

Formal Hydrogen Transfer Reactions and the Effects of Non-Redox Active Metal Cations

by

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Abstract

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Preface

Preface stuff

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List of Symbols and Abbreviations

BDE	bond dissociation enthalpy
BEP	Bell-Evans-Polanyi
BnO [•]	benzyloxyl radical
CHD	cyclohexadiene
CumO [•]	cumyloxyl radical
DFT	density-functional theory
DNA	deoxyribonucleic acid
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
E_a	activation energy
FHT	formal hydrogen transfer
\mathcal{H}	Hamiltonian operator
HAT	hydrogen atom transfer
HB	hydrogen bond
HF	Hartree-Fock
HOMO	highest occupied molecular orbital
kcal mol ⁻¹	kilocalories per mole
K_x	equilibrium constant
k_x	rate constant
KSEs	kinetic solvent effects
LFER	linear free energy relationship
LFP	laser flash photolysis
M	molar concentration
MO	molecular orbital
MDA	malondaldehyde
NCI	non-covalent interaction
PCET	proton coupled electron transfer
PMP	1,2,2,6,6-pentamethylpiperadine
PES	potential energy surface

List of Symbols and Abbreviations

RNA	ribonucleic acid
ROS	reactive oxygen species
s	seconds
SOMO	singly occupied molecular orbital
SPLET	sequential proton loss electron transfer
STO	Slater-type orbital
TEA	triethylamine
THF	tetrahydrofuran
TS	transition state
Z	atomic number
ΔG	Gibbs free energy of reaction
ΔG^\ddagger	Gibbs free energy barrier of reaction
ΔH	enthalpy of reaction
ΔH^\ddagger	enthalpic reaction barrier of reaction
ΔS	entropic change of reaction
∇^2	Laplacian operator
σ_X	Hammett substituent parameter
ρ	sensitivity constant, or electron density

Acknowledgements

This is the place to thank professional colleagues and people who have given you the most help during the course of your graduate work.

Dedication

The dedication is usually quite short, and is a personal rather than an academic recognition. The *Dedication* does not have to be titled, but it must appear in the table of contents. If you want to skip the chapter title but still enter it into the Table of Contents, use this command `\chapter[Dedication]{}.`

Chapter 1

Introduction

1.1 Background

Radicals are chemical species that tend to be highly reactive due to the presence of one or more unpaired electrons. Living systems depend on radical processes as part of normal metabolism¹ but biomaterials, such as proteins, are susceptible to radical-induced damage. Radical-induced oxidation of biomaterials has been implicated in a number of degenerative disease states, including cancer, Alzheimer's disease, Parkinson's disease, and multiple sclerosis.^{2–5}

In biological systems, radicals are derived from many sources. Exogenous sources include solar radiation and air pollutants, while endogenous sources include *in vivo* transition metal-ion redox processes, such as the electron transport chain involved in cellular respiration.⁶ Some redox centres in the electron transport chain may transfer an electron to molecular oxygen, forming the superoxide anion ($O_2^{\cdot-}$). Superoxide is not a strong oxidant on its own, however it may become protonated to form the more reactive hydroperoxyl radical,⁷ or disproportionate spontaneously, or catalytically through metalloenzymes such as superoxide dismutase, leading to the formation of highly reactive oxygen-centred radicals. In fact, most oxygen-centred radicals derive from reactions of O_2 with redox-active metals.¹

Oxygen-centred radicals, known as reactive oxygen species (ROSs) in biology, are particularly important and common due to the previously described nature of aerobic respiration. The ROSs which are of primary concern are the highly reactive hydroxyl radicals (HO^{\cdot}), alkoxy radicals (RO^{\cdot}), superoxide ($HOO^{\cdot}/O_2^{\cdot-}$), and peroxy radicals (ROO^{\cdot}).¹ The oxidation of proteins by ROSs occurs through a radical chain mechanism which has been studied experimentally in detail.^{8,9} This chain reaction occurs when an ROS initiates a radical chain reaction through hydrogen atom transfer (HAT), single electron transfer, or addition reactions with protein substrates, leading to rapid propagation and formation of new radicals. HAT is an extremely important reaction in the context of oxidative damage. The focus of my work

1.1. Background

is on developing an understanding of the fundamental chemistry involved in protein oxidation.

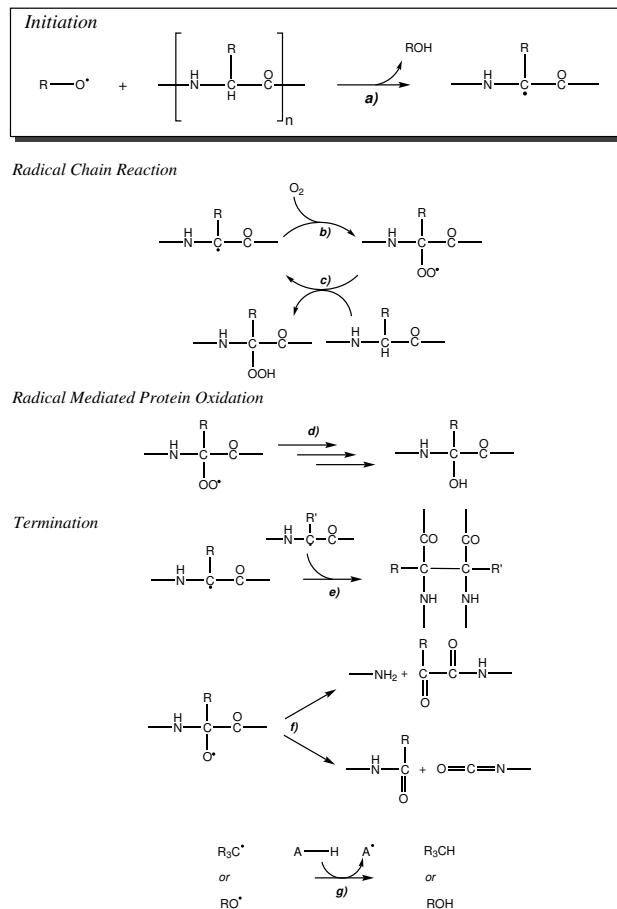
Proteins are the most abundant biomaterial in most biological systems,¹⁰ thus understanding their degradation is essential to understanding degenerative disease. Because proteins are composed of as many as 20 common amino acid side-chains, as well as the common peptide backbone, there are a large number of possible reactions. Some of the reactions involved in protein oxidation are shown in Scheme 1.1.

