation are identical, whilst the radical cation produced by the process of ionisation closely resembles the Wheland intermediate generated during the rate determining step. It is therefore proposed that IE should be a successful descriptor of reactivity, at least in electrophilic aromatic substitution reactions, because the ionisation of the aromatic substrate closely resembles the process occurring in the rate-determining step of the reaction. In essence, we are applying a version of the Hammond postulate to predict the influence of substituents and molecular structure on the rate and regioselectivity of the reaction.

The successful prediction of regioselectivity in these reactions can be explained by considering that the reactive site on the molecule should correspond to the point from which it is easiest to remove electrons. By definition ionisation involves removing the electron to infinity, whereas in the reaction the electron is removed from the aromatic ring to form the covalent bond with the electrophile. In contrast to FMO theory which only considers the localisation of the HOMO, the local ionisation energy has contributions from both the localisation of the HOMO and changes in the
electrostatic energy.

To the best of our knowledge this is the first attempt to rationalise why the model is such a good predictor or aromatic reactivity, and also provides a clue as to why the model may fail for different types of reaction (see Section 2.9), since the rate-determining step is not accurately modelled by the ionisation energy.

2.6. Quantitative Analysis

To test the hypothesis that the energy change in the rate-determining step of EAS reactions is approximated by average local IEs, these calculated energies were correlated against quantitative experimental measures of the reactivity of aromatic molecules with electrophiles (Figure 2.6, page 46).
Figure 2.6 - Correlations of average local ionisation energies calculated using B3LYP/6-311G* with experimental reactivity parameters. a) Hammett substituent constants. b) Mayr’s Nucleophilicity parameters. c) Partial rate factors for electrophilic substitution reactions at different carbon positions in benzene derivatives. d) A scale of average local ionisation energies including representative examples. Numerical data and references are provided in the appendices.

An excellent correlation was found between local IE values taken over the meta and para position of mono-substituted benzenes and Hammett substituent constants (Figure 2.6a), which are established as one of the most successful empirical descriptors of reactivity in aromatic molecules.[26] Whilst the correlations of $\sigma_m$ and $\sigma_p$ with IE are excellent, $\sigma^+$ constants introduced by Brown[27] are considered to be better descriptors of substituent effects when a positively charged transition state is stabilised by specific resonance effects. The correlation coefficient in this case is only 0.66 (Figure 2.7), however the excellent correlations with $\sigma_m$ and $\sigma_p$ show that the local IE can be used
as an estimate of the electron withdrawing or donating properties of a given substituent, and may allow substituent constants to be predicted for substituents where no experimental data exists.

Figure 2.7 – Correlation of average local ionisation energies calculated using B3LYP/6-311G* with Browns $\sigma^+$ constant.

To further examine the validity of local ionisation energies, high-quality kinetic data obtained under controlled conditions is required. Mayr and colleagues have made great progress towards the establishment of a standard scale of nucleophilicity.\textsuperscript{28,29} Local IE minima correlate with Mayr’s nucleophilicity parameters for a range of multiply-substituted benzenes and other heterocycles (Figure 2.6b). The correlation coefficient of 0.86, while statistically significant, at first glance may not seem particularly good, however it is reasonable considering that these data were acquired in different solvents (either acetonitrile or dichloromethane) and that the effects of multiple reactive sites are not taken into account.

The successful predictions of regioselectivity combined with the excellent correlations with Hammett constants suggest that local IE calculations may be able to predict the relative rates of substitution at the ortho, meta and para positions of a given compound (i.e the partial rate factors for each position), and therefore the relative proportion of products from a given reaction.

Local IEs plotted against experimentally determined partial rate factors for a
range of electrophilic aromatic substitution reactions, including bromination, chlorination, mercuration, ethylation and benzylation reactions are plotted in Figure 2.6c.\textsuperscript{30,31} A good correlation is obtained considering that the data were obtained from multiple sources and the range of reactions covered. Despite the simplicity of the IE model, this correlation is only 0.02 lower than that obtained from plots of the same data against calculated electrophile affinities,\textsuperscript{30} even though the electrophile affinity calculations are much more thorough and complex. This supports the hypothesis that average local IEs approximate the energy change in the rate-determining step for each regiochemical reaction pathway, which is explicitly calculated in the Electrophile Affinity model.

2.7. Estimation of Yields Based on IE Calculations

The yield of a given reaction is obviously very important and a simple model that allows the percentage yield of any given reaction to be estimated would be very useful to syntheticchemists. Figure 2.6c (page 46) allows a quantitative relationship to be formed between calculated local IE values and experimental partial rate factors, which in turn can be used to calculate the expected percentage yields of different regioisomers (Equation 2.1).

\textbf{Equation 2.1} \textit{predicted} % yield at position \textit{j} = \frac{n_j \exp(m \bar{I}_{S,j})}{\sum_j n_j \exp(m \bar{I}_{S,j})} \times 100\%

Where \( n_j \) is the number of equivalent aromatic positions \textit{j} that are available for substitution, \( m \) is the gradient of the graph determined in Figure 2.6c (\( m = -21.194 \)), and \( \bar{I}_{S,j} \) is the average local ionisation energy taken over each position \textit{j} (calculated using B3LYP/6-311G\* at the 0.002 electrons/bohr\(^3\) surface).
The accurate prediction of regioisomer ratios using IE surfaces is presented with a number of potential challenges. Firstly, as well as the properties of the nucleophile, yields are also dependent on the nature of the electrophile and steric effects, which are not considered in the IE model. Secondly, since small changes in the value of the IE result in exponential changes in the relative rates of reaction at different sites, the prediction of regioisomer ratios may be associated with significant errors. Nonetheless, the assertion that Equation 2.1 might be used for the semi-quantitative prediction of regioisomer yields is supported by the data in Figure 2.8, which shows that yields can be predicted with an accuracy of ±25%. The outliers in Figure 2.8 (marked with hollow circles) correspond to examples where steric effects have an important influence on the observed product ratios (iodobenzene and some polymethylbenzenes), which is not taken into account in the ionisation energy model.

Although Equation 2.1 could be used to predict regioisomer yields, a more easily accessible approach might take advantage of the ability to plot local ionisation energies on the surface of a molecule, in a similar fashion to electrostatic potentials. Provided that an appropriate colour scale is selected (see Section 2.2) the most reactive sites in a molecule are highlighted in red, while secondary reactive sites are revealed in orange/yellow (and occasionally green) and blue corresponds to sites where...
negligible experimental reactivity with electrophiles is observed. This facilitates the prediction of approximate regioisomer yields based on simple visual inspection of the local IE surface (Table 2.1).

<table>
<thead>
<tr>
<th>Average local IE at position $j$ ($\bar{I}_{S,j}$ /eV)</th>
<th>Colour of IE surface at position $j$</th>
<th>Approx. regioisomer yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \bar{I}_{S,\text{min}} )</td>
<td>Red</td>
<td>&gt;50 %</td>
</tr>
<tr>
<td>( \bar{I}_{S,\text{min}} + 0.05 ) to +0.1</td>
<td>Orange/Yellow</td>
<td>&lt;50 %</td>
</tr>
<tr>
<td>( \bar{I}_{S,\text{min}} + 0.2 )</td>
<td>Green</td>
<td>&lt;25 %</td>
</tr>
<tr>
<td>( \bar{I}_{S,\text{min}} + 0.4 )</td>
<td>Blue</td>
<td>Negligible</td>
</tr>
</tbody>
</table>

Table 2.1 - Optimised colour scale for visualising ionisation energy surfaces and the associated approximate regioisomer yield predictions.

One advantage of this graphical approach over some other computational methods is that the regioselectivity and approximate regioisomer yields can be quickly assessed without requiring separate calculations for each regiochemical reaction pathway.

2.8.0. Validation of the IE Method

Thus far, discussion of the utility of the average local ionisation energy has been largely confined to the quantitative aspects of electrophilic aromatic substitution reactions. Although quantitative predictions are much more useful than simple predictions of regioselectivity, the range of substrates for which the model gives accurate predictions must still be assessed. The remainder of this chapter is devoted to the validation of the local IE as a descriptor of reactivity in a wide range of aromatic substrates, along with an attempt to extend the model to include various non-aromatic compounds.
2.8.1. Benzene and Substituted Derivatives

The effects of substituents on the reactivity of benzene derivatives serves as an excellent starting point for examining the ability of local ionisation energy surfaces to predict the regiochemical outcome of electrophilic aromatic substitution reactions. Since high quality kinetic data are often not obtained during routine chemical synthesis, this larger scale validation of the IE approach will be performed by qualitative comparison of the IE surfaces with experimental reactivity patterns reported in the literature.

Figure 2.9 (page 51) compares the IE surfaces, ESPs and HOMO lobes for a variety of mono-substituted benzenes. Benzene itself is predicted by the IE approach to be equally reactive at all six carbon atoms, and this is also predicted by FMO theory if both degenerate HOMO and HOMO-1 orbitals are considered.
Figure 2.9 – (Page 52) Comparison of surface-encoded ionisation energy surfaces, electrostatic potentials, HOMO and HOMO-1 lobes of monosubstituted benzenes in relation to their experimental reactivity in electrophilic aromatic substitution reactions. The ionisation energy surfaces emphasising the relative reactivity of different molecules in the second row are plotted on a standardised scale from 8.7 eV (red) to 10.7 eV (blue). Electrostatic potentials are scaled from the lowest potential on each aromatic ring (red) to this value plus 15 kJ mol⁻¹ (blue). HOMO and HOMO-1 lobes correspond to 0.032 electrons/bohr³.

Benzene derivatives containing the strongest electron-donating groups possess large HOMO lobes over the ortho and para-positions, in line with their observed reactivity. Electrostatic potential minima have also been proposed for rationalising the reactive behaviour of aromatic molecules,[^32] however Figure 2.9 (page 52) shows that the minima are often localised over the substituents rather than the aromatic ring, even when the substituent may be far less reactive than the ring (e.g. trifluoromethylbenzene, anisole or nitrobenzene). If the localisation of electron density over substituents is ignored, and only the minima on the rings are considered, these secondary minima do coincide with the meta-position for molecules bearing electron-withdrawing substituents. Electrostatic surface potentials fail to predict the ortho/para-directing effects of electron-donating groups.

In contrast, the IE model correctly predicts the classic meta- and ortho/para-directing effects of substituents, including the halogens, which are exceptional in being electron-withdrawing yet ortho/para-directing. One possible explanation for the success of the IE model over FMO- and ESP-based theories is that these methods only model ground state properties and do not give information on the change from ground state to transition state. It has been suggested that FMO theory correctly predicts the reactivity of substrates that undergo so-called frontier-controlled reactions, but not those that are charge controlled.[^33]

The most interesting and theoretically challenging examples depicted in Figure 2.8 are provided by those molecules bearing substituents that are not classic ortho/para- or meta-directing groups. The anilinium cation is unusual in that it undergoes electrophilic substitution in the meta and para positions.[^8] The HOMO of the anilinium cation is no different to those of benzene rings containing meta-directing groups such as CF₃ or NO₂, however both the electrostatic and IE surfaces correctly predict that the para-position is most reactive, followed by the meta-positions.
As discussed above, the phenoxide anion is another example which does not conform to the classic rules, yet its regioselectivity is correctly predicted by the IE minima where other descriptors fail.

Finally, aromatic rings may also undergo ipso-substitution, where the initial substituent is replaced by the incoming electrophile. The IE surface of lithiated benzene in Figure 2.9 correctly predicts the most reactive site as being strongly localised near the point of contact with the lithium cation. Other metallated aromatics such as those employed in Grignard reactions or copper-mediated couplings give similar IE surfaces in accord with their reactivity (see Section 2.8.3). Organic aromatics may also undergo ipso-substitution as exploited in the synthesis of calixarenes.\textsuperscript{[34]} Trimethylphenyl silane is also known to undergo ipso-substitution.\textsuperscript{[35]}

The second row of IE surfaces in Figure 2.9 have all been set to the same scale in an attempt to define a general reactivity scale that can be used to quickly indicate the relative reactivity between aromatic molecules in EAS reactions. The scale ranges from 8.7 eV (red) to 10.7 eV (blue), with a lower IE\textsubscript{min} value indicating higher reactivity. Benzene has an IE\textsubscript{min} of 9.2 eV, which approximately defines the middle of the scale (green). Anionic substrates such as phenoxide are off the lower end of the scale, while cationic species such as the anilinium cation are off the higher end of the scale, however our study of a large range of neutral aromatic molecules confirms that the vast majority of these substrates fit within the defined scale.

### 2.8.2. Multiply-Substituted Benzene Derivatives

In addition to the mono-substituted benzenes described above, the IE model also successfully predicts substitution patterns in multiply-substituted derivatives (Figure 2.10, page 56). In para-nitrotoluene, both aromatic substituents direct to the same position to give a single product,\textsuperscript{[36]} while in para-fluorotoluene both the fluorine and methyl substituents have similar ortho/para-directing properties, but direct to different positions and a mixture of products is observed.\textsuperscript{[37]} In para-methylphenol, the hydroxyl group is a much stronger electron-donating group than the methyl group, so the outcome of the reaction is determined by the directing effects of the stronger hydroxyl group donor.\textsuperscript{[38]}

The difference in reactivity between 1,2,3-trimethylbenzene and 1,2,4-
trimethylbenzene highlights one of the limitations of the IE model. In the former case, the molecule reacts in the ortho-position relative to the 1- and 3-methyl groups and the two positions are equally reactive due to the molecular symmetry. This is correctly predicted by the IE surface, however in the latter case the IE surface incorrectly predicts the 3 and 5 positions to be equally reactive. The observed reactivity can be explained by the fact that the 3 position is more sterically hindered than the 5 position, hence the major isomer is the 5-substituted product. The difference in the steric environment between two reactive sites is not considered by the IE calculations and so the two sites are predicted to be equally reactive.

\[ N,N\text{-dimethyl-2-(trimethylsilyl)benzamide and 4-nitro-2-(trimethylsilyl)} \]
phenyl diethyl carbamate both undergo ipso-substitution reactions where the TMS group is substituted. 2-(trimethylsilyl)phenyldiethyl carbamate also undergoes ipso-substitution, but in this case minor products are observed in both positions meta to the TMS group.

\[ N,N\text{-diethyl-2-methoxybenzamide reacts in the ortho and para positions, relative to the methoxy group, with equal amounts of the two isomers being observed.} \]
\[ N,N\text{-dimethyl-2-methoxy-6-(trimethylsilyl)benzene and 2-methoxy-6-(trimethylsilyl)phenyl diethyl carbamate show the same regioselectivity pattern, however in these cases the ortho position is more favoured than the para.} \]

Finally, 3,5-dinitrosalicylic acid reacts via an ipso-substitution mechanism at the carboxylic acid position.
Figure 2.10 (Page 56) - Experimental reactivity patterns and corresponding calculated average local ionisation energy surfaces and minimum values ($I_{s, \text{min}}$) at the 0.002 electrons/bohr$^3$ surface for multiply-substituted benzenes. References for the observed reactivity patterns are given in the main text.
2.8.3. Metallated Aromatics Employed in Cross-Coupling Reactions

Metal catalysed cross-coupling reactions are widely employed in organic synthesis as an efficient method for the synthesis of otherwise difficult to obtain molecular structures.\(^{41,42}\) Palladium-catalysed reactions in particular have had such a great impact on synthetic chemistry that Heck, Negishi and Suzuki shared the 2010 Nobel Prize in chemistry for their work on palladium-catalysed cross couplings in organic synthesis.\(^{43}\)

Figure 2.11 shows some of the metallated aromatic compounds used in organic synthesis. Phenyl lithium,\(^{44,45}\) sodium,\(^{46}\) and zinc chloride,\(^{47}\) all undergo *ipso*-substitution reactions with halogens, making them useful precursors for palladium-catalysed reactions. Trimethylphenyl silane also undergoes a range of *ipso*-halogenation reactions,\(^{39,48-52}\) and can be useful intermediates to achieve unusual substitution patterns.\(^{53}\) A range of other metals is also used in cross-coupling reactions, including mercury,\(^{54,55}\) indium,\(^{56}\) germanium,\(^{41}\) and tin\(^{54}\) although these are not as commonly used as their palladium and lithium counterparts.