Initial abstraction (Reaction **a**) often occurs at the α -carbon position ($\alpha\text{-CH}$), forming a carbon-centred radical ($\alpha\text{-C}^\bullet$) which is partially delocalized in the π -system of the neighbouring amide and carbonyl groups. Studies have indicated that the stability of $\alpha\text{-C}^\bullet$ is determined by stereo-electronic considerations related to the planarity of the amide group.¹¹ As such, steric bulk in the side-chains, as well as local protein structure (helix, sheet, etc.) can constrain radical geometries. For example, the most stable α -carbon radicals occur at glycine residues in antiparallel β -sheets, whereas other bulkier residues and secondary structures lead to loss of captodative stabilization.¹² Amino acid side-chains are also susceptible to oxidation. Those side-chains containing sulphur,¹³ as well as tyrosine (which has a fairly weak phenolic O-H bond of about 89 kcal mol⁻¹),¹⁴ are particularly susceptible to oxidation.

Propagation of the radical chain reaction occurs through various processes. In the presence of molecular oxygen, rapid addition occurs at the newly formed $\alpha\text{-C}^\bullet$ (Reaction **b**), generating a peroxy radical, which can carry forward through further HAT reactions (Reaction **c**).¹⁵ The mechanism involved in the radical mediated oxidation of proteins has been studied experimentally using techniques involving ionizing radiation.^{16,17} The course of this process is complexly dependent on the availability of either singlet oxygen (${}^1\text{O}_2$), or superoxide ($\text{O}_2^\bullet-$) or the protonated form, peroxy radical ('OOH). A detailed analysis of this process is outside the scope of this thesis, but ultimately, these reactions lead to the generation of a hydroxyl-amide (Reaction **d**).

The radical chain reaction can be terminated through several mechanisms, including protein-protein cross-linking (Reaction **e**), or protein fragmentation (Reaction **f**). Reactions with antioxidants (A-H, Reaction **g**) also terminate the chain reaction by removing the radical from the protein system. The sum total of all these processes contribute to the accumulation of oxidized proteins which are associated with many degenerative diseases.¹⁸ HAT reactions which are important steps in the initiation, propagation, and

1.1. Background



Scheme 1.1: Common reaction involved in the protein oxidation. The reactions are as follows: **a)** initiation of radical chain through abstraction by an oxygen centred radical to generate an α -carbon radical, **b)** radical addition of molecular oxygen, **c)** propagation of the radical chain reaction generating another α -carbon radical and a peroxide. **d)** Radical mediated protein oxidation proceeds through multiple steps involving oxygen centred radicals and molecular oxygen result in the generation of a hydrogen-amide. Termination of the radical chain reaction can occur in several ways, including: **e)** possible cross-linking mechanism of two carbon-centred radicals, **f)** possible fragmentation pathways of an oxygen-centred radical intermediate, or **g)** HAT with an antioxidant.

1.2. Details of HAT reactions

termination reactions of protein oxidation are investigated in this thesis.

1.2 Details of HAT reactions

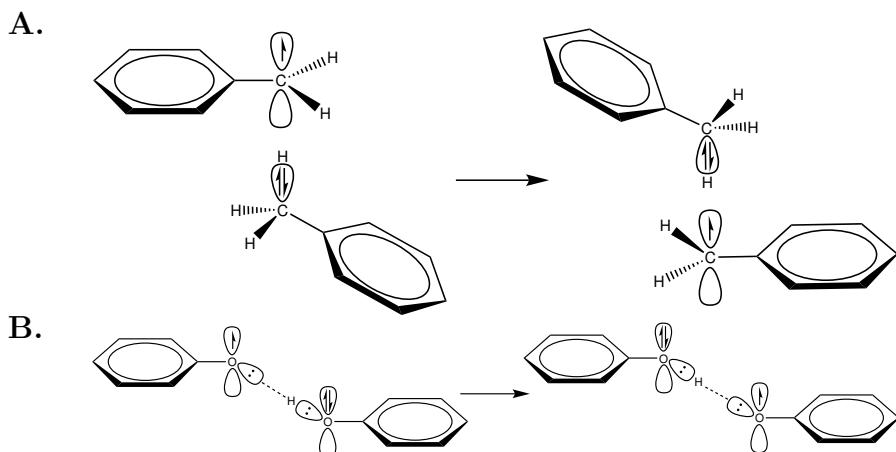
Developing an understanding of protein and other biomolecular oxidation requires an understanding of the deceptively simple HAT reactions involved. Formal HAT reactions are a fundamental radical chemical transformation that have been studied for more than a century.^{19,20} From an experimental perspective, HAT reactions which involve oxygen-centred radicals and non-radical organic substrates are reasonably well characterized: the effects of different solvents are well understood.²¹ However, the main challenge faced by many experiments is elucidating the mechanistic details of a reaction. This is a problem that can be examined by quantum chemistry, which is the approach that I shall take. Background on the theory used in this thesis is given in Chapter 2.

In order to investigate HAT reactions, we need to consider the mechanism in detail. For a simple HAT reaction, there exists several possible mechanisms by which this transformation can occur. The two most common concerted mechanisms are direct HAT and proton-coupled electron transfer (PCET). At the basic level, direct HAT involves the transfer of an electron and proton through the same set of acceptor/donor orbitals, while PCET involves the transfer of an electron and proton through different sets of orbitals. In practise, this distinction is poorly described, and this topic is still in active discussion in the literature.^{22–32}

The prototypical example demonstrating the difference between direct HAT to PCET comes from the work of Mayer et al.,²³ that describes the self-exchange reactions of benzyl-toluene and phenoxy-phenol, shown in Scheme 1.2. In their work, the transition state (TS) structures were obtained through theoretical studies. These complexes are oriented so that the aromatic rings are trans relative to one another. In this geometry, the benzyl-toluene pair undergoes direct HAT, with the $2p - \pi$ orbital of the benzylic carbon radical oriented at the benzylic hydrogen on toluene. This is described as direct HAT, as the orbital containing the radical overlaps with the C-H σ^* anti-bonding orbital, and thus the transfer of the H atom occurs through the same set of orbitals (see Scheme 1.2 A).

For the phenoxy-phenol pair (see Scheme 1.2 B), a fairly strongly hydrogen bonded pre-reaction complex is first formed with a binding enthalpy ΔH of $-8.1\text{ kcal mol}^{-1}$. As a result of this strong interaction, the TS structure is such that the phenoxy radical nominally occupies an oxygen $2p$ orbital.

1.2. Details of HAT reactions



Scheme 1.2: Self-exchange reactions of the **A.** benzyl-toluene couple through direct HAT **B.** phenoxy-phenol couple through PCET.