The reactivity of all of the compounds discussed above is correctly predicted by the IE model (Figure 2.11, page 58). Given this success, perhaps IE surfaces could be used to aid in the development of new cross coupling reactions by helping to identify different metals that could be used in such applications.
Figure 2.11 - Experimental reactivity patterns and corresponding calculated average local ionisation energy surfaces and minimum values ($\bar{I}_{S, \min}$) at the 0.002 electrons/bohr$^3$ surface for phenyl derivatives used in metal-catalysed cross-coupling reactions and ipso-substitution reactions. Calculations were performed using the LACVP combination of basis sets where DFT/B3LYP/6-311G* was not supported.
2.8.4. Five-membered Heterocycles

Figure 2.12 shows the ionisation energy surfaces for a series of 5-membered heterocycles. Most of these compounds react via a standard electrophilic aromatic substitution mechanism, although furans may proceed through an addition-elimination mechanism. As in a typical EAS reaction it is the position of the initial attack of the electrophile that determines the regiochemistry of the final product. The reduced aromatic character of furan is reflected in the ability of furan to undergo oxidation reactions with osmium tetroxide to give the dihydroxy product via an osmate ester intermediate (hollow arrows in Figure 2.12, page 60).

The position of the minimum value on the IE surfaces of thiophene, furan and pyrrole are noteworthy. In thiophene the minima are located over the centre of the carbon atoms of the 2 and 5 positions, whereas in the other two molecules the minima are located closer to the centre of the formal double bonds. This is a consequence of the greater aromatic character of the $sp^2$-hybridised carbons in thiophene compared with furan and pyrrole. Ionisation energy surfaces of unsubstituted alkenes are similar in that the minimum is located over the centre of the double bond. These molecules all react through the equivalent 2 and 5 positions under standard electrophilic substitution conditions.

Pyrroles substituted with an electron withdrawing group in the 2-position react primarily in the 4-position. This is in contrast to the corresponding thiophenes and furans. Pyrroles with electron withdrawing groups in the 3-position display the same reactivity as do the corresponding thiophenes and furans.

The effect of electron donating groups in pyrroles, thiophenes and furans can be deduced from the directing effects of the substituents and are all correctly predicted by the IE model. Electron-rich pyrroles tend to be highly reactive and unstable, which is reflected in the lower minimum IE value compared with the corresponding furans and thiophenes.

Imidazole and thiazole react in a similar manner, with 5-substitution being the major reaction pathway, however imidazole can also undergo oxidation with osmium tetroxide (unfilled arrow). Oxazole tends to undergo addition rather than substitution (unfilled arrow).
2.8.5. Fused Five-Membered Heterocycles

The fused five-membered heterocycles indole,[61],[97],[60] benzofuran[60],[98] and benzothiophene[99],[60],[100],[98] react much as do their non-fused counterparts, with the 5-membered ring being more reactive in all cases than the benzene ring to which they are fused. The regioselectivity of indolizine is perhaps more difficult to predict using the concepts of resonance theory, however the IE surface corresponds well with the observed reactivity (Figure 2.13).[101],[102]

The imidazopyridine compounds demonstrate one of the caveats of the IE model, namely that the protonation state of the molecule must be considered in the calculation. The cationic species is much less reactive than the non-protonated compound and so the reaction generally occurs on the neutral molecule.[103] Imidazo[1,5-a]pyridine is interesting in that the regioselectivity prediction of the model is different for the protonated and unprotonated states. This compound is found
to react in the 1 position, and not on the benzene ring. In this case, the significantly lower IE value makes it obvious that the much more reactive neutral compound is the reactive species, however this example does indicate that the method may be able to offer insights into mechanisms where the precise nature of the reactive species is not certain, or provide a basis for rationalising the observation of unexpected regioisomers.

**Fused 5-Membered Heterocycles**

![Diagram of various heterocycles with their respective ionization energies]

*Figure 2.13* - Experimental reactivity patterns and corresponding calculated average local ionisation energy surfaces and minimum values ($\bar{I}_{S,\text{min}}$) at the 0.002 electrons/bohr$^3$ surface for fused 5-membered heterocycles. Unfilled arrows indicate sites where oxidation reactions occur.

### 2.8.6. Biphenyl and Naphthyl Derivatives

Naphthalene is an important chemical in the chemical and pharmaceutical industries. It is used in the synthesis of 2-naphthol, which is used as a precursor to various dyes, pigments and other pharmaceuticals. Figure 2.14 (page 62) shows the IE surfaces for some naphthalene and biphenyl derivatives. Naphthalene undergoes a range of electrophilic substitution reactions, including nitration, halogenation, and acylation, but can also undergo addition and oxidation reactions.
While both rings in naphthalene are equally reactive, substituent effects can alter the relative reactivity of the two rings. 1-Methoxynaphthalene reacts in the 2 and 4 positions (ortho and para to the methoxy substituent).\textsuperscript{[110]} The IE surface predicts both the 2 and 4 positions to be equally reactive, however experimental observations show that the para-isomer is the major product.\textsuperscript{[74]} This discrepancy between observation and prediction can be explained by the steric hindrance at the 2-position.

In contrast, 2-methoxynaphthalene has secondary reactive sites at the 6 and 8 positions, in addition to the primary reactive site at the 1-position.\textsuperscript{[110],[111],[112],[74]}

Electron-withdrawing groups, as expected, have the opposite effect. These groups deactivate the substituent-bearing ring, making the second ring the most reactive. Both 1- and 2-nitronaphthalene react at the 5 and 8 positions.\textsuperscript{[70],[113-115]} While both of these positions are equally reactive in 2-nitronaphthalene,\textsuperscript{[115]} the 8-position in 1-nitronaphthalene is more reactive than the 5-position. This is correctly predicted by the IE surface and may be due to different through-bond effects or due to the presence of through-space effects in 1-nitronaphthalene (see Chapter 3).
Figure 2.14 (page 62) - Experimental reactivity patterns and corresponding calculated average local ionisation energy surfaces and minimum values ($\bar{I}_{s,\text{min}}$) at the 0.002 electrons/bohr$^3$ surface for biphenyl and naphthalene derivatives. Unfilled arrows indicate sites where oxidation reactions occur.

2.8.7. Pyridine Derivatives

Pyridine is less reactive than benzene,$^{116-117}$ and also differs in that it is not the neutral form which undergoes electrophilic substitution, but rather the pyridinium ion.$^{118}$ Although the IE surface predicts the correct regioselectivity, the minimum IE value of 15.4 eV suggests that the pyridinium ion is not very reactive. When the pyridine ring is substituted with electron donating groups, the effect of the nitrogen and the substituent compete and the regioselectivity is determined by the substituent, which typically has a stronger effect than the nitrogen.$^{119-122}$

Pyridine N-oxide demonstrates the importance of running the calculation on the actual reactive species, as the regioselectivity of the non-protonated N-oxide and its protonated form is markedly different. Pyridine N-oxide reacts in the ortho and para positions,$^{123,124}$ with a preference for para-substitution, whereas upon protonation the regioselectivity changes and meta-substitution is observed.$^{124,125}$ Like the pyridinium cation, the IE value would suggest that the protonated N-oxide has low reactivity.
2.8.8. Quinoline Derivatives

Quinoline derivatives consist of a pyridine ring fused to a benzene ring. Two isomeric forms of quinolone exist - quinoline and isoquinoline – which differ in the positioning of the nitrogen atom. In contrast to naphthalene, where both rings are equally reactive, the pyridine ring in quinoline is much less reactive than the benzene ring. Both quinoline and isoquinoline undergo a variety of halogenation reactions\cite{126-134} at the 8 and 5 positions. While quinoline reacts primarily in the 8 position, in isoquinoline it is the 5 position which is most reactive. The IE surface of quinoline correctly predicts the regioselectivity, however in isoquinoline the IE minimum is located on the pyridine ring. Since the IE surface of the isoquinolinium ion does correspond to the observed...
reactivity this suggests that it is the cation that is overwhelming present in solution under the reaction conditions employed where this regioselectivity is observed.

The reactivities of quinoline and isoquinoline N-oxides also differ from each other. While the most reactive position of quinoline N-oxide is correctly identified by the IE surface, in the case of isoquinoline N-oxide it is again the surface of the cationic species that corresponds to the observed reactivity.\textsuperscript{[135]-[136]}

The difference in reactivity of the two forms of chromone and quinolone are correctly predicted by the IE surfaces.\textsuperscript{[137]-[140]}

Figure 2.16 - Experimental reactivity patterns and corresponding calculated average local ionisation energy surfaces and minimum values ($\overline{I}_{\text{e, min}}$) at the 0.002 electrons/bohr$^3$ surface for quinoline derivatives. Striped arrows indicate protonation sites.

2.8.9. Aromatic Compounds Containing 7-Membered Rings

Azulene is an isomer of naphthalene which has one 7-membered and one 5-membered ring. The name of this compound is derived from its dark blue colour and is derived from the Spanish word azul ("blue"). It undergoes electrophilic substitution at the 3
position,[112] as indicated on the IE surface.

The dihydro-1,4-diazepinium cation has been described as quasi-aromatic due to its propensity to undergo electrophilic substitution reactions similar to those of true aromatic substrates. These unusual substitution reactions are highly-selective for the 6 position and accordingly the calculation ionisation energy minimum is localised over this position.[141-145]

Substitution reactions of tropolone proceed primarily through the equivalent 3 and 7 positions, with some 5-substituted product also observed.[146],[147] In the protonated cationic form of tropolone the regioselectivity pattern is reversed, with the 5 position being the most reactive site followed by the 3 and 7 positions.[146],[147] Although the 3 and 7 positions are equivalent, the orientation of the hydrogen bonds the orientation of the hydrogen bonding groups breaks the symmetry in the fixed conformations shown in the calculated IE surfaces.

![Image of 7-Membered Aromatics](image)

Figure 2.17 - Experimental reactivity patterns and corresponding calculated average local ionisation energy surfaces and minimum values ($\bar{I}_{E, \text{min}}$) at the 0.002 electrons/bohr$^3$ surface for 7-membered aromatics. References for the observed reactivity patterns are given below.

2.8.10. Polycyclic Aromatic Compounds

Polycyclic aromatic hydrocarbons (PAHs) were studied by Fukui in his development of FMO theory.[3] While all of these compounds undergo electrophilic substitution, in common with compounds such as furan (see above) some PAH are known to
participate in oxidation reactions.[148-150]  

Figure 2.18 - Experimental reactivity patterns and corresponding calculated average local ionisation energy surfaces and minimum values ($\bar{I}_S$, min) at the 0.002 electrons/bohr$^3$ surface for polycyclic aromatics. Values in parentheses refer to the values taken over regions with double-bond character as discussed in the main text. References for the observed reactivity patterns are given below. Unfilled arrows show sites where oxidation reactions occur.

The reactivity of triphenylene$^{[151],[99],[108]}$ and fluoranthene$^{[151]}$ is correctly predicted by
the IE surface, however the interpretation of some of the other surfaces is perhaps not so straightforward (Figure 2.18). The IE minimum in anthracene is found over the centre of the bond between carbons 1 and 2, reflecting its tendency to undergo oxidation reactions at this position.\cite{148,152,153} If one considers only the values over the centres of the carbon atoms, then the lowest value is found over the 9 position, where electrophilic substitution occurs.\cite{108,99,154} A similar situation is found in pyrene, where oxidation occurs at the double bond between carbons 4 and 5\cite{155} (global IE minimum), while electrophilic substitution occurs at the 1-position\cite{108,151,99} (lowest IE located over a carbon atom). Similar patterns are observed in the IE surfaces of alkenes (Figure 2.19), where the minima are located over the centre of the double bond, suggesting that these molecules have significant double bond character.

**Figure 2.19** – Calculated average local ionisation energy surfaces and minimum values ($\tilde{I}_{\text{S, min}}$) at the 0.002 electrons/bohr$^3$ of ethylene and trans-2-butene, showing the minima located over the centre of the double bond. This is similar to some of the minima observed in polycyclic aromatic hydrocarbons shown in Figure 2.18

The reactivity of borazarophenanthrenes have been shown to be particularly challenging to predict, with FMO theory and the Fukui function both failing to predict the observed regioselectivity.\cite{5,6} However, IE surfaces are in agreement with the experimental data.\cite{108,149,156-158}

The reactivity of chrysene\cite{106,151,99,159,160,108} and benzo(c)phenanthrene\cite{108,149} is similar to that observed in phenanthrene, however in these cases two of the four rings are equally reactive due to the symmetry of the molecules. Both of these compounds also undergo oxidation with osmium tetroxide.\cite{150,161}
One further interesting curiosity is provided by bisbenzo[3,4]cyclobuta[1,2-a:1',2'-c]biphenylene, whose central ring is best described as a cyclohexatriene with alternating single and double-bonds, rather than being benzenoid in character.\textsuperscript{[162],[163]} In accord with the experimental observations, the IE minima lie over the double-bond regions in the central ring and not the outer aromatic rings. The IE surfaces calculated for the minimised and crystal structures of this molecule are also sensitive to bond lengths and bending induced by crystal packing forces, giving local IE minima of 9.0 and 8.8 eV for each respective structure.\textsuperscript{[164]} Also of note is the similarity of the locations of IE minima in polycyclic aromatics compared to the recent direct observations of bond order obtained using noncontact atomic force microscopy.\textsuperscript{[165]}

### 2.9. Application of the Model to Non-Aromatic Compounds

Aromatic compounds undergoing electrophilic aromatic substitution reactions generally follow the same basic reaction pathway which is well approximated by the removal of an electron from the substrate. As a consequence, local IE calculations often successfully predict the reactive behaviour of a wide range of aromatic substrates. Non-aromatic compounds, by contrast, have a much greater variety of reaction mechanisms and therefore the IE method is not expected to be universally applicable to all types of electrophilic substitution and addition reactions.

Mayr and colleagues have compiled an extensive database of nucleophilicity parameters, $N$ for a wide range of compounds.\textsuperscript{[14]} We therefore attempted to correlate $N$ with the minimum IE values of these compounds. As expected, the results were mixed. Reasonable correlations were obtained for a variety of compound classes including carbocyclic and heterocyclic arenes, phosphorus nucleophiles, diazo compounds, pyridines, enamines, isocyanides and conjugated-1,3-dienes (Figure 2.20, page 70), though in some cases the number of data points were limited. Several other classes of compounds gave poor correlations, including alkenes, nitrogen nucleophiles, ylides, silyl enol ethers and allyl silanes (Figure 2.21, page 70).
In some cases it is difficult to rationalise why the reactivity of one class of molecules is predicted successfully while that of another class is not. For example, phosphorous lies directly beneath nitrogen on the periodic table, both react by similar mechanisms
via their lone pairs, so the two elements might be expected to display very similar properties, yet one group is predicted well, and the other is not. The contrast between alkenes and dienes is also surprising. Alkene nucleophilicity is poorly predicted by calculated IEs, despite the fact that it has been shown that log \( k_{\text{rel}} \) for \( m\text{-CPBA} \) expoxidation of alkenes correlates with experimentally determined IE values of the alkene substrate.\(^{166} \) Solvent effects are probably minimised, as all of the data plotted was obtained in DCM, however, different substrates may be solvated differently, and this may affect their reactivities. This would provide an explanation as to why the IE model fails in some cases, as solvent effects are not considered.

All of the data sets that gave reasonable correlations were plotted on the same graph to assess the ability of the model to directly compare the reactivities of a diverse range of molecules in a quantitative manner. The correlation coefficient in this case is 0.64, which suggests that it may be more appropriate to consider each class of molecules individually, rather than on a single reactivity scale. The most likely explanation for the varying levels of success is that each class of molecules reacts via different mechanisms and therefore have different energy profiles, the rate determining step of which may or may not be reasonably approximated by the IE calculations.

### 2.10. Caveat Emptor

Like every predictive model, local ionisation energy calculations have advantages and drawbacks. Some of these have been alluded to previously in this chapter, however it is useful to provide a summary of each.

Firstly, the ionisation energy of a molecule is an observable, measurable property that has a real physical meaning. The model is also chemically intuitive and the surfaces are easy to interpret. Both of these points are in contrast to other models which are often based on abstract concepts that have an obscure physical meaning. It is also apparent that the information being encoded on the IE surface resembles the process by which the reaction takes place for some classes of reaction. The nucleophilic substrate can be thought of as giving up an electron to form a covalent bond with the electrophile.

Another advantage of the model is its simplicity. Only one simple calculation is required, which considers only the ground state structure of the substrate. No
knowledge of the transition state is required, unlike more complex methods such as the recently proposed Electrophile Affinity model,\textsuperscript{[30]} which requires calculation of the transition state structure and requires several calculations to be performed before any deductions about the reactivity of a given aromatic substrate can be made.

Thirdly, the graphical representation means that it is easy to compare the relative reactivities and regioselectivities of several compounds very quickly. This is in contrast to FMO theory, where the HOMO orbitals can be very complex and difficult to interpret, even in relatively simple systems. Orbital degeneracy must also be taken into account in the FMO approach.

The ionisation energy model may also be of use in predicting previously overlooked physicochemical phenomena that contribute to the reactivity of aromatic compounds. For example, the IE surfaces of 1-phenyl-9-fluorenone and 3-phenyl-9-fluroeneone suggest that a phenyl ring may be more reactive towards electrophilic aromatic substitution (see Chapter 3).

The IE model is based on simple gas-phase calculations, and there are certain points which must be considered in its application to solution-phase reactions.

Firstly, solvent effects are not taken into account in the calculation of gas-phase ionisation energies. Care must be taken to ensure that any experimentally determined rate constant (or any parameter derived from this kinetic data) is obtained in the same solvent before being used to validate the IE model of reactivity. This should minimise errors associated with solvent effects, which can clearly have a great influence on the rate of a reaction. Similarly, predictions of relative reactivities are only valid for reactions performed under the same reaction conditions.

Secondly, the protonation state of the substrate must be considered. For example, nitration reactions typically employ strongly acidic conditions, meaning that calculations must be performed on the protonated substrate rather than the neutral form. Large changes in reactivity can occur upon protonation, both in terms of the rate of the reaction, but also in terms of regioselectivity. To illustrate this point, the NH\textsubscript{2} group in aniline is an ortho/para-directing group, whilst NH\textsuperscript{+} is unusual in that it directs to the meta and para positions.\textsuperscript{[167]}

Thirdly, the IE model is purely based on electronic effects and does not take into account any steric factors that may influence the outcome of the reaction.
Similarly, the size and shape of the incoming electrophile also has a role in determining the outcome of the reaction. Thus, steric factors must be taken into account separately when using IE calculations to predict the reactivity of a given molecule. Another phenomenon that may not be predicted by the IE model is neighbouring group participation, in which the incoming electrophile is directed to a particular position by intermolecular interactions such as hydrogen-bonds or electrostatic effects.

Additionally, the IE model can only be used as a reactivity descriptor for reactions which are under kinetic control. Reactions whose outcomes are determined by thermodynamics rather than kinetics, e.g. aromatic sulfonation, cannot be predicted correctly by the IE model.

One final criticism of the IE model is that there is currently no way to predict where the method would be expected to be a reliable reactivity descriptor and where it would be expected to fail. The only way to validate the utility of the model is to compare the predictions for each type of reactions with experimental data, which can be a time-consuming process.

2.11. Conclusions

In summary, experimental observations spanning over 150 years of synthetic developments in the field of aromatic chemistry have been used to evaluate the predictive capacity of average local ionisation energy calculations and several other reactivity models. This large-scale systematic analysis has exposed numerous synthetically useful regioselectivities that are not predicted by many popular methods including resonance theory, FMO theory, the Fukui function and electrostatic models. Many of these simple theoretical approaches fail to account for the reactivity of aromatic molecules because kinetic reactivity cannot usually be extrapolated from ground-state properties (such as HOMOs and ESPs). Even though the Fukui function considers the changes in the HOMO coefficients between the ground-state and an intermediate resembling the transition-state formed in the rate-determining step, it still fails to account for the reactivity patterns observed in simple aromatic compounds.\[6,168,10\]

In contrast, calculated average local ionisation energies have been shown to
approximate the energy change accompanying the rate-determining step in the reactions of electrophiles with aromatic molecules when steric demands are low. Despite its simplicity, the IE method enables visualisation of the fundamental electronic factors governing reactivity in kinetically controlled aromatic reactions. Thus, numerous examples have been highlighted where reactivity predictions derived from resonance theory fail, but where IE surfaces succeed due to its apparent ability to take resonance, inductive effects and bond strain into account.

Local ionisation energy is not a universally applicable model, and IE surfaces do not correspond to the observed reactivity patterns in several classes of molecules (section 2.9). There are also several considerations that must be taken into account when using IE surfaces as a predictive model (section 2.10). Despite these limitations, this analysis has established IE surfaces as providing the most comprehensive simple rationalisation of aromatic reactivity to date. Since IE surfaces are both easily interpreted and provided as standard in popular computational chemistry software, it is hoped that the approach will assist in the development of new synthetic strategies, mechanistic understanding and chemical education.
References

Chapter 3

An Investigation into Through-Space Effects and Their Influence on Reactivity

Abstract

Non-covalent interactions are fundamental forces that underpin the behaviour of many chemical and biological species. The study of these effects is often complicated by the fact that the observed behaviour is a result of several effects working in tandem. Previous work in the Cockroft group showed that through-space electrostatic effects can influence the conformational equilibrium in a series of simple molecular torsion balances.\[1\] This project aims to determine whether these through-space effects can influence the reactivity of an aromatic ring. Calculations show more negative electrostatic potentials in aromatic rings positioned close in space to an electron rich atom such as oxygen, while ionisation energy surfaces also predict an increase in the nucleophilicity of these rings relative to those too far away to interact with donor atom. These predictions were tested experimentally in a number of experimental model system, however further work is required to clearly determine whether through-space effects play a significant role in governing chemical reactivity.

3.1. Introduction

The effect of substituents on the properties of aromatic rings has long been known to chemists. The electron-donating or electron-withdrawing properties of substituents can be quantitatively measured using Hammett \(\sigma_m\) and \(\sigma_p\) constants,\[2-4\] while \(\sigma^*\) constants serve the same purpose in aliphatic systems.\[5-7\] The field substituent constant, \(F\) and the resonance substituent constant, \(R\) can be derived upon further analysis of the Hammett equation.\[8-10\] As their names suggest, these measure the through-bond resonance and field contributions to the electronic effects of substituents.\[8\] Molecular electrostatic surface potentials\[11,12\] have also proved to be a popular way to study the inductive\[13\] and resonance\[14\] effects of substituents.

A recent paper by Wheeler concludes that the effects of substituent on aromatic
rings (and in particular regard to \(\pi\)-stacking and cation-\(\pi\) interactions) can be explained solely in terms of the through-space effects of the substituents. It is even claimed that resonance effects play “no significant role”.\(^{[15]}\) It is also suggested that the observed changes in ESP surfaces above the centre of aryl rings is not necessarily due to changes in \(\pi\)-electron density but are primarily caused by the through-space effects of the substituents.

Previous computational studies have attempted to determine the effects of substituents in model systems, most notably by Houk\(^{[16]}\) and Suresh.\(^{[17]}\) A computational study by Wheeler and Houk in 2008 compared the interaction energy of the substituted and unsubstituted component in a series of benzene dimers (Figure 3.1, page 82). By comparing the interaction energy of the benzene dimer (a) with that of the benzene-substituted benzene (b) and H-X (c) complexes they found that the interaction energy \(E_{\text{int}}\) correlates with \(\sigma_m\), showing that the electron donating or withdrawing properties of the substituent have an important effect on the interaction energy. Analogous studies with perfluorinated benzene complexes leads to the same conclusion, however the fact that the two sets of interaction energies are strongly correlated \((r^2 = 0.9)\) shows that the substituent effects do not operate through the \(\pi\)-system of the aryl ring (i.e. through resonance). The authors therefore conclude that there is a direct interaction between the substituent and the non-substituted aryl ring.\(^{[16]}\)

The authors propose that a model of stacking interactions,\(^{[18]}\) cation-\(\pi\) interactions\(^{[19]}\) and anion-\(\pi\)\(^{[20]}\) interactions based on these through space effects can explain the observed substituent effects in such systems, with polarisation of the \(\pi\)-system playing only a minor role.
Suresh was able to calculate the contributions of inductive, resonance and through-space effects of substituents using the model system in Figure 3.2[17] Complex (a) measures the inductive effect of the substituent X. No resonance effects are possible although there may be some through-space interaction. The inductive and through-space effects in complex (a) can be dissected apart by subtracting the interaction energy of complex (d) – the through space effect – from that of complex (a). Complexes (b) and (c) allow the resonance effects to be quantified. The energy of complex (b) includes a contribution from resonance whereas complex (c) does not because the substituent in this case is not in the plane of the aromatic ring and the whole system is not conjugated. Thus, the resonance energy can be calculated by subtracting the energy of complex (c) from that of complex (b). Complex (d), where the substituent is not connected to the aromatic ring, is used to measure the through space interaction energy.[17]

Figure 3.2 – Complexes used by Suresh to determine the contribution to the interaction energy of the phenyl ring and substituent X. Complex (a) measures the combined inductive and through space contributions, (b) measures the resonance contribution since the alkene is conjugated to the aromatic ring, (c) switches off the resonance contribution by having the alkene out of the plane of the ring and therefore the system is not fully conjugated. Complex (d) measures the through space contribution. The inductive contribution can be found by subtracting the interaction energy of (a) from that of (d).

Using this method, they find that substituents that are classically considered as 'electron-withdrawing' have a large through-space effect, whereas 'electron-donating'
substituents interact mainly through resonance. In contrast to Wheeler and Houk, they conclude that cation-π interactions are not dominated by one single type of interaction, but by the combined effects of inductive, resonance and through-space effects.\(^{[17]}\)

Molecular electrostatic surface potentials (ESPs) are often used to rationalise non-covalent interactions, including cation-π interactions\(^{[21]}\) and stacking interactions,\(^{[22-24]}\) however Wheeler and Houk argue that there is a widely held misconception about the effect of substituents on ESP surfaces.\(^{[25]}\) Their analysis of the ESPs of a number of molecules ranging from simple substituted benzenes to more complicated structures such as substituted anthraquinones and the antimalarial drug crypolepine show that changes in the ESP of the aromatic rings arises mainly due to through-space interactions with the substituents.\(^{[25]}\) They also point to the success of molecular mechanics force fields in describing supramolecular assembly\(^{[26]}\) as evidence for this through-space interaction, since force fields do not model changes in the aryl π-system and so would be expected to be poor models in systems where π-π interactions are dominant.

ESPs have also been used to quantify both through-bond and through-space effects in substituted alkyl, alkenyl and alkynyl arenes (Figure 3.3).\(^{[27]}\) By measuring the minimum ESP value over the aromatic ring in each case, the through-space effect was found to contribute 79.6% in the alkyl system (a). In the unsaturated analogues the through bond effects are dominant (55%).\(^{[27]}\) This seems to suggest that the through-space interaction in such systems is stronger than the inductive effect, but approximately the same as resonance effects.

![Figure 3.3](image-url)

*Figure 3.3 – Systems studied by Suresh and colleagues in their assessment of through-bond and through-space effects.*
Through-space effects have been identified experimentally in studies of carboxylic acids.\textsuperscript{[28-30]} In particular, it has been observed that 2'-substituted biphenyl-4-carboxylic acids are weaker acids than their 4'-substituted counterparts.\textsuperscript{[28]} This was previously attributed to the steric bulk of the 2'-substituent causing the \(\pi\)-electrons of the adjacent ring to be displaced towards the carboxylic acid, lowering its acidity. However, through-space electronic effects may be involved. These compounds are similar to the biphenyl derivatives presented later in this chapter as a means to study the effect of through-space interactions on reactivity.

Similarly, in studies of the ionisation constants of substituted bicyclo[2.2.2]octane carboxylic acids, the magnitude of the substituent effect was found to be similar to that found in meta- and para-substituted benzene derivatives, despite no resonance contribution being possible in the bicyclooctane system.\textsuperscript{[29]}

Previous work in the Cockroft group studied through-space effects on the electrostatic properties of aromatic rings using molecular torsion balances (Figure 3.4).\textsuperscript{[1]} Changes in the ESP near the central ring caused by through-space interactions affected the free energy of folding of the balance, providing a relatively simple way of measuring the magnitude of the through-space effects. This study may constitute the first experimental measurement of the through-space influence of substituents on remote functional groups. The effect of these interactions on the folding free energy was found to correlate with ESP calculations. The project presented in this chapter builds on this previous work measuring through-space effects.

![Figure 3.4](image.png)

**Figure 3.4** – Molecular torsion balances used to experimentally measure through-space effects of substituents.
3.2. Background and Aims of the Project

It is well-known that substituents directly bonded to an aromatic ring affect the reactivity of the ring towards electrophilic substitution (Chapter 2). Analysis of calculated ESPs from other work being conducted in the Cockroft group suggested the possibility that the nucleophilicity of an aromatic ring might be increased when the oxygen atom of a carbonyl group is held close in space in biphenyl derivatives (Figure 3.5a). It is important to note that these calculations do not represent the lowest energy conformers, but were instead performed to assess the maximum possible through-space influence of a proximal oxygen atom. In contrast, the ESP of the para-phenyl-carboxylic acid did not show an increase in electrostatic potential on either of the aromatic rings (Figure 3.5b).

Figure 3.5 – ESP surfaces of 2- and 4-biphenylaldehyde, showing the increased negative value of the electrostatic potential of the phenyl ring on compound (a). All surfaces are coloured using a scale from −100 (red) to +100 kJ mol⁻¹ (blue).

The increased negative value of the ESP is evidenced only on the side of the ring facing the oxygen, and the 'underside' of the ring does not show any significant change in ESP, as expected for a through-space field effect. Based on this observation, the IE surfaces of the ortho- and para-phenyl benzaldehydes were calculated. Based on the work presented in Chapter 2, the decrease in the local IEs might predict that the compound shown in Figure 3.6a would be more reactive to electrophilic substitution than the compound shown in Figure 3.6b.
Thus, the aim of this project was to assess the potential through-space effects of a variety of substituents on the reactivity of aromatic rings, and to determine whether these predicted changes in reactivity could be detected experimentally.

3.3. Computational Survey of Through-space Substituent Effects

Taking inspiration from earlier work on biphenyl carboxylic acids,\cite{28-30} and previous formyl balances synthesised in the group (Figure 3.4, page 84), average local ionisation energy calculations were performed to assess which types of substituents might be expected to give significant changes in nucleophilic reactivity via through-space effects. Local average ionisation energy surfaces were computed for a series of biphenyl compounds using DFT/B3LYP/6-311G*. This combination of functional and basis set was found to be optimal in the prediction of the outcome of electrophilic substitution reactions (Chapter 2). The results are summarised in Figure 3.7 (page 87), which compares the IE surfaces of 2-substituted biphenyl compounds with the corresponding 4-substituted control compounds (in which no through-space effects should be apparent).
With the exception of the amino group, all of the substituents studied are predicted to increase the reactivity of the non-substituted ring when in the 2'-position. The behaviour of the amino group can be explained by the fact that the lone pair of the nitrogen points away from the ring. Substituents bearing carbonyl groups seem to display the greatest effect, the difference of 0.43 eV between the active and control biphenylaldehyde derivatives being particularly large. Provided that the ionisation energy model is reliable, then the difference in reactivity between these two compounds would be anticipated to be similar to that between benzene and toluene (see Chapter 2).

The nitro group is interesting because although it is an electron-withdrawing group through resonance, it appears to act as though it is electron-donating through
space (though it should be noted that this is a through-space effect and no electrons are actually being donated). The predicted increase in reactivity is similar to that in the biphenyl ester example.

Halogen donors donate electrons via resonance when directly bonded to aromatic rings, but in general inductive and field effects mean that overall halogens have a deactivating effect in electrophilic reactions. In contrast, this behaviour is reversed via through-space interactions, but the difference between the active and control compounds is only ~0.1 eV, which may be difficult to observe experimentally.

Although the predicted differences in reactivity of most of the computational model compounds should be experimentally observable (assuming that the IE model is valid), biphenyl compounds are not ideally suited to experimental studies, since the aryl-substituent bond is free to rotate, thereby altering the geometry of the through-space interaction. Indeed, it is likely that an electron-rich atom such as oxygen will point away from an electron-rich aryl ring given freedom to rotate. For this reason it is necessary to lock the geometry of the aryl-oxygen through-space interaction in the experimental model compounds.

3.4. Pyridine $N$-Oxide Derivatives

Due to the conformational flexibility of the biphenyl compounds used in the initial survey of through-space substituent effects, an alternative experimental model system was sought. Since oxygen atoms were identified as being one of the most interesting substituents capable of inducing significant through-space activating effects, it was proposed that phenylpyridine-$N$-oxides might provide a suitable starting point (Figure 3.8, page 89). The ‘activated’ compound in which the oxygen atom was positioned above the adjacent ring has a minimum ionisation energy approximately 0.3 eV lower than that of the control. Such a difference in reactivity should be detectable by experiment since it approximately corresponds to the difference in reactivity between benzene and anisole (see Chapter 2).
3.4.1. Synthesis of Target Compounds

The synthesis of 2- and 4-pyridine-N-oxides was achieved by heating the corresponding phenylpyridine in acetic acid with hydrogen peroxide at 120°C, following a literature procedure. The reactions gave moderate yields of 55% and 61% respectively.