Therefore, in order to undergo direct HAT, the hydrogen bond between the OH and O lone-pair must break, and a new, weaker hydrogen bond with the nominally O-centred radical must form. Alternatively, the hydrogen bonded pre-reaction complex geometry does allow the orbital containing the radical to overlap with the $2p$ lone pair of and the phenol moiety, and the conjugated aromatic π systems. As a result, the TS complex singly occupied molecular orbital (SOMO) is of π -symmetry and highly delocalized. Accordingly, the proton and electron are transferred through different sets of orbitals. The reaction has an enthalpic barrier height (ΔH^\ddagger) of 5.0 kcal mol^{-1} relative to the hydrogen bonded complex, so that the barrier is 3.1 kcal mol^{-1} below the separated reactants.

The work by Mayer et al.²³ suggests that hydrogen bonding is a necessary, but not sufficient, condition for PCET to occur. This then implies that PCET is not possible between molecules which do not possess hydrogen bonding moieties, such as carbon atoms. Work by other authors has shown this to be untrue.^{26,33} In particular, DiLabio and Johnson²⁶ demonstrated that Mayer et al.²³ neglected the important contributions of $\pi - \pi$ interactions and lone pair- π interactions. Additional calculations revealed the existence of a TS structure for the benzyl-toluene couple which is 3.7 kcal mol^{-1} lower in energy than previously reported. This structure orients the aromatic rings 34° relative to one another, allowing for optimal

1.2. Details of HAT reactions

$\pi - \pi$ overlap. Analysis of the TS structure highest-occupied molecular orbital (HOMO) reveals bonding character between the two π -system, while the SOMO shows anti-bonding character between the π -systems, as well as both C-H bonds. Thus, there exists a net partial bonding interaction between the two π -systems, opening up an additional electronic channel for PCET to occur. DiLabio and Johnson also suggest that the phenol-phenoxy couple likely prefers a π -stacked TS structure, and compare this to a structural analogue, a naturally occurring tyrosyl-tyrosine couple, which they demonstrated proceeds through a PCET mechanism. Other authors have confirmed the existence of a π -stacked TS structure for the phenol-phenoxy couple.^{31,32,34} In the work of Muñoz-Rugeles et al.³², an approach utilizing natural population analysis along the intrinsic reaction coordinate, it was demonstrated that both the benzyl-toluene couple and phenoxy-phenol couple favour a π -stacked TS structure and undergo formal HAT through a PCET mechanism. Interestingly, they also showed that reaction barrier heights for the PCET mechanism are systematically lower than those for related direct HAT mechanism.

Bearing in mind there is not an obvious way to explore the related differences in mechanism experimentally, computational examination of formal HAT reactions enables analysis of the mechanism of these reactions. Through careful investigation, a general distinction between a direct HAT mechanism and PCET mechanism can be achieved. In doing so, important insight is gained from understanding the electronic behaviour of these reactions. In this vein, the investigation of the physico-chemical nature of HAT reactions shall be the central theme of this thesis.

Consider for a moment the potential energy surface (PES) for an arbitrary chemical reaction, which is a complex hypersurface that depends on many variables. Theoretical methods can be used to generate a full PES, however, this quickly becomes computationally infeasible as the number of atoms in a system increases. Typically this problem can be simplified by examining only the relevant degrees of freedom. Often, the two most important coordinates can be isolated, giving a three-dimensional PES. Furthermore, in chemistry we often simplify this problem to two-dimensions using the so-called intrinsic reaction coordinate, which is the lowest energy cross section of a higher dimension PES. This yields a reaction coordinate diagram, as is illustrated below in Figure 1.1.

In a typical reaction coordinate diagram, the reactants begin to interact and form a pre-reaction complex. Given sufficient energy, the reaction will proceed over the top of the energy barrier through a transition state (TS) complex. After the chemical transformation is completed, a post-reaction

1.2. Details of HAT reactions

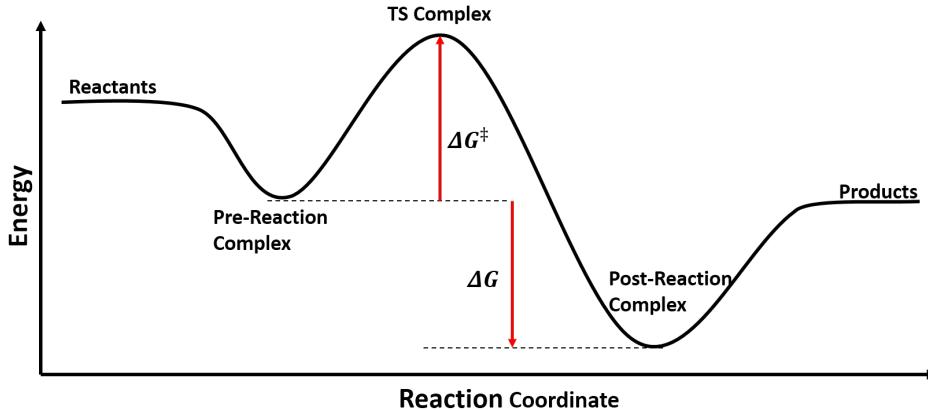


Figure 1.1: A typical reaction coordinate diagram.

complex is formed until the products are able to separate. This is a somewhat simplified description, as it only broadly describes a chemical transformation. In particular, the roles of substrate-radical and substrate-radical-medium interactions along the reaction coordinate are not fully described. This is in fact a key point, as a thorough understanding of these interactions continues to be a hole in the literature.

Consequently, recent work from our group, in collaboration with our experimental colleagues at the University of Rome Tor Vergata, has focused on the importance of substrate-radical interactions in determining the kinetics of HAT reactions. Specifically, it has been shown that the three-dimensional structures of oxygen-centred radicals, as well as the organic substrates, impact the nature of the interactions involved in HAT reaction pathways.³⁵ In our work, we utilize primarily the benzyloxy radical (BnO^\cdot) and cumyloxy radical ($CumO^\cdot$), which serve as a proxy to biological oxygen-centred radicals. This is primarily due to the fact that reactions involving BnO^\cdot and $CumO^\cdot$ are relatively long lived in solution, and can be monitored using time-resolved laser flash photolysis (LFP) techniques. These radicals are somewhat different than biologically relevant radicals such as HO^\cdot , and as a result, the reactivity trends pertaining to the substrates can be somewhat masked by the properties of the radical, such as steric bulk,³⁶ or non-covalent binding.³⁷ Nonetheless, through a careful combination of theoretical and experimental techniques, reactions involving BnO^\cdot and $CumO^\cdot$ with a variety of organic substrates have been used to develop a great deal of insight with respect to the role of structure in both the radicals and substrates, and

1.3. Research goals

resulting intermolecular interactions.