Scheme 3.1 – Synthesis of 2- and 4-phenylpyridine-N-oxide.

3.4.2. Kinetic Experiments

Previous reports of mild halogenation reactions of chlorobenzene led us to examine the reactivities of 2- and 4-phenylpyridine-N-oxide. These compounds have very similar local ionisation energy values to that of chlorobenzene (9.34, 9.57 and 9.58 eV, respectively) and therefore would be expected to react under similar conditions. It was
decided to monitor the reaction kinetics using NMR spectroscopy. The main advantage offered by this method over HPLC methods is that the reaction can be performed in an NMR tube to allow continuous monitoring throughout the course of the reaction. A few factors limit the type of reaction that can be performed however; the solvent had to be non-volatile and deuterated, while the temperature had to be kept relatively low (less than 80°C) to avoid evaporation of solvent and avoid damage to the spectrometer.

A series of reaction conditions were considered before settling on a halogenation reaction using *N*-bromosuccinimide (NBS) in acetonitrile (Table 3.1).

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Solvent (dry)</th>
<th>Catalyst</th>
<th>Temperature/Time</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCS</td>
<td>DCM</td>
<td>None</td>
<td>25 °C / 3 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>NBS</td>
<td>DCM</td>
<td>None</td>
<td>25 °C / 3 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>NIS</td>
<td>DCM</td>
<td>None</td>
<td>50 °C / 18 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>NIS</td>
<td>CHCl₃</td>
<td>None</td>
<td>25 °C / 3 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>NIS</td>
<td>CHCl₃</td>
<td>C₁₄H₁₀O₄</td>
<td>50 °C / 18 h</td>
<td>Observed colour change</td>
</tr>
<tr>
<td>NIS</td>
<td>MeCN</td>
<td>FeCl₃</td>
<td>70 °C / 3 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>NBS</td>
<td>MeCN</td>
<td>None</td>
<td>70 °C / 3 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>NBS</td>
<td>MeCN</td>
<td>FeBr₃</td>
<td>75 °C / 3 h</td>
<td>Increase of succinimide peak</td>
</tr>
</tbody>
</table>

*Table 3.1* – Summary of reactions performed. All reactions were tested using chlorobenzene (similar local IE value) as substitute. Test reactions were performed by Eugene Choon Guobin, an exchange student in the group.

Reactions using NBS and NIS in chloroform and DCM gave no reaction despite being left for 18 h, while bromination using NBS in deuterated acetonitrile with an iron trichloride catalyst gave a reaction after three hours at 75 °C. The presence of the iron in the catalyst did not seem to affect the spectra acquired by NMR, and the relative rates of reaction of the 2- and 4-phenyl compounds should not be affected provided that the catalyst loading is the same in each case. The reaction also does not proceed at room temperature, allowing for convenient preparation of NMR samples.
The reaction was followed by measuring the change in the signal of the succinimide by-product because the aromatic region of the spectrum was too cluttered to reliably follow any individual peak. Figure 3.10 shows a portion of the NMR spectra of the kinetic experiments. The 2-phenylpyridine-N-oxide experiment (Figure 3.9a) shows an increase in the succinimide signal over time, whereas the control experiment with 4-phenylpyridine-N-oxide shows no increase in the succinimide peak (Figure 3.9b)

![Figure 3.9](image)

**Figure 3.9** – $^1$H NMR spectra of the reaction between NBS and 2-phenylpyridine-N-oxide (a) and 4-phenylpyridine-N-oxide (b). Only the portion of the spectra showing the NBS peak (*) and the succinimide peak (*) is shown (3.1 - 2.7 ppm). Each experiment was run for 3 h with spectra taken at 15 minute intervals.

The presence of the succinimide peak in the control experiment is thought to be caused by reaction of NBS with acetic acid remaining from the 4-phenylpyridine-N-oxide synthesis, due to the difficulty in purifying these compounds. The experiment was repeated taking care to remove all traces of acetic acid. Spectra acquired at the beginning and end of this experiment show no succinimide signal and no change in the NBS signal after 3 hours. Mass spec data (Figure 3.10, page 91) suggested that no brominated 4-phenylpyridine-N-oxide is formed.
After 15 minutes, the integral of the succinimide peak was 0.24, while that of the NBS peak was 1.02 (relative to the acetonitrile peak which was set to 1.00). At the end of the experiment these integrals were 0.37 and 0.9 respectively, giving an increase in the succinimide signal of 10%.

Although these results seemed promising, the multiple possible reaction sites on the activated aromatic ring, and the difficulty in purifying the starting compounds and mixture of products obtained from the reaction meant that an alternative experimental system was sought.

3.5. Fluorenone Derivatives
Given the difficulties in isolating the pyridine N-oxide starting materials and products, phenyl-substituted fluorenone derivatives were envisioned as being suitable for experimental studies as the molecular structure locks the geometry of the carbonyl-aryl through-space interaction such that the oxygen is always over the ring. Figure 3.11 shows the local ionisation energy surfaces for the active and control compounds. The difference between the minimum values is 0.36 eV, therefore the difference in reactivity should be experimentally observable.
Two series of compounds can be devised based on a fluorenone core: one where the carbonyl oxygen is converted to other functional groups and another where the spacer that links the two phenyl rings is varied to change the molecular geometry. This allows both the range of functional groups that display the activating effect and the extent to which the through-space effect is dependent on the geometry of the aryl-oxygen interaction to be examined.

### 3.5.1. Computational Studies

Local ionisation energy calculations were performed on a series of fluorenone derivatives. Figure 3.12 (page 94) shows the results for a series of compounds where the carbonyl groups has been substituted.
Many of the substituents depicted in the figure display the expected activating effect (with the exception of NO$_2$, NH$_3^+$ and the triple bond systems - see below). The effect predicted in the sulfur compounds 2a and 2b is as strong as that predicted in fluorenone itself, as is the effect in the selenophene compounds 3a and 3b. However, the activating effects are most pronounced in fluorenone itself compared with its control compound. This is probably due to the lower electrostatic potentials of the substituents examined compared to the carbonyl oxygen. In addition, some of the singly-bonded substituents had different geometries compared to the double-bonded carbonyl oxygen, placing these alternative substituents in a more offset position over the adjacent ring.

With the NH$_3^+$ compounds 5a and 5b a deactivating effect was observed as might be expected; the 2'-substituted compound 5a was predicted to be less reactive than the 4'-substituted compound 5b. This can be rationalised as arising from the large field effects originating from the positive charge on the NH$_3^+$. A similar, but weaker effect is predicted in the nitro compounds 10a and 10b. In this case, the electron-rich oxygen atoms are twisted away from the ring, while the partially positively charged nitrogen atom is positioned over the adjacent ring, which is presumably the origin of the deactivating effect. Since even substituents with the same donor atoms, like the hydroxyl group in compound 6, show a much weaker effect than their double bonded counterparts, it can be concluded that the reason for the smaller magnitude of the effect is most likely due to the different geometry of the aryl-substituent interaction.

The compounds with triple bonds (cyano compounds 11a and 11b and alkyne compounds 12a and 12b) are not predicted to display any activating effect, perhaps due to the lower electrostatic potentials of these functional groups.

### 3.5.2. Synthesis of Target Compounds

A few procedures for the synthesis of fluorenone derivatives were found in the literature. The first attempt to synthesise the active compound followed a literature procedure$^{[33]}$ involving the lithiation of fluorenone followed addition of tributylborate
and acid to give the boronic acid (Scheme 3.2).

\[
\begin{align*}
\text{O} & \xrightarrow{1)} \text{Me} \xrightarrow{2)} n\text{-BuLi} \xrightarrow{3)} \text{B(OBu)}_2 \xrightarrow{4)} \text{H}^+ / \text{H}_2\text{O} \\
\text{HO} & \xrightarrow{\text{O}} \text{B-OH}
\end{align*}
\]

**Scheme 3.2** - First attempt at the synthesis of 9-phenylfluorenone.

This reaction proved unsuccessful despite numerous attempts. The lithium-\(N\)-methyl-piperazide compound is generated *in situ* in benzene, the solvent may not have been sufficiently dry, causing the butyl-lithium to react with the water rather than the fluorenone.

A similar set of conditions was used in a procedure beginning with biphenyl-2-carboxylic acid. The carboxylic acid was first substituted with the desired electrophile (a phenyl ring in this case) using an *ortho*-directed lithiation strategy.\[^{[34]}\] This procedure also failed to produce the desired product. It is likely that the final product was unstable due to its light-sensitivity.

\[
\begin{align*}
\text{OH} & \xrightarrow{1)} s\text{-BuLi} \xrightarrow{2)} \text{PhI, -78 °C} \xrightarrow{3)} \text{H}^+ \\
\text{OH} & \xrightarrow{\text{O}} \text{OH}
\end{align*}
\]

**Scheme 3.3** – Attempted synthesis of 9-phenylfluorenone from biphenyl-2-carboxylic acid.

Following this result, an alternative literature procedure was attempted\[^{[35]}\] that used more forceful conditions and an excess of Schlosser’s base to promote the ring closing reaction (Scheme 3.4, page 97).
Scheme 3.4 – Attempted synthesis of 9-phenylfluorenone using Schlosser’s base to facilitate the ring closing reaction.

The two-step procedure was attempted without success, likely for the same reasons as the failure of the earlier synthesis in Scheme 3.3, namely the light sensitivity of the triphenylcarboxylic acid.

A one-pot reaction was then attempted at a higher temperature and 3.5 equivalents of Schlosser’s base were added to deprotonate the biphenylcarboxylic acid at the 2'-position. The deprotonated compound is then expected to cyclise to give the dimetallated dialkoxide. Addition of sec-butyllithium followed by bromobenzene would then arylate the dialkoxide, to subsequently give the 9-phenylfluorenone target by acid hydrolysis (Scheme 3.5).

Scheme 3.5 – Attempted one-pot synthesis of 9-phenylfluorenone.

After repeated failures, it was eventually decided to abandon the fluorenone route due to the probable instability and light sensitivity of the desired product. A new series based on naphthalene was devised instead.

3.6. Naphthalene Derivatives

After repeated unsuccessful attempts to synthesise the fluorenone compounds, a series of naphthalene derivatives was devised to provide some preliminary data on the
through-space effects of some substituents (Figure 3.13).

![Diagram of naphthalene derivatives](image)

**Figure 3.13** - Naphthalene derivatives to test the influence of through-space effects on reactivity.

The active compounds 1-acetonaphthone and 1-nitronaphthalene have an oxygen atom above the unsubstituted ring, hence through-space interactions should be present in these compounds. The inactive compounds introduce a methyl substituent in the 2-position, which alters the geometry of the aryl-oxygen interaction and should switch off the through-space effects. The control compounds cyanonaphthalene and trifluoromethynaphthalene have similar electronic properties to the active compounds except that no through-space interaction is possible in these compounds.

### 3.6.1. Naphthalene Computational Studies

A study of the local ionisation energy surfaces of the six naphthalene compounds was performed in the same way as for the previous series. The energy surfaces are depicted in Figure 3.14 (page 99).
Figure 3.18 - Local ionisation energy surfaces of the six naphthalene compounds used in this study. All surfaces are set to a scale of $I_{S,min}+0.4$ eV. Quoted values are given in electronvolts and were read over the 5- and 8-positions.

The compounds a)i and b)i show a difference in reactivity between the 5- and 8-positions on the naphthalene rings, which should be large enough to observe experimentally. Compounds a)ii and b)ii introduce a methyl group in the two position to alter the orientation of the 1-substituent. In this way the through space effects should be reduced or switched off altogether, and indeed the IE surfaces predict no difference in reactivity between the 5- and 8-positions.

The CF$_3$ and CN substituted control compounds demonstrate equal reactivity over the 5 and 8 positions, and no through-space effects should occur in either
Five of the six compounds shown in Figure 3.13 were found to be commercially available. Thus, a preliminary kinetic study was performed using these five compounds.

3.6.2. Preliminary Kinetic Experiments

Preliminary kinetic experiments attempted to use HPLC to monitor the progress of the reactions, in the hope that the 5- and 8-substituted products could be separated. With this in mind, we settled on using a halogenation reaction using $N$-chlorosuccinimide (NCS) and iron trichloride. Each compound would be subjected to the same reaction conditions (Figure 3.21) for the same length of time, followed by analysis of the product mixtures by HPLC to determine the relative rates of reaction and the distribution of products (Scheme 3.6).

**Scheme 3.6** - Chlorination reaction used to determine the relative reactivity of the naphthalene compounds used in this study.
Unfortunately, the separation on the chromatograms was too poor for any definitive conclusions to be drawn, and there was insufficient time for this work to be refined, since experimental efforts were being directed towards more fruitful endeavours (Chapter 5). It is hoped that future work in the group should be able to build upon this pilot investigation, since the model compounds seem to be promising candidates for
3.7. Conclusions and Future Direction

It can be concluded from results on pyridine-N-oxides that the through-space effects do have an influence on the reactivity of aromatic rings, but unfortunately these types of compounds were difficult to purify, and had multiple reactive sites, limiting the scope of more thorough investigations. Synthesis of fluorenone derivatives proved to be more challenging than expected, possibly due to the limited stability of such compounds. However, a series of naphthyl derivatives that host through-space effects that could be switched on and off (according to IE calculations) have been identified that are mostly commercially available. Preliminary kinetic investigations on these compounds were inconclusive, but it is hoped that further investigations in the group will establish an improved HPLC assay that will allow the quantification of through-space effects on the reactivities of these compounds.

3.8. Experimental Procedures

Unless otherwise stated, all compounds were purchased from commercial sources and were used without further purification. All reactions were performed under an atmosphere of N₂(g) and unless otherwise stated, all reactions were performed using anhydrous solvents. Column chromatography was performed using Fluka Analytical Silica Gel 60 (35-70 µm) purchased from Sigma-Aldrich and thin layer chromatography was performed on aluminium backed plates with a coating of Merck Keiselgel 60F₂₅₄.

Unless stated otherwise, NMR spectra were recorded on a Bruker AV500 or AV400 spectrometer at 298 K and analysed using MestReNova software. All NMR coupling constants (J) are reported in Hz and are reported to 1 decimal place. Chemical shifts are reported in ppm, downfield from tetramethylsilane, and are quoted to 2 decimal places (¹H NMR) and 1 decimal place (¹³C NMR). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ¹³C NMR assignments refer to multiplicity. EI mass spectrometry was performed by laboratory services at the University of Edinburgh with a Micromass
HPLC experiments were performed using a Gilson Model 303 HPLC system with a refractive index detector. Separation of the products was performed with a Varion Dynamax column (250 x 24 mm) at room temperature. Elution was applied at a flow rate of 10 ml/min using a 1:1 ethyl acetate:hexane solvent mixture. The column was regenerated by washing with 100% hexane.

**General procedure for bromination reactions (NMR Kinetics experiments)** To a solution of the appropriate phenylpyridine-N-oxide (50 mg, 0.29 mmol) in deuterated acetonitrile (1 mL) was added N-bromosuccinimide (52 mg, 0.29 mmol) and iron (III) trichloride (4.7 mg, 0.1 equiv). The reaction mixture was then transferred to an NMR tube and heated in the NMR spectrometer at 75 °C for 3 h. A spectrum was acquired every 15 minutes for the duration of the reaction. At the end of the reaction, the reaction mixture was allowed to cool to room temperature and extracted via gravity filtration. The filtrate was then concentrated in vaccuo, extracted with ethyl acetate and to give an oil that used for further analysis:

- **A mixture of brominated 2-phenylpyridine-N-oxides** was obtained as a brown oil (23 mg, 46%). EI mass spectrometry: m/z obtained: 171.0 (2-phenylpyridine-N-oxide), 249.9 (mono-brominated).

- **A mixture of brominated 4-phenylpyridine-N-oxides** was obtained as a yellow oil which was identified as the starting material. EI mass spectrometry: m/z obtained: 171.1 (4-phenylpyridine-N-oxide).

**2-phenylpyridine-N-oxide.** To a solution of 2-phenylpyridine (200 mg, 1.3 mmol) in acetic acid (6 mL), hydrogen peroxide (0.97 mL, 20 mmol) was added. After refluxing at 120 °C for 18 h, the reaction mixture was allowed to cool, concentrated, and
extracted with ethyl acetate. The organic layer was dried, evaporated, and purified by column chromatography (silica gel, 5% methanol in ethyl acetate) to give the final compound as white crystals (121 mg, 61%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.36 (d, $J$ = 6.4, 1H), 7.90 – 7.79 (m, 2H), 7.56 – 7.39 (m, 4H), 7.35 – 7.21 (m, 2H), $^{13}$C NMR (126 MHz, CDCl$_3$) δ 149.34, 140.55, 132.66, 129.62, 129.29, 128.32, 127.43, 125.65, 124.54, M.P. 142 ºC, IR: 1240 cm$^{-1}$ (N$^+$-O$^-$)

4-phenylpyridine-N-oxide. To a solution of 4-phenylpyridine (200 mg, 1.3 mmol) in acetic acid (6 mL), hydrogen peroxide (0.97 mL, 20 mmol) was added. After refluxing at 120 ºC for 18 hr, the reaction mixture was allowed to cool, concentrated, and extracted with ethyl acetate. The organic layer was dried, evaporated, and purified by column chromatography (silica gel, 5% methanol in ethyl acetate) to give the final compound as off-yellow white crystals (109 mg, 55%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.70 (d, $J$ = 7.2 Hz, 2H), 7.68 (dt, $J$ = 8.3, 2.3, 2H), 7.54 - 7.56 (m, 2H), 7.51 - 7.53 (m, 2H), 7.49 (s, 1H) $^{13}$C NMR (126 MHz, CDCl$_3$) δ 139.36, 138.80, 136.15, 129.37, 129.21, 126.40, 123.72, M. P. 150 ºC, IR: 1237 cm$^{-1}$ (N$^+$-O$^-$).

Morpholine Lithium Salt BuLi (350 mg, 5.55 mmol) was added dropwise to a solution of morpholine (500 mg, 5.55 mmol) in hexane (10 mL). The resulting salt solution was used in the synthesis of 9-fluorenone-1-boronic acid without further purification.
9-Fluorenone-1-Boronic Acid

Fluorenone (1 g, 5.55 mmol) in hexane (100 mL) was added to a solution of morpholine lithium salt (500 mg, 5.55 mmol) in hexane (10 mL) and stirred at room temperature for 30 min under an atmosphere of nitrogen. BuLi (350 mg, 5.55 mmol) was added and the mixture was refluxed for 10 h. After cooling to room temperature and the addition of THF (120 mL), the mixture was cooled to –78 °C and tributyl borate (3.71 g, 1.6 mmol) was added dropwise. The stirred mixture was allowed to warm to room temperature overnight. After acidic workup, the boronic acid was used without further purification.

Attempted synthesis of 2,6-diphenylbenzoic acid

sec-BuLi (0.42 mL, 5 mmol, 1 equiv) was added dropwise under nitrogen at -78 °C over a period of 30 min. After 2.5 h stirring at -78 °C the mixture was treated with an excess of iodobenzene (2.8 mL, 25 mmol). The solution was then allowed to warm to room temperature overnight, after which water (30 mL) was added. The aqueous phase was washed twice with diethyl ether (40 mL) and acidified to pH 1 with HCl (4 M). The aqueous phase was then extracted with diethyl ether (2 x 40 mL). The combined organics were washed with water (2 x 25 mL), dried with MgSO₄ and concentrated in vacuo. Only unreacted starting material was observed.

Second attempted synthesis of 2,6-diphenylbenzoic acid

sec-BuLi (0.92 mL, 11 mmol, 2.2 equiv) was added dropwise under nitrogen at -78 °C over a period of 30 min. After 2.5 h stirring at -78 °C the mixture was treated with an excess of iodobenzene (2.8 mL, 25 mmol). The solution was then allowed to warm to room temperature overnight, after which water (30 mL) was added. The aqueous phase was washed twice with diethyl ether (40 mL) and acidified to pH 1 with HCl (4 M). The aqueous phase was then extracted with diethyl ether (2 x 40 mL). The combined organics were washed with water (2 x 25 mL), dried with MgSO₄ and concentrated in vacuo. Only unreacted starting material was observed.
temperature overnight, after which water (30 mL) was added. The aqueous phase was washed twice with diethyl ether (40 mL) and acidified to pH 1 with HCl (4 M). The aqueous phase was then extracted with diethyl ether (2 x 40 mL). The combined organics were washed with water (2 x 25 mL), dried with MgSO₄ and concentrated \textit{in vacuo}. Only unreacted starting material was observed.

\begin{center}
\includegraphics[width=0.2\textwidth]{9-Phenylfluorenone.png}
\end{center}

\textbf{Attempted synthesis of 9-Phenylfluorenone} $n$-BuLi (1.13 g, 17.2 mmol, 3.5 equiv) was added to a suspension of potassium tert-butoxide (1.97 g, 17.6 mmol, 3.5 equiv) in benzene (15 mL) at room temperature. After 5 min stirring, 2-biphenyl carboxylic acid (1.00 g, 5.04 mmol, 1 equiv) in benzene (10 mL) was added. The mixture was then stirred for 1 h at 60 °C. The reaction was cooled to r.t. before $n$-BuLi (0.66 g, 10 mmol, 2 equiv) was added dropwise and the mixture stirred at 60 °C for a further 2 h. After being cooled gradually to r.t., the solution was quenched with the bromobenzene (7.91 g, 5.04 mmol, 1 equiv). The mixture was stirred overnight after which water (20 mL) was added. The aqueous layer was extracted with ethyl acetate (3x30 mL), acidified with aqueous HCl (4 M), and extracted with diethyl ether (3 x 30 mL). The crude mixture was concentrated under vacuum and purified by column chromatography on silica (cyclohexane: ethyl acetate, 9:1). Only unreacted starting material was observed.
References

Chapter 4

Can the Local Ionisation Energy Predict Nucleophilic Reactivity?

Abstract
Following the success of the local ionisation energy as a model of reactivity in electrophilic aromatic substitution, this chapter will explore whether the model can be modified in order to predict the outcome of nucleophilic substitution. Preliminary studies of the ability of the model to predict the regiochemical outcome and relative reactivity of various molecules indicates that the method is not a viable alternative to current theories.

4.1. Introduction
Given the success of the local ionisation energy model in predicting electrophilic aromatic substitution reactions, we considered whether the model could be of any use in modelling nucleophilic substitution reactions. Nucleophilic aromatic substitution reactions are much less common than their electrophilic counterparts, and these types of reactions only occur on electron deficient aromatic substrates.

Four mechanisms have been proposed to account for the observed outcomes of nucleophilic aromatic substitution reactions,\(^1\) The first of these is known as the S\(_{\text{N}}\)Ar reaction, which is analogous to the S\(_{\text{E}}\)Ar mechanism (Figure 4.1a). This is a two-step reaction, the first of which involves the formation of the anionic intermediate and is usually rate determining. Evidence for this mechanism comes from isolation of Meisenheimer intermediates\(^2,\)\(^3\) and their identification by NMR\(^4\) and X-ray crystallography.\(^5\)
The second mechanism is an $S_N1$ reaction (Figure 4.1b) and is particularly important in the reaction of diazonium salts.\[^6\] Aside from kinetic evidence for this mechanism\[^7\], the $[\text{Ar}^+\text{N}_2]$ complex (as opposed to the $\text{ArN}_2^+$ molecule) has been trapped with carbon monoxide in water with formation of the corresponding arenecarboxylic acids.\[^8\]

In the reaction of chlorobenzene with $\text{NH}_2^-$ (Figure 4.1c), isotopic labelling
experiments\textsuperscript{[9]} showed that the observed product contained a mixture of 1- and 2-substituted anilines. This was explained by an elimination/addition mechanism proceeding \textit{via} a benzyne intermediate.\textsuperscript{[9]} Elimination of the chlorine substituent forms the benzyne intermediate. Subsequent addition of NH$_2$ can occur at either side of the triple bond, resulting in the observed product mixture. Further evidence for this mechanism comes from studies showing that di-\textit{ortho}-substituted derivatives do not react under these conditions since it is not possible to form the intermediate.\textsuperscript{[8]}

Unexpected product ratios in the reaction of 5- and 6-iodo-1,2,4-trimethylbenzene with KNH$_2$ in ammonia (Figure 4.1e) led to the proposal of a free radical mechanism (Figure 4.1d),\textsuperscript{[10]} known as the S$_{RN}1$ mechanism.\textsuperscript{[11]} If the benzyne mechanism was in operation, then the product ratios for the reactions of the 5- and 6-isomers would be expected to be the same, however this is not the case.\textsuperscript{[10]} The product ratios can be explained by the radical mechanism since the radical is formed by abstraction of the iodine substituent.

The fact that there are multiple mechanisms at work in nucleophilic aromatic substitution reactions makes modelling these types of reaction much more difficult than the relatively simple electrophilic aromatic substitution where only one mechanism occurs. Despite this, an attempt was made to modify the local ionisation energy model so as to determine the outcome of nucleophilic aromatic substitution reactions.

\section*{4.2. Aims of the Project}

The local ionisation energy can be defined as the energy required to remove an electron from a given point on the surface of a molecule.\textsuperscript{[12]} The success of this method in modelling electrophilic substitution reactions led us to investigate whether the reverse process could model nucleophilic substitution reactions. The electron affinity of a molecule is defined as the energy released when an electron is added to the neutral form of the molecule in the gaseous state.\textsuperscript{[13]} Thus, the local electron affinity\textsuperscript{[14]} may be of use in the prediction of nucleophilic reactivity. Unfortunately, local electron affinity is not parameterised in the \textit{Spartan} software that we utilise in the calculation of the local ionisation energy. We therefore performed a systematic study to determine whether any empirical pattern could be seen in the local ionisation energy surfaces to
give information about nucleophilic reactivity.

Since electron affinity is essentially the reverse of the ionisation energy (Figure 4.2), a series of local ionisation energy calculations were performed on the charged forms of the aromatic substrates to determine whether the locations of either the minimum or maximum local ionisation energy corresponded with the nucleophilic reactivity of the substrate.

4.3. A Preliminary Survey of Substrates Bearing Electrophilic Sites

Initially, local IE calculations were performed on some substituted aromatic compounds that are known to undergo nucleophilic aromatic substitution. The results are summarised in Figures 4.3 and 4.4.
Figure 4.3 (Page 111) - IE surfaces of some benzene derivatives calculated at various charge states using DFT/B3LYP/6-311G*. Surfaces are scaled to highlight the maximum IE value in blue ($\text{IE}_{\text{max}} - 4 \text{ eV}$), and the quoted $\text{IE}_{\text{min}}$ values are given in eV. References for the observed reactivity patterns: chlorobenzene,$^{[9]}$ pentafluoronitrobenzene,$^{[15]}$ 2-hydroxynaphthalene.$^{[16]}$

Chlorobenzene undergoes nucleophilic substitution at the 1 and 2 positions$^{[9]}$ via the benzyne mechanism, while pentafluoronitrobenzene reacts in the $\text{para}$ position relative to the nitro group.$^{[15]}$ This is an example of the rare $\text{S}_{\text{RN2}}$ mechanism, which is analogous to the $\text{S}_{\text{N2}}$ mechanism observed in non-aromatic substrates.$^{[17]}$ 2-hydroxynaphthalene undergoes $\text{ipso}$-substitution with ammonia in the presence of sodium bisulphate.$^{[16]}$ In this case it is the sulfonic acid of tetralone (formed by addition of sodium bisulphate to hydroxynaphthalene followed by tautomerisation) that reacts with the nucleophile.$^{[18]}$

While the $\text{IE}_{\text{max}}$ surfaces of 2-hydroxynaphthalene highlight the OH proton (the most acidic), none of the surfaces correspond to the observed reactivity patterns.
Similarly, the IE_{\text{min}} surfaces also fail to predict the observed reactivity patterns. Upon further investigation it was found that in the reaction of hydroxynaphthalene with ammonia in the presence of sodium bisulfite (the Bucherer reaction), the hydroxynaphthalene tautomeries to tetralone following the loss of a proton.\cite{18} It is the sulfonic acid of tetralone (row 4 in figures 4.3 and 4.4) which reacts with the ammonia.\cite{18}

Since the acidic proton of 2-hydroxybenzene is highlighted by the IE_{\text{max}} surfaces, the IE calculations were performed on a series of molecules in order to determine whether the method can be used to estimate the strength of an acid. Despite previous work which found a correlation between local ionisation energy minima and the pK_{a}s of ten azines and azoles,\cite{19} plots of the data in Tables 4.1 and 4.2 (Appendix 7) show no correlation between pK_{a} and either the minimum or maximum IE values.

<table>
<thead>
<tr>
<th>Name</th>
<th>pK_{a}</th>
<th>IE_{\text{max}} (+1 Charge State)</th>
<th>IE_{\text{max}} (0 Charge State)</th>
<th>IE_{\text{max}} (-1 Charge State)</th>
<th>IE_{\text{max}} (-2 Charge State)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>16.0</td>
<td>28.8</td>
<td>15.4</td>
<td>9.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Water</td>
<td>15.7</td>
<td>46.5</td>
<td>15.9</td>
<td>10.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Hydrocyanic Acid</td>
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<td>15.9</td>
<td>9.9</td>
<td>12.7</td>
</tr>
<tr>
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<td>4.8</td>
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<td>16.1</td>
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<tr>
<td>Hydrofluoric Acid</td>
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<td>15.9</td>
<td>11.8</td>
<td>13.7</td>
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<tr>
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<td>18.8</td>
<td>9.6</td>
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<tr>
<td>Hydrochloric Acid</td>
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<td>40.3</td>
<td>14.2</td>
<td>9.0</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Table 4.1 - pK_{a} and maximum IE values of various compounds bearing acidic protons calculated at various charge states. All IE values are quoted in eV. pK_{a} data taken from ‘Organic Chemistry, 6th Edition’ by John McMurry, Table 2.3, page 46.
Since it might be expected that bond polarity would have an influence on reactivity, we next examined whether the local IE could reproduce the bond polarity in a series of simple molecules (Figures 4.5 and 4.6). Although the IE\textsubscript{max} surfaces of the +1 charge state and the IE\textsubscript{min} surfaces of the neutral charge state identify the lone pairs of oxygen and nitrogen atoms, there is no obvious trend relating IE to bond polarity. For example, the maximum IE value obtained from calculations on the +1 charge state in acetonitrile is located on the δ\textsuperscript{−} nitrogen atom, whereas in methyl-lithium it is located on the δ\textsuperscript{+} lithium atom.

More significantly, and more in line with the expectation that the average local ionisation energy surface of the −1 state might be similar to the average local electron affinity surface, the locations of the IE minima of the −1 charge state of various examples appear to correspond with known sites of nucleophilic attack. Specific examples include protons positioned alpha to carbonyl groups (e.g. in acetic acid), alcohol protons (e.g. methanol), and δ\textsuperscript{+} carbon atoms in carbonyl compounds (e.g. acetaldehyde), and carbon atoms of substrates for S\textsubscript{N}2 reactions (e.g. methyl chloride). This appears to be a promising result, the results are not always completely consistent since neither the carbonyl carbon, nor the alpha protons are highlighted in methyl acetate for example.

<table>
<thead>
<tr>
<th>Name</th>
<th>pK\textsubscript{a}</th>
<th>IE\textsubscript{min} (+1 Charge State)</th>
<th>IE\textsubscript{min} (0 Charge State)</th>
<th>IE\textsubscript{min} (-1 Charge State)</th>
<th>IE\textsubscript{min} (-2 Charge State)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>16.0</td>
<td>17.5</td>
<td>9.6</td>
<td>4.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Water</td>
<td>15.7</td>
<td>23.2</td>
<td>9.3</td>
<td>4.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Hydrocyanic Acid</td>
<td>9.3</td>
<td>20.4</td>
<td>10.8</td>
<td>2.0</td>
<td>2.4</td>
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<tr>
<td>Acetic Acid</td>
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<td>Nitric Acid</td>
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<td>2.5</td>
</tr>
<tr>
<td>Hydrochloric Acid</td>
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<td>20.4</td>
<td>10.1</td>
<td>3.3</td>
<td>5.5</td>
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</table>

Table 4.2 - pK\textsubscript{a} and minimum IE values of various compounds bearing acidic protons calculated at various charge states. All IE values are quoted in eV.
<table>
<thead>
<tr>
<th>Charge State:</th>
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<th>-1</th>
<th>-2</th>
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<tr>
<td>Acetic Acid</td>
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<td><img src="image7.png" alt="Image" /></td>
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<tr>
<td>Acetyl Chloride</td>
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<td><img src="image11.png" alt="Image" /></td>
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<tr>
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<tr>
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<tr>
<td>Methyl Magnesium Bromide</td>
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<td><img src="image26.png" alt="Image" /></td>
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<td><img src="image42.png" alt="Image" /></td>
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<td>Methyl Lithium</td>
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</tbody>
</table>

**Figure 4.5** (Page 115) and **Figure 4.6** – IE surfaces of various compounds showing the location of the IE<sub>max</sub> and IE<sub>min</sub> values respectively. Surfaces were calculated using DFT/B3LYP/6-31G*. Compounds adapted from 'Organic Chemistry, 6th Edition' by John McMurry, Table 5.1, page 141.
4.5. Computational methods

Minimised molecular geometries and molecular surfaces were calculated using Spartan '08, with DFT/B3LYP/6-311G*, unless otherwise stated. Ionisation energies are plotted on the 0.002 electrons/bohr$^3$ density surface. Ionisation energy surfaces of +1, -1 and -2 charge states were obtained by performing a single-point energy calculation on the minimised structure while varying the charge state. Ionisation energy surfaces emphasising minima are scaled from the average local ionisation energy minimum on the molecular surface, $I_{S,min}$ (red) to $I_{S,min} + 0.4$ eV (blue) of each molecule, while surfaces emphasising maxima are scaled from the average local ionisation energy minimum on the molecular surface, $I_{S,max}$ (blue) to $I_{S,max} - 0.4$ eV (red) of each molecule.