1.3 Research goals

With respect to the work in this thesis, in Chapter 3 the importance of the left-hand side of Figure 1.1 shall be examined by studying how the pre-reaction complex impacts HAT reactions. There has been limited investigation of the importance of pre-reaction complex formation for HAT reaction.³⁸ This is problematic, as oxygen-centred radicals can hydrogen bond with substrates as both acceptors and donors.³⁹ These hydrogen bonding interactions, in addition to the other non-covalent interactions between the radical and substrate, lead to the formation of a pre-reaction complex. Accordingly, the formation of a pre-reaction complex is a fundamental step in protein oxidation.

The specific aim of Chapter 3 is to investigate the effects of non-covalent binding in the pre-reaction complex, with respect to the well-known, but phenomenological, Arrhenius equation. As of yet, there is no framework which relates the non-covalently bound pre-reaction complex to kinetic results. I ask the simple question: Does there exist a direct correlation between the Arrhenius pre-factor and the non-covalent binding that occurs in the pre-reaction complex formed for HAT reactions? To address this question, I examine the non-covalent binding in the pre-reaction complex in a series of related HAT reactions. Arrhenius parameters for the systems of interest in this work were previously tabulated,⁴⁰ and consist of thermoneutral or nearly thermoneutral reactions involving the formation and destruction of oxygen-centred radicals. These reactions are related to the phenol-phenoxy self-exchange reaction, where a relatively strong pre-reaction complex is expected.

Then in Chapter 4, the right-hand side of Figure 1.1 is considered, where the effects of bond dissociation enthalpies (BDEs) on HAT rate constants are examined. BDEs are central to the understanding of reactions with respect to thermodynamics. In addition to this, there exists a tremendous amount of literature in which BDEs are linked to chemical reactivity, especially for HAT reactions.^{19,25,41–43} There exists a linear free energy relationship (LFER) called the Bell-Evans-Polanyi (BEP) principle,^{44,45} which states that the difference in activation energy (E_a) for two related reactions is proportional to the differences in reaction enthalpy (ΔH):

$$E_a = E_0 + \alpha\Delta H \quad (1.1)$$

1.3. Research goals

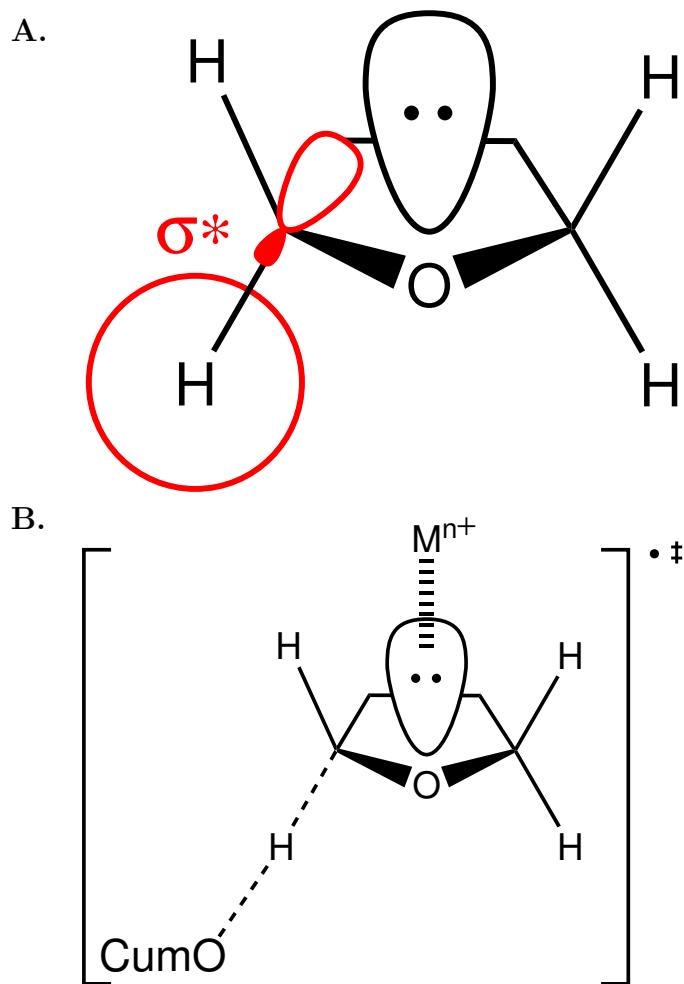
where E_0 is the activation energy of a reference reaction, and α , a constant which characterizes the position of the TS along the reaction coordinate. This relationship has been more generally used to compare larger families of reactions. Despite the widespread use of the BEP principle, the validity of this relationship is not well described.

I probe the validity of the BEP principle, with the aim to determine how generally it may be applied. This is achieved by relating accurate, theoretically determined C-H BDEs for species that undergo abstraction at the appropriate C-H position, to the experimentally determined HAT rate constants. HAT reaction rate constants depends on many factors. However, by using rate constants determined under specific conditions (LFP with CumO[•] in acetonitrile at 298K), the differences in reactivity depend mainly on the differences in chemical properties of the substrates of interest. Therefore, I hypothesize that if the BEP relation is valid, there should exist two relationships for C-H bonds: one in which the incipient radical is delocalized into a π -system (benzylic-allylic), and the other in which the remaining alkyl radicals are largely localized.

Finally, recent experimental results show that non-redox active metal cations, which are found ubiquitously in biological systems, have an inhibitory effect on HAT reactions involving oxygen-centred radicals. This has been demonstrated experimentally for substrates which undergo abstraction from sites adjacent to heteroatoms (e.g. amines, amides, and ethers). Under various stoichiometric ratios, these metal cations have effects ranging from full inhibition to partial deactivation of HAT reactivity.^{46–48} This effect has been attributed partially to the effects of hyperconjugative overlap. Take for example tetrahydrofuran (THF), shown in Scheme 1.3. Normally, there exists C-H bond weakening hyperconjugative overlap of electron density from one of the oxygen lone-pairs and the adjacent C-H σ^* anti-bonding orbitals. The interaction of a metal cation with the oxygen lone-pairs removes electron density from this interaction, thus increasing the C-H bond strength. As a result, the reactivity of this bond is decreased, as observed from the experimentally-measured 3.2-fold decrease in the rate constant for HAT with CumO[•] in acetonitrile from $6.65 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ to $7.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ in the presence of 1.0 M Mg(ClO₄)₂.⁴⁶

The nature of the interactions between non-redox active metal cations and organic substrates is poorly understood. This problem is explored in Chapter 5, with the aim to understand the fundamental physico-chemical properties that lead to the observed trends in reactivity. The experimentally observed effects have led us to hypothesize that the presence of non-redox active metal cations has a chemo-protective effect against the radical-induced

1.3. Research goals



Scheme 1.3: **A.** Hyperconjugative overlap in tetrahydrofuran. **B.** The non-redox active metal cation accepts electron density from the heteroatom lone pair, reducing overlap with the C-H σ^* anti-bonding orbital, and increasing the C-H bond strength, thus destabilizing the TS complex.