4.6. Conclusions and Possible Future Directions

The local ionisation energy model works well in describing electrophilic substitution reactions. An initial survey of a range of molecules suggests that the local IE$_{min}$ of substrates that have been given a single, negative, in silico charge might correspond to the electrophilic reactive sites. However, the range of possible nucleophilic reactions that might occur as substrates are varied makes comparisons difficult. For example, deprotonation, elimination, or concerted mechanisms each with different rate-determining steps might be in competition with one another (e.g. E1, E2, S$_{N}$1, S$_{N}$2, or addition-elimination reactions). For example, the ionisation energy surfaces of aromatic substrates in different charge states do not seem to correspond to the reactive sites in nucleophilic aromatic substitution reactions. However the small scope of the aromatic substrates covered and mechanistic differences might explain the lack of a correlation with the calculated properties. Further work in this area will need to be rigorously compared with specific reactions where the mechanistic details are known with a high degree of certainty.

A possible future direction for this project is to compare the results of this method to local electron affinity surfaces calculated using software such as Gaussian, where custom surface-encoded properties can be defined by those with sufficient expertise. Ultimately, it is hoped that systematic comparison with these types of
surface-encoded properties might yield a useful simple model for nucleophilic reactions in which attack of the incoming nucleophile is the rate-determining step, in much the same way that the local ionisation energy surfaces can be used to visualise reactivity in electrophilic aromatic substitution reactions.
References

Chapter 5

Cooperativity in Hydrogen Bond Networks

Abstract

Non-covalent interactions are prevalent throughout biology and chemistry. They play a role in determining the structure of biological molecules such as proteins and nucleic acids, and in the formation of supramolecular architectures. Cooperativity is a property of non-covalent interactions which can arise through changes in polarisation or changes in conformation induced by the first binding event. Cooperativity is central to the understanding of molecular recognition processes such as ligand binding and hydrogen bonding. This project aims to quantify the polarisation-induced cooperative effect of an internal hydrogen bond on the binding strength of a second hydrogen to a hydrogen-bond acceptor. A series of molecules based on catechol, 1,8-naphthalenediol and 2,2’-biphenol were studied both computationally (by analysis of calculated molecular electrostatic surface potentials) and experimentally using a $^{31}$P NMR titration method. The increase in binding affinity is shown to be dependent upon the geometry of the internal hydrogen bond and also to be significantly greater than that predicted by the electrostatic potentials of single-point interactions at the end of a hydrogen bonded chain.

5.1 Introduction

Hydrogen bonding is an important type of non-covalent interaction that is prevalent throughout chemistry and biology. Cooperativity arises when the interplay of two or more interactions cause the system to behave differently than would be expected based upon considerations of the individual interactions.$^{[1]}$ Molecular recognition in both biological and synthetic self-assembling systems often depend on large numbers of non-covalent interactions where cooperative effects can therefore play a significant role.$^{[2]}$ Due to the influence of cooperative effects and secondary interactions, the binding strength of such complexes cannot be estimated simply by calculating the sum total of the energy of each individual non-covalent bond.$^{[2],[3]}$ For example, the binding
of biotin to streptavidin is observed to be one thousand times greater than would be expected based on the assumption that the binding strength corresponds to the sum of the individual interaction energies.\textsuperscript{[2]} This demonstrates the importance of being able to account for cooperative effects in predictive models of ligand binding, since it can have substantial effects on the behaviour of the system.

Despite its obvious importance in biology, there is no ‘unified’ definition of cooperativity,\textsuperscript{[2]} however these effects can be classified according to the manner in which they arise. Allosteric cooperativity occurs when the binding of one ligand or molecule influences the binding of a different ligand, as is often observed in proteins.\textsuperscript{[4],[5]} Chelate cooperativity (often referred to as the chelate effect) is more common in organometallic chemistry, where ligands with multiple binding sites to the same metal centre display much greater affinity for that metal than ligands that bind through only one atom.\textsuperscript{[6]}

When the binding energy derived from non-covalent interactions is greater than that calculated by the sum of the individual interactions, they are said to be acting in a positively cooperative manner, when the reverse is true and the binding energy is less than would be expected, they are said to be acting in a negatively cooperative manner.\textsuperscript{[2]} Both positive and negative cooperative interactions can occur in the same system, and in such cases the effect leading to the most thermodynamically stable complex dominates.\textsuperscript{[2]}

As noted above, biology is replete with examples of cooperativity, particularly allosteric cooperative effects among enzymes and other non-catalytic proteins. One of the most well-known examples of a non-catalytic enzyme is haemoglobin, which transports oxygen through the bloodstream. Haemoglobin exists as a tetramer,\textsuperscript{[7]} with each of the four subunits containing a haeme group that binds oxygen through an iron atom. Each binding event induces a change in the protein structure such that subsequent binding events occur with higher affinity.\textsuperscript{[8]} It has been proposed that the successively higher binding affinities are not due to positive cooperativity, but rather represent consecutive binding events showing decreasing negative cooperativity.\textsuperscript{[2]} Myoglobin is another oxygen transporter that exists as a monomer resembling one of the haemoglobin subunits.\textsuperscript{[2]} It has been suggested that the affinity of myoglobin for oxygen is strong due to the fact that, unlike haemoglobin, it does not have any entropic
cost associated with reorganisation of the protein structure.\cite{2} In addition, binding of a ligand to an allosteric site can induce polarisation effects that are transmitted through the system to affect the binding of a second ligand to a secondary binding site.\cite{9} Cooperative non-covalent interactions are thought to have a significant role in achieving the remarkable catalytic activity of enzymes, although a plethora of effects and interactions are at work in such systems making it difficult to ascertain the precise role of cooperative effects.\cite{10}

Cooperative interactions are not limited to biology. Several examples can be found in the literature of synthetic organic systems that utilise cooperative effects in catalysis\cite{10} and in the assembly of supramolecular complexes.\cite{11} Rebek and colleagues synthesised the first non-enzymatic system to display allosteric cooperativity in solution.\cite{7} Their molecule consists of two crown ethers linked through a biphenyl core (Figure 5.1). Upon binding of the first metal centre, the structure rotates around the biphenyl C-C bond, altering the dimensions of the second binding site making addition of the second metal atom more favourable. Cyclodextrin derivatives display similar behaviour when titrated against organic guest molecules in aqueous solution.\cite{4}

![Figure 5.1 - The first non-enzymatic system displaying allosteric cooperativity.](image)
In the examples mentioned above, cooperative effects are induced by a change in conformation of the molecule, whereas polarisation-induced cooperativity can be considered a distinct phenomenon.\textsuperscript{[9]} In systems where this type of cooperativity exists, the total electrostatic interaction energy is increased to an extent greater than would be predicted based on the charge distributions of each individual molecule, due to the changes in polarisation caused by the first binding event. For example, several groups have shown how this type of cooperativity influences protein folding using the assembly of artificial β-sheets from synthetic peptides as a model system.\textsuperscript{[12],[13]} The cooperative effect in these systems is evidenced by the fact that the assembled three-stranded sheet is significantly more stable than the two-stranded counterpart, which has been suggested to arise from polarisation of the amide bonds by hydrogen bonding.\textsuperscript{[13]} Similarly, Hunter \textit{et al} have synthesised a series of amide oligomers in which self-assembly is driven by hydrogen bonding along an amide backbone (Figure 5.2).\textsuperscript{[11]}

![Diagram](image)

\textbf{Figure 5.2} - Amide bond polarisation changes upon oligomer formation.

Using NMR titration methods, Hunter found that formation of the ternary amide complex has an association constant greater than would be expected based on the stability of the binary complex. This is explained by the presence of a network of hydrogen bonds which increase the strength of the individual interactions by altering the polarisation of the hydrogen bonding groups.

Molecular zipper complexes have also been extensively studied by the Hunter group (Figure 5.3).\textsuperscript{[11],[14],[15],[16]} The self-assembly of these complexes is directed by
both hydrogen bonding and π-π interactions.[11] Dimeric species have been observed in chloroform by concentration-dependent NMR experiments.[14] However, the longer oligomers are found to be interact more strongly with each other, suggesting that cooperative effects play a role in the formation of these double-stranded molecules.[15] The Gibbs free energy of binding, ΔG, increases with increasing oligomer length and was found to range from -7 to -27 kJ mol⁻¹.[14]

![Figure 5.3 - Zipper complex studied by the Hunter group.](image)

Eblinger and Schneider developed a series of α.ω-diamides and α.ω-dicarboxylates as hydrogen-bond donors and acceptors, respectively.[17] They found that as the alkyl spacer group between the diamides increased in length, the observed ΔG of complexation became less favourable by a much smaller amount than expected. They concluded that ‘the efficiency of molecular recognition processes suffers less than generally assumed from the presence of rotatable bonds’. [17] This has implications for the design of synthetic receptors, since the degree of preorganisation (or rigidity) in the molecule may not need to be as great as previously thought, allowing the design of more flexible receptors.

Studies in liquid water show that hydrogen-bonding networks affect the aggregation of molecules in the bulk.[18], [19] Water contains a dynamic mixture of different (H₂O)ₙ clusters, with the trimer (n = 3) being particularly abundant.[18] The formation of these clusters means that hydrogen bonds in bulk water are 2-3 times
stronger than those formed by monomeric water molecules. Addition of \( \text{H}^+ \) to water leads to the formation of \( \text{H}^+(\text{H}_2\text{O})_n \) clusters, and in this case, the hexamer \( (n = 6) \) was found to be most stable.

Cooperative effects in solvents can be utilised in catalysis. Fluorinated alcohol solvents such as trifluoroethanol, hexafluoro-2-propanol and 1-phenyltrifluoroethanol form dimers and trimers, which enhance their hydrogen bond donor ability. Their strong donor ability makes them excellent solvents for epoxidation reactions. For example, hexafluoro-2-propanol was shown to increase the rate of alkene epoxidation by hydrogen peroxide by five orders of magnitude. The hydrogen peroxide is activated towards the alkene due to the influence of hydrogen bonding with the fluorinated alcohol cluster.

Organocatalysts have also been designed that make use of cooperative hydrogen bonding. Smith et al synthesised a thiourea catalyst designed to emulate the positive cooperativity found in enzymes (Figure 5.4). They achieved high catalytic efficiency in a Mukaiyama-Mannich reaction, which required lower catalyst loading and gave higher enantioselectivity than conventional catalysts.

Xu and colleagues took a slightly different approach to control enantioselective catalysis. Use of ortho-nitrobenzenesulfonic or trifluoromethansulfonic acid in the Povarov reaction (involving the cycloaddition of \( N \)-aryl imines to electron-rich alkenes) led to a rapid, but non-selective reaction. Addition of a bifunctional urea or thiourea with a sulfanilamide group inhibits formation of the endo reaction pathway, leading to a 99% enantiomeric excess of the exo product.
Several studies into the fundamental behaviour of cooperative effects have been performed using dihydroxyphenol (catechol) derivatives. In the 1970s indirect measurements suggested that hydrogen bond enthalpies between catechol and an acceptor were very different from those in phenol and 2-methoxyphenol (guaiacol). Monitoring the formation of hydrogen bonded complexes by IR spectroscopy, they found that formation of the 1:1 complex with catechol and an acceptor (THF, DMSO or \(n\)-Bu\(_2\)S) caused a greater frequency shift than did the corresponding phenol complex. This was proposed as being due to the effect of the intramolecular hydrogen bond in catechol on intermolecular binding. However, in common with many other IR spectroscopy-based studies of non-covalent interactions, direct measurements of the binding enthalpy were not made, but instead were extrapolated from correlations of the observed directly measured complexation enthalpies.

Similar experiments in diethyl ether-carbon tetrachloride solutions revealed that the intramolecular hydrogen bond in catechol and pyrogallol was disrupted by the ether and both compounds form complexes with more than one ether molecule.
Only DMSO was found to disrupt the intramolecular bond in guaiacol (See Figure 5.5) [25] Later studies probed how these cooperative interactions affect the rate of radical hydrogen abstraction from catechols [28] and naphthalenediols. [27] The phenoxyl radical is stabilised by the adjacent hydroxyl groups, giving these compounds excellent antioxidant properties. [28]

Figure 5.5 – Disruption of internally bound hydrogens in (a) catechol, (b) pyrogallol and (c) guaiacol

In 2010, the Varfolomeev group used IR spectroscopy to study cooperative effects in complexes of catechol with various hydrogen bond acceptors. [24] The total hydrogen bond enthalpy and the strength of the cooperative effect was found to vary with different bases. They also reported a positively cooperative enhancement of the strength of the intramolecular hydrogen bond upon binding of an acceptor to the free hydrogen. They report that the polarisation of the intramolecular hydrogen bond is affected more strongly than that of the intermolecular interaction. [28]

Ortho substituted catechol derivatives have been used to study intramolecular hydrogen bonding on chloride anion binding. [29] NMR titrations revealed that anion
binding was greatly influenced by the size of the ring formed by the intramolecular interactions (Figure 5.5).

**Figure 5.6** - Catechol derivatives studies as possible chloride anion receptors.

Compounds that formed 5- and 7-membered rings exhibited anion binding, with compounds forming a 7-membered ring showing the highest affinity (Figure 5.6). Compounds that formed a 6-membered ring were found not to bind chloride, however addition of DMSO disrupts the internal hydrogen-bond network and allows anion binding to occur (Figure 5.7).[29]

**Figure 5.7** - DMSO disrupts the internal hydrogen bonding of catechol derivatives, allowing anion binding to take place.[29]

Despite these previous studies into cooperative effects in systems based on catechol, there has been a lack of properly controlled systematic studies that have directly
quantified free energy changes as the nature of the hydrogen bond network is varied.

5.2 Aims and Experimental Design
This project aims to build on the earlier studies of cooperative effects in phenol derivatives to determine the extent to which cooperative effects affect the binding strength of a range of aromatic alcohols to an external hydrogen bond acceptor in solution. Three series of compounds will be investigated based on catechol, naphthalenediol and biphenol. By measuring the binding constants and calculating the Gibbs free energy values of the complexation of these and some control compounds, we hope to determine both the magnitude of the cooperative effect and the extent to which it is dependent on the geometry of the internal hydrogen bond.

5.3 Design of Target Compounds and Titration Experiments
The cooperative effect would be expected to exist in chains of repeating hydrogen-bond donors and acceptors such as those that can formed using linear arrays of hydroxyl groups.[30] These types of chained hydrogen bonding interactions should be expected to alter the polarisation of the terminal hydrogen bond donors, affecting its ability to bind to an external hydrogen bond donor.

This study takes advantage of the fact that phenol groups are one of the strongest hydrogen bond donors that also feature a proximate acceptor sites making them well suited to the study of cooperative effects in hydrogen-bonding interactions.[30] Figure 5.7 shows the expected polarisation effects in the three classes of compounds to be studied.