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oxidation of biomaterials such as proteins.

In using theory to study HAT reactions, I hope to contribute to a better understanding of the fundamental properties which govern these reactions, and thus develop insights into the many important biological processes in which HAT takes place.

Chapter 2

Theory

2.1 The quantum mechanical approach

The fundamental properties governing all of chemistry are dictated by the quantum mechanical wave functions, Ψ . Therefore, in quantum chemistry we seek solutions to the non-relativistic time-independent Schrödinger equation

$$\mathcal{H} |\Psi\rangle = E |\Psi\rangle \quad (2.1)$$

where \mathcal{H} is the Hamiltonian operator for a system of nuclei and electrons, and Ψ is the wave function, defined as the set of eigenvectors with energy eigenvalues E .⁴⁹ For a system with N electrons and M nuclei, the full Hamiltonian in atomic units is

$$\begin{aligned} \mathcal{H} = & -\sum_{i=1}^N \frac{1}{2} \nabla_i^2 - \sum_{A=1}^M \frac{1}{2M_A} \nabla_A^2 - \sum_{i=1}^M \sum_{A=1}^M \frac{Z_A}{r_{iA}} \\ & + \sum_{i=1}^N \sum_{j>i}^N \frac{1}{r_{ij}} + \sum_{A=1}^M \sum_{B>A}^M \frac{Z_A Z_B}{R_{AB}} \end{aligned} \quad (2.2)$$

In this equation, Z_A is the atomic number of nucleus A with a mass M_A divided by the mass of an electron. The Laplacian operators ∇_i^2 and ∇_A^2 represent differentiation with respect to the coordinates of the i th electron and A th nucleus. The first and second terms are the kinetic energies of the electrons and nuclei, respectively. The third term represents the Coulomb attraction between electrons and nuclei with distance r_{iA} . The fourth and fifth terms represent repulsion between two electrons with distance r_{ij} , and between two nuclei with distance R_{AB} , respectively.

Nuclei move slowly relative to electrons, due to their much greater mass. This is the central pillar of the Born-Oppenheimer approximation that is nearly always applied in molecular electronic structure calculations. The application of this approximation allows for the simplification of Equation 2.2: using a separation of electronic and nuclear variables, the second term for

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nuclear kinetic energy is solved separately. Also, the last term of nuclear repulsion is constant, and thus is generally ignored. This leaves us with the electronic Hamiltonian

$$\mathcal{H}_{elec} = - \sum_{i=1}^N \frac{1}{2} \nabla_i^2 - \sum_{i=1}^M \sum_{A=1}^M \frac{Z_A}{r_{iA}} + \sum_{i=1}^N \sum_{j>i}^N \frac{1}{r_{ij}} \quad (2.3)$$

Unfortunately, it is only possible to exactly solve the Schrödinger equation for the full electronic Hamiltonian \mathcal{H}_{elec} in the simplest of cases: when there is only one electron (H , H_2^+ , He^+ , Li^{2+} , etc). Note that since we will always work within the Born-Oppenheimer approximation, the subscript *elec* is usually dropped. In order to proceed to systems with multiple electrons, we must make further approximations.

2.1.1 Spin and Spatial Orbitals

We will refer to the wave function of a single particle as an orbital. Naturally then, as we will deal with electrons in molecules, we shall refer to their wave functions as molecular orbitals (MOs). To fully describe electrons we must consider a spatial and spin component to the overall wave function. A spatial orbital $\psi_i(\mathbf{r})$, is a function of the position vector \mathbf{r} , and describes the distribution of an electron in all space. It is usually assumed that spatial MOs form an orthonormal set such that

$$\langle \psi_i(\mathbf{r}) | \psi_j(\mathbf{r}) \rangle = \int d\mathbf{r} \psi_i^*(\mathbf{r}) \psi_j(\mathbf{r}) = \delta_{ij} \quad (2.4)$$

where the left-hand side is standard Dirac *bra-ket* notation representing the same integral in the middle. The right-hand side of Equation 2.4 is the standard Kronecker delta.

The spin of an electron is represented by two orthonormal functions $\alpha(\omega)$ and $\beta(\omega)$, or spin up and spin down. If a wave function describes both the spatial distribution and spin of an electron it is a spin orbital, $\chi_i(\mathbf{x})$, where \mathbf{x} represents both the spatial distribution and spin coordination of an electron ($\mathbf{x} = \{\mathbf{r}, \omega\}$). Since $\psi_i(\mathbf{r})$ and $\alpha(\omega)/\beta(\omega)$ are orthonormal, so too is $\chi_i(\mathbf{x})$

$$\langle \chi_i(\mathbf{x}) | \chi_j(\mathbf{x}) \rangle = \delta_{ij} \quad (2.5)$$

2.1.2 The Hartree product

The first steps towards describing an N electron wave function come from the work in the late 1920s by Hartree. The early *Hartree method* took an

2.1. The quantum mechanical approach

approach in which the wave function of N non-interacting electrons (Ψ^{HP}) is described by the product of N spin orbitals, known as a *Hartree product*:

$$\Psi^{HP}(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N) = \chi_i(\mathbf{x}_1)\chi_j(\mathbf{x}_2)\dots\chi_k(\mathbf{x}_N) \quad (2.6)$$

In such a system the Hamiltonian has the form of a sum of N independent operators

$$\mathcal{H} = \sum_{i=1}^N \hat{h}(i) \quad (2.7)$$

where $\hat{h}(i)$ is

$$\hat{h}(i) = -\frac{1}{2}\nabla_i^2 + V(\mathbf{r}_i) \quad (2.8)$$

such that the first term describes an electron's kinetic, and the second term describes potential felt by a single electron. If we consider the case which ignores electron-electron repulsion, then case V describes only the nuclear-electron attraction. Alternatively, the electron-electron repulsion may be included as an average potential.

Solutions to the Schrödinger equation for this system of non-interacting electrons are facile to obtain as each $h(i)$ depends only on the variables of $\chi_i(\mathbf{x}_i)$, so that

$$\mathcal{H} |\Psi^{HP}\rangle = E |\Psi^{HP}\rangle \quad (2.9)$$

gives an eigenvalue energy solution E that is the sum of N spin orbital energies ε_i

$$E = \varepsilon_1 + \varepsilon_2 + \dots + \varepsilon_N \quad (2.10)$$

While this theory does allow one to calculate energies for an N electron system, it has a basic deficiency: the antisymmetry principle of wave functions is not obeyed. The antisymmetry principle states that the electronic wave function must change sign (be antisymmetric) with respect to the exchange of spacial and spin coordinate of any two electrons. Hartree accounted for this by nominally applying the Pauli exclusion principle, however, this description is still incomplete in the sense that it does not describe the statistical nature of quantum particles.

2.1.3 Slater determinants

In order to satisfy the antisymmetry principle, a linear combination of Hartree products can be taken. Although the method was first utilized independently by Heisenberg⁵⁰ and Dirac,⁵¹ this method is called a *Slater determinant* after Slater.⁵² For an N electron system, a Slater determinant is written as

$$\Psi(\mathbf{x}_1, \dots, \mathbf{x}_N) = \frac{1}{\sqrt{N!}} \begin{vmatrix} \chi_i(\mathbf{x}_1) & \chi_j(\mathbf{x}_1) & \cdots & \chi_k(\mathbf{x}_1) \\ \chi_i(\mathbf{x}_2) & \chi_j(\mathbf{x}_2) & \cdots & \chi_k(\mathbf{x}_2) \\ \vdots & \vdots & \ddots & \vdots \\ \chi_i(\mathbf{x}_N) & \chi_j(\mathbf{x}_N) & \cdots & \chi_k(\mathbf{x}_N) \end{vmatrix} \quad (2.11)$$

where $1/\sqrt{(N!)}$ is a normalization factor. This simple mathematical trick ensures antisymmetry since the interchange of two electrons requires the exchange of two rows in the determinant, which changes the sign. Normally the short-hand form, which implicitly includes the normalization factor and assumes the ordering of electrons is $\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N$, is written as only the diagonal elements of the determinant:

$$\Psi(\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_N) = |\chi_i \chi_j \cdots \chi_k\rangle \quad (2.12)$$

Slater determinants are completely dependent on the spin orbitals from which it is formed, to within a sign. Therefore, Slater determinants also form an orthonormal set. Additionally, the introduction of antisymmetry into the Hartree product incorporates so-called *exchange correlation*. This means that the motion of two electrons with parallel spin are correlated. However, since the motion of electrons with opposite spin are not correlated, a single determinant wave function is said to be uncorrelated.

2.1.4 The Hartree-Fock approximation

Now that we have a method for describing many-electron wave functions, we can consider the computation of molecular properties. The cornerstone of quantum chemistry is the *Hartree-Fock method* (HF), otherwise known as the self-consistent field method. The main principle of the HF method is to approximate electron-electron interactions with an average potential. We begin with a single Slater determinant for an N electron system in the ground state:

$$|\Psi_0\rangle = |\chi_1 \chi_2 \cdots \chi_N\rangle \quad (2.13)$$

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By applying the variational method to the Schrödinger equation, we hope to find the lowest possible ground state energy, E_0 . One applies the variational principle by choosing a trial wave function (ϕ) dependent on some number of parameters. These parameters are optimized so that the expectation value of the energy is minimized:

$$E_0 \leq \langle \phi | \mathcal{H} | \phi \rangle \quad (2.14)$$

The trial wave function minimizes E_0 only when $\phi = \Psi_0$, the ground state wave function.

Within the Hartree-Fock approximation, we approximate the full electronic Hamiltonian \mathcal{H} with a related operator \hat{H}_0 :

$$\hat{H}_0 = \sum_{i=1}^N \hat{f}(i) \quad (2.15)$$

where $\hat{f}(i)$ is the Fock operator of the i -th electron, defined as

$$\hat{f}(i) = -\frac{1}{2} \nabla_i^2 + \sum_{A=1}^M \frac{Z_A}{r_{iA}} + v^{HF}(i) \quad (2.16)$$

The first two terms are familiarly the non-interacting one electron Hamiltonian, $\hat{h}(i)$. The third term, $v^{HF}(i)$, is the average potential experienced by each electron in the presence of other electrons.

With these approximations, the quantum problem is now reduced to solving the eigenvalue Hartree-Fock equation of the form

$$\hat{f}(i)\chi(\mathbf{x}_i) = \epsilon_i\chi(\mathbf{x}_i) \quad (2.17)$$

Solving Equation 2.17 directly is computationally very challenging, as there are infinite possible solutions. However in 1951, Roothaan⁵³ demonstrated that the problem can be simplified by expanding each spin orbital into a linear combination of a known finite number K basis functions:

$$\chi_i = \sum_{\mu=1}^K C_{\mu,i} \phi_{\mu} \quad (2.18)$$

where $C_{\mu,i}$ is a weighting coefficient and ϕ_{μ} is a basis function. As K approaches ∞ , the set $\{\phi_{\mu}\}$ becomes more complete and the energy approaches the so-called *Hartree-Fock limit*, or the exact energy in the Hartree-Fock approximation. One is, however, always limited to a finite number of basis functions, leaving deficiencies in the desired wave function Ψ_0 .

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The expansion of spin orbitals into a basis allows Equation 2.17 to be written in terms of the *Roothaan matrix equation*

$$\mathbf{FC} = \mathbf{SC}\varepsilon \quad (2.19)$$

where $\mathbf{F} = \sum_{l,m} \langle \chi_l | \hat{f}(i) | \chi_m \rangle$ is the Fock matrix, $\mathbf{S} = \sum_{l,m} = \langle \chi_l | \chi_m \rangle$ is the orbital overlap matrix. \mathbf{C} is the orbital coefficient matrix, and ε is the diagonal matrix of orbital energies ε_i , which are generally the desire solutions. By performing a transformation of basis to an orthonormal basis, the overlap matrix \mathbf{S} becomes the identity matrix $\mathbb{1}$, and simplifies the problem. Thus, utilizing 2.19 reduces the problem to the of diagonalisation \mathbf{F} . Unfortunately, this must be done iteratively, as \mathbf{F} depends on its own solution, hence the name self-consistent field method.

2.1.5 Basis sets

Choosing optimal basis functions can help significantly in terms of determining the ground state wave function Ψ_0 . Quantum chemists rely on the choice of *basis sets*, defined as the vector space in which an *ab initio* problem is defined. Basis sets usually refer to the set of one particle functions, which are used to form MOs in a linear combination of atomic orbitals (LCAO-MO) like approach. For a system with N electrons, the LCAO-MO approach gives $N/2$ occupied orbitals in the ground state. The remaining basis functions in a set are combined to give *virtual* (unoccupied) orbitals.