![Figure 5.7 - Definition of the free and internally bound protons, along with the expected polarisation effects in catechol, 1,8-naphthalenediol and 2,2'-biphenol. A = acceptor.](image)

Figure 5.8 - Definition of the free and internally bound protons, along with the expected polarisation effects in catechol, 1,8-naphthalenediol and 2,2'-biphenol. A = acceptor.
The internally bound hydrogen atom should be expected to be far less able to bind to an acceptor, while the free hydrogen should be able to bind an external hydrogen bond acceptor. If a sufficiently strong hydrogen bond acceptor is present in solution, then the internal hydrogen bond in catechol may be out competed (Figure 5.9b). Furthermore, it may also be possible that the internal hydrogen bond is retained but that this ‘bound’ proton is able to form a weak secondary hydrogen bonding interaction (Figure 5.9a). It is possible to control for either of possibilities shown in Figures 5.8a and 5.8b, by examining the binding properties of the control compound shown in Figure 5.9d, in which the terminal free OH is ‘capped’ by a methyl group (OMe in Figure 5.9d).

**Figure 5.9** – Possible binding events and control compounds to model for them.

Using NMR titration protocols (see below), the binding constant of each molecule and an acceptor can be determined. From this the free energy can be calculated using equation 5.1.

**Equation 5.1**

\[
\Delta G = -RT\ln K
\]

Assuming that a 1:1 complex is formed and that the second binding event does not occur, the strength of the internal hydrogen bond can be calculated from equation 5.2, while the strength of the cooperative effect can be expressed as a percentage increase in binding energy, allowing comparison over a range of conditions (e.g. variation of solvent and H-bond geometry).
In catechol, the internal hydrogen bond forms a pseudo-5-membered ring (Figure 5.11). Performing the same NMR titration experiments with 1,8-naphthalenediol and 2,2'-biphenol, along with appropriate controls, allows the dependence of the cooperative effect on the geometry of the internal hydrogen bond to be examined by changing the size of the pseudo-ring to 6 and 7 members respectively. The full range of compounds to be examined in this study is shown in Figure 5.12. Using methoxy groups in the control compounds allows the effect of the hydrogen bonds to be evaluated while keeping the electronic properties of the ring essentially equivalent to the compound of interest.

The choice of an appropriate hydrogen bond acceptor is as important as the donor. Tributyl phosphine oxide was chosen in this study as it is known to be one of the strongest acceptors available, is soluble across a range of solvents and has been used in the study of similar hydrogen bonding systems. In addition, this allows the use of $^{31}$P NMR spectroscopy, making the interpretation of spectra simple.
Figure 5.12 – Hydrogen bond donor molecules of interest in this study.

The NMR titration procedure used in this study is similar to those used elsewhere to examine H-bonded complexes. However, rather than keeping the concentration of the host (acceptor) constant and varying the concentration of the guest (donor), a host-guest solution of a known concentration is added in varying amounts to deuterated solvent. In this way the ratio of the concentration of the two compounds is always 1:1, minimising the chance of forming higher order complexes and making the results much simpler to interpret.

The choice of solvent is also important since the hydrogen bond donor and acceptor properties of the solvent will have an effect on the data. Solvent choice is based on a number of factors including the solubility of compounds of interest, applicability of use in NMR, ease of handling, cost and availability. It is also desirable
that the obtained association constants, $K$, are within the detection range of NMR spectroscopy.

Taking into account these factors, along with data from a study of the binding of tri-$n$-butylphosphine oxide with perfluoro-$ tert $-butyl alcohol across a range of solvents,$^{[30-31]}$ deuterated chloroform was chosen as an appropriate solvent for initial titration experiments. Chloroform is a relatively weak hydrogen-bond donor and a poor acceptor,$^{[30-31]}$ and is relatively inexpensive. Furthermore, existing literature data suggests that the range of association constants that would be expected fall within the range where NMR titrations can be used.$^{[30-31]}

### 5.4 Synthesis of Target Molecules

4-Methoxybiphen-1-ol and 6-methoxynaphthalen-1-ol were synthesised by Nicholas Dominelli Whiteley during his undergraduate final-year project. The syntheses of these compounds are presented here for the sake of completeness. All catechol derivatives were commercially available, as was 2,2’-biphenol. The remaining compounds of interest were synthesised as outlined below.

#### Scheme 1 – Synthesis of 2’-methoxybiphen-1-ol

Following the procedure of Harrowven et al.$^{[32]}$ the synthesis of 2’-methoxybiphen-1-ol was achieved by treating 2,2’-biphenol with methyl iodide and potassium carbonate in acetone at room temperature (Scheme 1). The product was isolated in a respectable 68% yield after column chromatography, along with some dimethylated biproduct and unreacted starting material.

#### Scheme 2 – Synthesis of 4’-methoxybiphen-1-ol

Following the procedure of Harrowven et al.$^{[32]}$ the synthesis of 4’-methoxybiphen-1-ol was achieved by treating 2,2’-biphenol with methyl iodide and potassium carbonate in acetone at room temperature (Scheme 1). The product was isolated in a respectable 68% yield after column chromatography, along with some dimethylated biproduct and unreacted starting material.
Scheme 2 shows the synthesis of 4'-methoxybiphen-1-ol via a Suzuki coupling reaction under “Wet Fu” conditions\[^{[33]}\]. This reaction worked rather well, with the desired product being obtained in 95% yield, along with some unreacted starting material.

1,8-Naphthalenediol is an important compound in this study, since it is both a compound of interest and serves as the starting material for the synthesis of its mono-methylated derivative. Its synthesis was achieved by modifying a long-established procedure\[^{[34],[35]}\] involving heating a solid mixture of the commercially available 1,8-naphthosultone and potassium hydroxide to 300 °C (Scheme 3). The safety of the procedure was improved by performing the reaction in a high-temperature oven in place of the original method using a bunsen burner with a steel beaker.

![Scheme 3 – Synthesis of 1,8-naphthalenediol](image)

The synthesis of 8-methoxynaphthalenediol (Scheme 4) was achieved by treating 1,8-naphthalenediol with dimethylsulfate and sodium hydride in THF under nitrogen for 16 hours.\[^{[36]}\] Dimethylsulfate was used as a strongly electrophilic alkylating agent after previous attempts to synthesise this compound using methyl iodide were unsuccessful. The negative charge of the mono-deprotonated intermediate of the reaction is stabilised by a bridging internal hydrogen bond between the two oxygen atoms and conjugation with the aromatic rings.

![Scheme 4 – Synthesis of 8-methoxynaphthalen-1-ol](image)

6-Methoxynaphthalene-1-ol was synthesised in a two-step procedure from 6-methoxy-
1-tetralone as shown in Scheme 5. The first step involved $\alpha$-bromination of the ketone using copper(I) bromide *via* what is believed to be a disproportionation reaction following a literature procedure.\textsuperscript{[37]} The second step employs lithium carbonate and lithium bromide, affording the desired product in 57% yield following aromatisation and loss of HBr.\textsuperscript{[38]}

![Scheme 5](image_url)

**Scheme 5** – Synthesis of 6-methoxynaphthalen-1-ol

### 5.5 Computational Studies

Electrostatic potential (ESP) surfaces of the donor compounds were calculated using the software Spartan ’08. Calculations were performed using density functional theory (DFT), employing the B3LYP functional and the 6-311G* basis set. Figure 5.13 shows the ESP surfaces and the value of the ESP at the hydrogen atom of interest (highlighted in red). The numerical results are summarised in Table 5.1

<table>
<thead>
<tr>
<th>Compound</th>
<th>ESP / kJ mol(^{-1}) (DFT)</th>
<th>ESP / kJ mol(^{-1}) (HF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechol</td>
<td>293.1</td>
<td>309.9</td>
</tr>
<tr>
<td>Guaiacol</td>
<td>193.8</td>
<td>209.2</td>
</tr>
<tr>
<td>4-Methoxyphenol</td>
<td>258.5</td>
<td>277.3</td>
</tr>
<tr>
<td>Gallol</td>
<td>296.8</td>
<td>318.6</td>
</tr>
<tr>
<td>1,8-Naphthalenediol</td>
<td>314.2</td>
<td>355.5</td>
</tr>
<tr>
<td>8-Methoxynaphthalene-1-ol</td>
<td>141.3</td>
<td>159.2</td>
</tr>
<tr>
<td>6-Methoxynaphthalene-1-ol</td>
<td>251.4</td>
<td>284.1</td>
</tr>
<tr>
<td>2,2’-Biphenol</td>
<td>312.1</td>
<td>325.9</td>
</tr>
<tr>
<td>2’-Methoxybiphen-1-ol</td>
<td>120.5</td>
<td>144.2</td>
</tr>
<tr>
<td>4’-Methoxybiphen-1-ol</td>
<td>175.4</td>
<td>204.6</td>
</tr>
</tbody>
</table>

*Table 5.1* – A comparison of ESP values of the hydrogen bond donors calculated using DFT and HF methods.
Figure 5.13 (Page 136) – ESP surfaces of the hydrogen bond donors used in this study. The ESP values quoted are those over the proton indicated in red. The scale was set from $-250 \text{ kJ mol}^{-1}$ (red) to $+250 \text{ kJ mol}^{-1}$ (blue) and the surfaces and values shown were calculated using DFT / B3LYP / 6-311G*.

Based on the results obtained from the DFT calculations for those compounds in the catechol series, catechol itself might be expected to display a binding affinity 13% greater than that of the 4-methoxyphenol control compound if it is assumed that electrostatic potentials scale linearly with the interaction free energies.\textsuperscript{[39]} Using the same electrostatic assumptions, gallol, which has three hydroxyl groups in a row, would be predicted to have a binding constant 15% greater than 4-methoxyphenol. These computations might suggest that the magnitude of the co-operative effect is reduced upon increasing the length of the H-bond network. The negative control guaiacol (2-methoxyphenol) is predicted to have a binding constant 25% lower than 4-methoxyphenol, suggesting that the internal H-bond is more favourable than that to an external acceptor. However, these interpretations of the calculations are likely to be limited by the expectation that electrostatic potentials scale with the predicted binding energies, and by the fact that any stabilisation of charge via delocalisation upon complexation is not considered by looking at the electrostatic potentials of isolated molecules.

Similar results are obtained from electrostatic calculations on the naphthalenediol series. The electrostatic potential of the terminal hydroxyl group in 1,8-naphthalenediol has a value 25% higher than the 6-methoxynaphthalene-1-ol control compound. This is a significantly larger increase than predicted in the case of catechol and may arise from differences in the geometry of the internal hydrogen bonds. The conformation of the 1,8-naphthalenediol might facilitate greater orbital overlap between the hydrogen and oxygen atoms in the internal hydrogen bond, thereby allowing a more efficient donation of charge and a more significant co-operative effect. The negative control in this case was found to have an ESP 44% lower than the 1,8-naphthalenediol compound, suggesting that the internal hydrogen bond is stronger than found in guaiacol, and is again consistent with a more favourable H-bond geometry in the case of the 1,8-naphthalenediol.

The biphenol series is predicted to show an even greater enhancement of electrostatic potential due to internal H-bonds, with 2,2’-biphenol being found to have
an ESP 78% greater than that of the 4’-methoxy control compound, while the 2’-methoxy control was found to have an ESP that was 31% lower than the parent compound.

The ESP calculations were also performed using Hartree-Fock (HF) theory, using the same 6-311G* basis set. Although the absolute values of the ESP surface tended to be higher than those obtained with DFT, the same general trends are observed (Table 5.1).

5.6 Binding Studies

Binding studies to determine the association constants of the donor molecules with tri-n-butylphosphine oxide were performed using NMR spectroscopy. The titration procedure is given in the experimental section.

The results from NMR titrations of the catechol series in chloroform are summarised in Table 5.2. Catechol was determined to a free energy of binding of −16.2 kJ mol\(^{-1}\) ± 0.9 to tri-n-butylphosphine oxide, almost double that of the 4-methoxyphenol control compound. This may suggest that cooperative effects in this system make an essentially additive contribution to the overall binding energy, which is in agreement with earlier work where the effect of additional hydrogen-bond donors along an amide chain on proton chemical shifts was found to be additive.\(^{[40]}\) The small positive binding energy measured with guaiacol show that the phenolic hydrogen does not bind significantly to tri-n-butylphosphine oxide. This shows that the energy barrier to breaking the intramolecular hydrogen bond in guaiacol (and therefore catechol) is sufficiently large to block competitive binding with the tri-n-butylphosphine oxide acceptor added to the solution.
### Table 5.2 – Results from NMR binding studies on the catechol series in chloroform. (a) titration was not repeated. Errors given are twice the standard deviation of each experiment.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Bound</th>
<th>$K / \text{M}^{-1}$</th>
<th>$\Delta G / \text{kJ mol}^{-1}$</th>
<th>Error</th>
<th>Conc. Range / mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechol</td>
<td>88</td>
<td>684.0</td>
<td>−16.2</td>
<td>0.19</td>
<td>1.2 – 91.4</td>
</tr>
<tr>
<td>Guaiacol</td>
<td>34</td>
<td>0.9</td>
<td>+0.35</td>
<td>1.8</td>
<td>37.6 – 915.0</td>
</tr>
<tr>
<td>4-Methoxyphenol</td>
<td>60</td>
<td>35.5</td>
<td>−8.84</td>
<td>0.3</td>
<td>0.3 – 108.8</td>
</tr>
<tr>
<td>1,2-Naphthalenediol</td>
<td>87</td>
<td>661</td>
<td>−16.1</td>
<td>(a)</td>
<td>0.3 – 76.15</td>
</tr>
</tbody>
</table>

The same type of titration experiment was attempted using pyrogallol, which has three hydroxyl groups in a 1,2,3-arrangement respective to each other (Figure 5.12). Unfortunately this compound was found to be insoluble in chloroform, so it was decided to use acetonitrile in its place. Thus, to ensure that the results with the other compounds are strictly comparable, their binding constants were also measured in acetonitrile (Table 5.3).

### Table 5.3 - Results from NMR binding studies on the catechol series in acetonitrile. Errors given are twice the standard deviation of each experiment.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Bound</th>
<th>$K / \text{M}^{-1}$</th>
<th>$\Delta G / \text{kJ mol}^{-1}$</th>
<th>Error</th>
<th>Conc. Range / mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechol</td>
<td>74</td>
<td>117.0</td>
<td>−11.8</td>
<td>8.6</td>
<td>1.3 – 92.6</td>
</tr>
<tr>
<td>Guaiacol</td>
<td>59</td>
<td>3.9</td>
<td>−3.4</td>
<td>3.0</td>
<td>2.6 – 916.4</td>
</tr>
<tr>
<td>4-Methoxyphenol</td>
<td>53</td>
<td>21.8</td>
<td>−7.6</td>
<td>4.0</td>
<td>0.3 – 109.4</td>
</tr>
<tr>
<td>Gallol</td>
<td>77</td>
<td>287.0</td>
<td>−14.0</td>
<td>10.5</td>
<td>0.7 – 50.4</td>
</tr>
</tbody>
</table>

The binding energies were significantly less favourable than those measured in chloroform, since acetonitrile can act as a hydrogen-bond acceptor and thus competes with the phosphine oxide for the alcohol proton. However, the same conclusions can be drawn from this data, with catechol displaying a free energy of binding 55% greater than that of 4-methoxyphenol. Pyrogallol has a binding energy 84% greater than that of the 4-methoxyphenol control compound, suggesting that the polarisation effects may be extended over a chain of three hydroxyl groups, but that any cooperative effect...
decreases as the length of the chain increases. The binding energy of guaiacol was also found to be negative (compared to the small positive value in chloroform), showing that a favourable binding interaction with tri-\textit{n}-butylphosphine oxide can form in acetonitrile.

**Figure 5.14** – Graphical representation of the binding energies of the compounds used in this study. Numerical data is contained in tables 5.2, 5.3, 5.4 and 5.5. 8-Methoxynaphthalene-1-ol and 2'-Methoxybiphenyl-1-ol showed no observable binding.

This titration-based study cannot rule out the possibility that catechol and 1,2-naphthalenediol bind in a bifurcated manner rather than in the intended manner with one intramolecular and one intermolecular hydrogen bond is formed (Figure 5.16).

**Figure 5.16** - Bifurcated binding modes in (a) catechol and (b) 1,2-naphthalendiol.

Data from the guaiacol control compound indicate that it costs at least 8 kJ mol\(^{-1}\) to
break the intramolecular hydrogen bond in catechol (Figure 5.17). Furthermore, if the bifurcated conformation was the dominant binding mode then this would mean that the energy gained upon formation of the bifurcated interaction energy would need to be at least \(-24\,\text{kJ mol}^{-1}\) to be consistent with the experimentally observed binding energy of \(-16\,\text{kJ mol}^{-1}\), and the thermodynamic cycle shown in Figure 5.17.