Early basis sets were composed of *Slater-type orbitals* (STOs), due to their resemblance to the atom orbitals (AOs) of the hydrogen atom. These are functions of the form

$$\phi_i^{STO}(\zeta, n, a, b, c, x, y, z) = N r^{n-1} e^{-\zeta r} x^a y^b z^c \quad (2.20)$$

where N is a normalization constant, ζ is a constant related to the effective nuclear charge of the nucleus, r is the distance of the electron from the atomic nucleus, n is a natural number that plays the role of the principle quantum number, and x , y , and z are cartesian coordinates. The angular component $x^a y^b z^c$ describes the shape of the function, such that if $a+b+c=0$ ϕ_i^{STO} is of *s*-type; if $a+b+c = 1$, ϕ_i^{GTO} is of *p*-type, and so forth. Although STOs approximate the long and short range behaviour of atomic orbitals correctly, performing integration with these functions is computationally very demanding, due primarily to the complexity of the integrals involved describing in electron-electron interactions.

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$$\phi_i^{GTO}(\alpha, a, b, c, x, y, z) = N e^{-\alpha r^2} x^a y^b z^c \quad (2.21)$$

where N is a normalization constant, α is the orbital exponent coefficient, x , y , and z are cartesian coordinates, r is the radius ($r^2 = x^2 + y^2 + z^2$), and the angular portion is described the same as in an STO. It takes a linear combination of several GTOs to represent the same function as an STO. These linear combinations of GTOS are known as *contracted GTOs* (CGTO) with n GTOs combined as

$$\phi_i^{CTGO}(\alpha, a, b, c, x, y, z) = N \sum_{i=1}^n c_i e^{-\alpha r^2} x^a y^b z^c \quad (2.22)$$

where c_i is referred to as the contraction coefficient which describes the weighting of each GTO. Although it requires more GTOs than STOs to accurately describe the atomic orbitals, the integrals can be computed 4–5 times faster, and thus calculations involving GTOs are much more efficient.⁵⁴

Basis set nomenclature

Standard basis sets are composed of basis functions which represent atomic orbitals and that each basis function is a CGTO composed of several GTOs. A *minimal basis set* is one in which each AO is represented by a single basis function. To more accurately represent AOs, more basis functions should be used, although basis set size needs to be balanced with computational cost. Larger basis sets are referred to by their cardinal number, the number of basis functions which represent each AO. When two basis functions are used to represent each AO, this is called a *double-zeta* basis set. If three basis functions represent each AO, this is called a *triple-zeta* basis set. Generalized, a basis set is N -zeta in size when N basis functions are used per AO.

A *split-valence* basis set is one in which a single basis function is used to represent each core AO, while more basis functions are used to represent the valence AOs. Constructing basis sets in this way can help reduce the computational cost while still accurately representing the electrons which are most important to chemistry.

Additional basis functions are often added to basis sets in order to correctly describe molecular properties. *Polarization functions* are basis functions which are one or more angular momentum channels greater than the natural electronic configuration of an atom. For example, a single *p*-type

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basis function can be added to the minimal basis of a hydrogen atom. Polarization functions are essential to accurately describe chemical bonding, as the presence of other atoms distorts the spherical symmetry of a single atom's AOs.⁵⁵ *Diffuse functions* are basis functions which extend further into space, typically by the inclusion of a very shallow Gaussian function (small ζ exponent). Diffuse functions are necessary to accurately describe anions, very electronegative atoms, and large systems in which NCIs are important.

Commonly used basis sets

A large number of basis sets currently exist in the literature.⁵⁶ While not all basis sets are created equally, we shall briefly describe four of the most commonly used basis sets used in quantum chemistry.

Pople-style basis sets

Perhaps the most utilized basis sets in chemistry are those arising from the group of Pople.^{57–59} These basis sets were defined by fitting to HF wave functions. The earliest of these basis sets are the minimal STO-NG basis sets, where N describes the number of GTOs that go into each contraction.

The practise of using minimal basis sets has diminished significantly as technology has advanced, thus these basis sets are largely considered out of date. It is more common to utilize the split-valence basis sets, denoted as $n - ijG$ or $n - ijkG$ for double and triple zeta split-valence basis sets, respectively. In this system of notation, n represents the number of GTOs that comprise the core AOs, and i, j, k describe the number of GTOs for contractions in the valence AOs. Polarization functions are denoted either with asterisks or with the specific shell and number of functions which are being added. Diffuse functions are denoted with either a single or double “+”, indicating diffuse s and p -type functions for non-hydrogen atoms, and the addition of diffuse s -type functions for hydrogen, respectively. For example, the $6-31+G(d,p) \equiv 6-31+G^{**}$ double-zeta basis set is one which has: 6 GTOs per core AO, 3 GTOs for the first valence set of AOs, and 1 GTO for the second, along with s and p diffuse functions of the heavy atoms, a single d polarization function of heavy atoms, and a single p polarization function of hydrogen atoms.

Correlation consistent basis sets

Post-Hartree-Fock methods (*vide infra*) are commonly used in quantum chemistry. In 1989, Dunning^{60–62} identified that the use of basis sets opti-

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mized for HF were inappropriate for post-HF methods. The basis sets that came from Dunning and co-workers, which are referred to as “correlation consistent” basis sets are commonly used in, but not limited to, state of the art wave function calculations. These basis sets are said to be correlation consistent as they treat electron correlation (*vide infra*) in a manner which systematically approached the complete basis set limit. Correlation consistent basis sets are denoted as “cc-pVN Z ”, where $N=D,T,Q,5,6,\dots$ is the cardinal number of the basis set. These are large sets containing polarization functions by default and can be additionally augmented with diffuse functions, denoted by “aug.” An variant of these basis sets which are used for including core-correlation are denoted by “cc-pVCN Z ”.⁶³ A commonly used basis set is aug-cc-pVTZ, which is a triple-zeta basis set with implicit polarization functions and specified diffuse functions on all atoms.

Polarization consistent basis sets

The polarization consistent basis sets have been developed by Jensen and coworkers.^{64–67} The polarization consistent basis sets have been developed to systematically complete basis set limit in density-functional theory calculations through the use of higher order polarization functions. The notation adopted is “pc- X ”, where X is the cardinal number of the basis set minus one (i.e. $X = N-1$). Polarization functions are included by default in these basis sets, and additional diffuse functions can be specified with the same “aug” notation as the correlation consistent basis sets.