![Equilibria between the cooperative and bifurcated binding modes of catechol with tributylphosphine oxide.](image)

The value of \(-24\,\text{kJ mol}^{-1}\) for the bifurcated binding mode would seem surprisingly favourable given that a single H-bond between 4-methoxyl phenol and tri-\(n\)-butylphosphine oxide in acetonitrile was measured to be \(-7.6\,\text{kJ mol}^{-1}\) (Table 5.3). Thus, it could be reasoned that two of these interactions is worth \(-15.2\,\text{kJ mol}^{-1}\), while any entropic chelate benefit on simultaneously binding two donors vs. one donor is likely to be little more than \(-6\,\text{kJ mol}^{-1}\), giving a maximum favourable interaction energy of \(-21\,\text{kJ mol}^{-1}\) for the bifurcated binding mode. However, the energy cost of forming the conformation required for bifurcated binding in catechol is likely to be significantly higher than the energy cost of simply breaking the internal H-bond in guaiacol (\(+8\,\text{kJ mol}^{-1}\)) since the bifurcated complex results in two polar hydroxyl protons being pointed towards each other, which would represent a significant repulsive electrostatic interaction. This analysis is only suggestive, and future work will involve the synthesis of a molecular balance where bifurcated binding can be excluded to determine the binding mode of the catechol motif (see Future Work...
The results of binding studies in the naphthalenediol series are summarised in Table 5.4. The main difference in this system compared to catechol regarding hydrogen bonding is the geometry of the internal hydrogen bond. The geometry of hydrogen bonds greatly influences their interaction energy\(^{[41]}\) and so this should have an effect on the strength of any cooperative interactions. The binding of the 8-methoxynaphthalene-1-ol control compound was too weak to be observed by NMR spectroscopy. 1,8-naphthalenediol was found to have a binding energy of \(-16.3 \text{ kJ mol}^{-1}\), which represents a 40% increase in interaction energy over the control compound. Although the value of the binding energy is very similar to that of catechol, the cooperative effect was found to be only half as strong (catechol is 83% stronger than 4-methoxyphenol).

Results with the biphenol derivatives showed similar trends to the other two series. The binding of the 2’-methoxybiphen-1-ol compound could not be observed by NMR. 2,2’-biphenol was found to have a binding energy of \(-12.7 \text{ kJ mol}^{-1}\), which is

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Bound</th>
<th>(K / \text{M}^{-1})</th>
<th>(\Delta G / \text{kJ mol}^{-1})</th>
<th>Error</th>
<th>Conc. Range / mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,8-Naphthalenediol</td>
<td>88</td>
<td>710.0</td>
<td>-16.3</td>
<td>10.4</td>
<td>1.3 - 92.2</td>
</tr>
<tr>
<td>8-Methoxynaphthalene-1-ol</td>
<td>&lt;5%</td>
<td>&lt;5</td>
<td>~0</td>
<td>-</td>
<td>0.2 - 98.9</td>
</tr>
<tr>
<td>6-Methoxynaphthalene-1-ol</td>
<td>71</td>
<td>107.0</td>
<td>-11.6</td>
<td>-(a)</td>
<td>3.9 - 76.8</td>
</tr>
</tbody>
</table>

Table 5.4 - Results from NMR binding studies on the naphthalene series in chloroform. (a) Titration was not repeated due to time constraints. Errors given are twice the standard deviation of each experiment.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Bound</th>
<th>(K / \text{M}^{-1})</th>
<th>(\Delta G / \text{kJ mol}^{-1})</th>
<th>Error</th>
<th>Conc. Range / mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,2’-Biphenol</td>
<td>72</td>
<td>167</td>
<td>-12.7</td>
<td>1.21</td>
<td>0.4 - 111.7</td>
</tr>
<tr>
<td>2’-Methoxybiphen-1-ol</td>
<td>&lt;5%</td>
<td>&lt;5</td>
<td>~0</td>
<td>-</td>
<td>0.2 - 80.4</td>
</tr>
<tr>
<td>4’-Methoxybiphen-1-ol</td>
<td>67</td>
<td>24.9</td>
<td>-8.0</td>
<td>-(a)</td>
<td>0.9 - 253.0</td>
</tr>
</tbody>
</table>

Table 5.5 - Results from NMR binding studies on the biphenol series in chloroform. (a) Titration was not repeated due to time constraints. Errors given are twice the standard deviation of each experiment.
58% stronger than that of the 4′-methoxybiphen-1-ol control compound.

Comparison of the results of the three series showed that the magnitude of cooperative effects is dependent on the geometry of the internal hydrogen bond, and is found to decrease in the order catechol > 2,2′-biphenol > 1,8- naphthalenediol. The results can be explained in terms of the size of the ring formed by the intramolecular hydrogen bond. In the case of the 5-membered ring (catechol), the directionality of the hydrogen bonds seems to be optimal for interaction strength and hence the greatest increase in binding affinity (largest cooperative effect) is observed in this system. The six-membered ring (1,8-naphthalenediol) may not have such favourable interactions due to the different hydrogen bond geometry. Calculations show that the distance between the two carbon atoms bearing the hydroxyl groups in 1,8-naphthalenediol is slightly larger the equivalent carbons in naphthalene (2.51 Å vs 2.45 Å). This slight distortion of the structure may be enough to sufficiently affect the hydrogen bond geometry to weaken the cooperative effects in this system. The seven-membered ring (2,2′-biphenol) has no such distortion, but the geometry is not as favourable for hydrogen bonding interactions as in catechol, hence the observed trend in cooperative effect strength.

5.7 Conclusions and Future Work

It can be concluded that cooperative effects in hydrogen-bond networks can have a significant effect on the binding energy to a strong H-bond acceptor. Although the magnitude of cooperative effects has been shown to diminish with increasing hydroxyl group chain length, the number of these interactions in large biological systems such as enzymes and DNA means that these effects may still be very important in determining the behaviour of the system. Furthermore, calculated electrostatic potentials taken over the hydroxyl groups on isolated molecules H-bond donors were not found to account for the experimentally observed cooperative effects suggesting that delocalisation may play an important mechanistic role in this type of cooperativity.

Future work in this area includes the synthesis of the formamide balance shown in Figure 5.14 and evaluation of its folding energies. The steric bulk of the tert-butyl group prevents formation of a cooperative binding event to an external acceptor, hence any binding to tri-n-butylphosphine oxide in this balance would be most likely be a
result of the bifurcated binding mode shown to the right of Figure 5.14. This work is already underway in the Cockroft group, who have experience in synthesising this type of molecular balance.\[42], \[43\]

![Chemical structures](image)

\[\Delta G_{\text{int}} = -3.7 \text{ kJ mol}^{-1}\]  \[\Delta G_{\text{int}} = -7.7 \text{ kJ mol}^{-1}\]

Figure 5.18 – Preliminary results from studies of the formaldehyde balances, along with a possible binding interaction with a phosphine oxide acceptor. These results were obtained by Hannah Paterson, an undergraduate project student in the lab. \(\Delta G_{\text{int}}\) refers to the interaction between the formyl carbonyl oxygen and the proton of the ortho-hydroxy group.

5.8 Experimental Procedures

All reagents were purchased from commercial sources and used without further purification. Unless otherwise stated, all reactions were performed under an atmosphere of \(\text{N}_2\). Flash column chromatography of reaction products was performed using Fluka analytical silica gel 60. Reactions were monitored by TLC on Merck aluminium sheets coated with silica gel 60F and visualised using light of wavelength 256 nm.

NMR data for titrations was recorded using a Bruker Biospin ARX600 spectrometer operating at 600 MHz, while NMR for compound characterisation was recorded on a Bruker Avance NMR Spectrometer operating at 400MHz. Deuterated chloroform was purchased from Sigma-Aldrich and used without further purification. All samples were dried in a vacuum oven overnight prior to the titration experiment. Each titration was performed in a vacuum oven dried septum-sealed NMR tube containing a starting volume of 350 \(\mu\text{L}\) of solvent. An internal standard of 10 mM methylene diphosphonic acid in \(\text{D}_2\text{O}\) was present in a sealed capillary tube. The spectrometer was manually tuned, locked and shimmed and the mixed host / gust solution was added in 1, 3, 5, 10, 10, 15, 20, 20, 30, 35, 40, 50, 75, 150, 250, 350 and
450 μL increments, recording a $^{31}$P NMR spectrum after each addition. Data was analysed using MestreNova and titration curves fitted using an Excel spreadsheet provided by Prof. Christopher A. Hunter (University of Sheffield).

$^{1}$H and $^{13}$C chemical shifts are reported in parts per million (δ) relative to tetramethylsilane and all coupling constants (J) are given in Hertz (Hz). $^{31}$P chemical shifts are reported in parts per million relative to 10 mM methylene diphosphonic acid in D$_2$O (ppm present as an internal standard contained within a sealed capillary tube). Melting points were determined using a Gallenkamp melting point apparatus. Ab initio calculations were performed using Spartan '08. Unless otherwise stated, geometry minimisations and electrostatic potentials were calculated using DFT/B3LYP/6-311G*.

**Preparation of 2’-methoxybiphenyl-2-ol** 2,2’-Biphenol (1 g, 5.37 mmol) was dissolved in acetone (15 mL). Methyl iodide (724 mg, 5.102 mmol, 0.95 equiv) was added followed by potassium carbonate (1484 mg, 10.741 mmol, 2 equiv) and the reaction stirred at room temperature for 16 h. Methanol (15 mL) was added and the reaction was stirred for a further 1 h. The resulting solution was filtered and solvents removed under reduced pressure. The remaining material was dissolved in ethyl acetate (30 mL) and acidified by the addition of 1 M HCl. The aqueous layer was then extracted with ethyl acetate (2 x 30 mL) and the combined organics were dried over magnesium sulfate. Solvent was removed in vacuo to give the crude product which was then purified by flash column chromatography (10–25% ethyl acetate in hexane gradient) to give 2’-methoxybiphenyl-2-ol (728 mg, 3.65 mmol, 68%). $^{1}$H NMR (400 MHz, CDCl$_3$): δ 7.38 – 7.43 (m, 2H), 7.29 (d, J = 1.6 Hz, 2H), 7.01 (td, J = 7.5, 1.1 Hz, 1H), 6.07 – 6.20 (m, 1H), 6.87 (m, 2H), 4.75 (s, 1H), 3.81 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.56, 154.72, 131.23, 130.96, 130.81, 130.39, 128.35, 120.98, 115.06, 111.36, , 55.69. MP: 113 °C. MS (ES) m/z 200.0 (M$^+$) Expected m/z: 200.08
Preparation of 4'-methoxybiphenyl-2-ol 2-Iodophenol (500 mg, 2.27 mmol), 4-methoxyphenol boronic acid (518 mg, 3.40 mmol, 1.5 equiv) and tricyclohexylphosphine (127 mg, 0.454 mmol, 0.2 equiv) were dissolved in dioxane. Pd_2(dba)_3 (108 mg, 0.114 mmol, 0.5 equiv), tribasic potassium phosphate (1448 mg, 6.818 mmol, 3 equiv) and water (3.6 mL) were added and the vessel was heated to 95 °C for 5 h. The mixture was then allowed to cool to room temperature, diluted with ethyl acetate and filtered through celite. The resulting solution was washed with 1 M HCl (3 x 60 mL), with addition of brine when necessary to prevent the formation of emulsions. The organic phase was then dried over magnesium sulfate and the solvent removed under reduced pressure to yield the crude 4'-methoxybiphenyl-2-ol. The crude product was purified by flash column chromatography (5–30 % ethyl acetate in hexane gradient) to give 4''-methoxybiphenyl-2-ol (432 mg, 2.16 mmol, 95%). ^1H NMR (400 MHz, CDCl_3): δ 7.51 (m, 2H), 7.28 (t, J= 8 Hz, 1H), 7.13 (m, 1H), 7.02 (m, 1H), 6.97 (m, 2H), 6.78 (ddd, J = 8.0, 2.5, 0.9 Hz, 1H), 4.82 (s, 1H), 3.85 (s, 3H). 13C NMR (101 MHz, CDCl_3) δ 159.43, 155.96, 142.77, 133.40, 130.08, 128.27, 119.52, 114.33, 113.79, 113.71, 55.50. MP: 116 °C. MS (ES) m/z 200.0 (M^+). Expected m/z: 200.08

Preparation of 1,8-naphthalenediol Potassium hydroxide pellets (4.51 g, 805 mmol) was ground into a fine powder using a mortar and pestle and placed into a silicon crucible. 1,8-naphthosultone (1.10 g, 5.34 mmol) was added and the powdered mixture was heated to 300 °C in a high temperature oven. The mixture was cooled to room temperature and washed with water, 4 M HCl, and finally ethyl acetate. The washings were adjusted to acidic pH by the addition of further 4 M HCl, further ethyl acetate was added and the mixture was then filtered. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organics were dried over magnesium sulfate and the solvent was removed in vacuo. The crude
product was then purified by flash column chromatography (30–50 % ethyl acetate in hexane gradient) to give 1,8-naphthlaenediol (630 mg, 3.93 mmol, 73%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.73 \text{ (s, 2H)}, 7.37 \text{ (dd, } J = 8.3, 1.0 \text{ Hz, 2H}), 7.29 \text{ (m, 2H)}, 6.79 \text{ (dd, } J = 7.5, 1.0 \text{ Hz, 2H})\). \(^1^3\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 152.70, 137.04, 126.72, 120.54, 114.52, 109.40\). MP: 145 ºC. MS (ES) \(m/z\) 160.0 (M\(^+\)) Expected \(m/z\): 160.05

**Preparation of 8-methoxynaphthalen-1-ol** 1,8-Naphthalenediol (100 mg, 0.574 mmol) was dissolved in dry THF (2 mL), followed by the addition of sodium hydride (23 mg, 0.574 mmol) and dimethyl sulfate (72 mg, 0.574 mmol). The reaction was then stirred at room temperature for 16 h, before being quenched with saturated ammonium chloride solution (6 mL). Water (10 mL) was added and the solution extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with HCl (20 mL) and brine (20 mL), and dried over magnesium sulfate. The solvent was then removed under reduced pressure giving crude 8-methoxynaphthalen-1-ol, which was purified by flash column chromatography (2:1 hexane: diethyl ether) to give the product (100 mg, 0.57 mmol) in 99% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 9.32 (s, 1H), 7.42 (dd, \(J = 8.3, 0.7 \text{ Hz, 1H}\), 7.32 (m, 3H), 6.88 (dd, \(J = 7.4, 1.3 \text{ Hz, 1H}\), 6.78 (d, \(J = 7.4 \text{ Hz, 1H}\)), 4.07 (s, 3H). \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 156.30, 154.62, 136.89, 127.87, 125.74, 122.01, 119.01, 115.21, 110.57, 104.04, 56.25\). MS (ES) \(m/z\) 174.0 (M\(^+\)) Expected \(m/z\): 174.07

**Preparation of 6-methoxynaphthalen-1-ol** Copper bromide (22.2 g, 9.31 mmol, 1.75 equiv) was added to ethyl acetate (8 mL) and brought to reflux. 6-Methoxytetralone (1 g, 5.68 mmol) was dissolved in chloroform (7 mL) and this solution was added to the copper bromide solution. Refluxing was then continued for a further 16 h. The solvents
were removed \textit{in vacuo}. The resulting material was dissolved in ethyl acetate (70 mL) and washed with 1 M HCl (60 mL). The organic phase was dried over sodium sulfate and the solvents were removed under reduced pressure to give crude 7-methoxy-2-bromo-2-tetralone (1.41 g), which was used in the next step without further purification.

Crude 7-methoxy-2-bromo-2-tetralone (13.1 mg, 5.14 mmol) was dissolved in dry DMF. Lithium bromide (10.5 g, 11.1 mmol) and lithium carbonate (770 mg, 10.4 mmol) were added and the reaction was heated for 3.5 h under reflux. The reaction mixture was then allowed to cool to room temperature before being acidified by the addition of 1 M HCl. This solution was then extracted with diethyl ether (3 x 50 mL). The combined organics were then washed with 1 M HCl (3 x 70 mL) and dried over sodium sulfate. The crude product was then purified by flash column chromatography (5–30% acetone in hexane gradient). A further column (DCM) was required to further purify the product, after which pure 6-methoxynaphthalen-1-ol (520 mg, 2.99 mmol, 57 % over two steps) was obtained. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.09 (d, $J = 9.0$ Hz, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.26 (m, 1H), 7.13 (m, 2H), 6.67 (dd, $J = 7.3$, 1.1 Hz, 1H), 5.17 (broad s, 1H), 3.92 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 197.23, 163.55, 146.96, 129.68, 126.37, 113.04, 112.64, 55.43, 38.92, 30.19, 23.40. MP: 88 °C. MS (ES) m/z 174.0 (M+) Expected m/z: 174.07
References