Ahlrich basis sets

The last basis sets we will mention are those developed by Ahlrich and coworkers.^{68,69} These are the “Def2” basis sets, named as such because they are the second generation of default basis set in the Turbomole quantum chemistry package.⁷⁰ Additionally, these basis sets have been developed so that consistent errors are obtained for nearly every element on the periodic table: a unique trait among modern basis sets. The nomenclature for these basis sets is fairly straightforward where either SV is used for split valence, or NZ is used for cardinal number. Addition of polarization and diffuse functions is specified with a P and D, respectively. For example, Def2-SVP is the basis set of split-valence double-zeta quality with polarization functions; Def2-TZVP is the triple-zeta basis set with polarization functions; Def2-QZVPD is the quadruple-zeta basis set with polarization and diffuse functions.

2.1.6 Post-Hartree-Fock methods

The HF method gives an approximation to the ground state wave function of a molecule for a reasonable computational cost (scaling with N^4 number of basis function). There is however, a lack of the complete description of *dynamical electron correlation*,⁷¹ and thus significant deviations from experimental results can be observed. Dynamical electron correlation is a measure of how much one electron's movement is affected by the presence of other electrons. As described previously, the HF method includes correlation through the average electron field potential term, however this field is in general, not static, thus correlation must be treated directly in order to obtain accurate results. The majority of methods take the HF wave function Ψ_0 as the starting point. Normally, the total energy is obtained by inclusion of an energy term for correlation E_{corr} , which can be defined as

$$E_{corr} = \Xi_{exact} - E_0 \quad (2.23)$$

E_{corr} is the difference between the full non-relativistic energy from the Schrödinger equation, Ξ_{exact} , and a reference ground state energy E_0 , usually the HF energy.

We shall briefly describe two important methods for accounting for electron correlation and obtaining E_{corr} : Møller-Plesset perturbation theory, and the related configuration interaction and coupled cluster theories.

Møller-Plesset perturbation theory

Møller-Plesset (MP) perturbation theory is a special case of Rayleigh-Schödinger perturbation theory in which the Hamiltonian for a system can be approximated by

$$\hat{H} = \hat{H}_0 + \lambda \hat{V} \quad (2.24)$$

where \hat{H}_0 is an unperturbed Hamiltonian, \hat{V} is a small perturbation, and λ is an arbitrary parameter which controls the size of the perturbation. The perturbed wave function and energy are expressed as a power series in λ :

$$\Psi = \lim_{m \rightarrow \infty} \sum_{i=0}^m \lambda^i \Psi^{(i)} \quad (2.25)$$

$$E = \lim_{m \rightarrow \infty} \sum_{i=0}^m \lambda^i E^{(i)} \quad (2.26)$$

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The MP method applies perturbations to HF by defining a *shifted* Fock operator \hat{H}_0 and *correlation potential* \hat{V} as

$$\hat{H}_0 = \hat{F} + \langle \phi_0 | (\hat{H} - \hat{F}) | \phi_0 \rangle \quad (2.27)$$

$$\hat{V} = \hat{H} - \hat{H}_0 \quad (2.28)$$

where ϕ_0 is the ground state Slater determinant of the Fock operator.

Within this formulation, the zeroth-order energy is the expectation of \hat{H} , which gives the HF energy. The first-order energy is

$$E_{MP1} = \langle \phi_0 | \hat{V} | \phi_0 \rangle = 0 \quad (2.29)$$

by Brillouin's Theorem of singly excited determinants. Thus, the first useful correction occurs at the second order of perturbation, which is known as MP2. Additional orders of perturbation are referred to as MP3, MP4, etc. The MP2 method has been popular in quantum chemistry because it scales with N^5 number of basis functions and is a significant improvement on the treatment of electron correlation compared to HF. One may expect higher order of perturbation theory to more accurately describe a system. Practically however, the expansions used in MPN theory do not converge smoothly to a limit with higher order of perturbation.⁷² As a result, for molecular properties calculated with MP3 or higher are not guaranteed to give more accurate results than MP2.

Configuration interaction and coupled cluster theory

The solutions to the HF method give a single determinant wave function which only describes the ground state electronic configuration. Configuration interaction (CI) is a post-HF method which describes a linear combination of Slater determinants to more accurately represent a system's wave function. The additional Slater determinants represent excited electronic configurations and can be singly excited (S), doubly excited (D), and so forth. This is represented as follows:

$$|\Psi\rangle = (1 + \sum_{j=1}^N C_j) |\phi_0\rangle \quad (2.30)$$

where C_j are operators which describes the j -th excitations of electrons. If all possible excitations are included in the CI equation, this is referred to as

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full CI (FCI). Extending FCI to an infinite basis set gives the exact solution to the Schrödinger equation.

Coupled cluster (CC) theory⁷³ is a similar approach to CI, but uses the so-called *exponential ansatz*

$$|\Psi\rangle = e^{\hat{T}} |\phi_0\rangle \quad (2.31)$$

where \hat{T} is the cluster operator, defined by n -electron excitation operators \hat{T}_n :

$$\hat{T} = \hat{T}_1 + \hat{T}_2 + \hat{T}_3 + \dots \quad (2.32)$$

Within the exponential ansatz, $e^{\hat{T}}$ is usually truncated and expanded in a Taylor series. For example, truncation at the \hat{T}_2 excitation operator gives

$$\begin{aligned} |\Psi\rangle &= e^{\hat{T}_1 + \hat{T}_2} |\phi_0\rangle \\ &= (1 + \hat{T}_1 + \hat{T}_2 + \frac{1}{2!} \hat{T}_1^2 + \hat{T}_1 \hat{T}_2 + \frac{1}{2!} \hat{T}_2^2 + \dots) |\phi_0\rangle \end{aligned} \quad (2.33)$$

Considering both CI and CC with single and double excitation (CISD and CCSD), the wave functions will include similar excitations, however inclusion of cross terms ($\hat{T}_1 \hat{T}_2$) in CCSD implicitly includes higher excitation levels. Additionally, the use of the exponential operator makes the CC formulation *size consistent*, which is the largest short coming of the CI method. Size consistency refers to the additivity of energies for an ensemble of molecules. That is, for a pair of molecules A and B, their energies must follow the relation

$$E_{AB}(r \rightarrow \infty) = E_A + E_B \quad (2.34)$$

Size consistency is a necessary requirement of a theoretical treatment to treat systems of molecules accurately. It is for this reason that CC has superseded CI as the dominant highly correlated method in quantum chemistry.

The inclusion of higher order excitations becomes decreasingly important with degree of excitation; however, the inclusion of triples is often found to be necessary for the accurate description of electron correlation (i.e. CCSDT). The computation of triples is prohibitively expensive in all but the simplest of systems, thus approximations based on perturbation theory are often used in substitution. The most commonly used perturbative triples method is CCSD(T), where the parenthesis indicate the use of perturbative arguments.

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Note also that traditionally, the use of CCSD(T) implies excitation of only the valence electrons, unless otherwise stated.

CCSD(T) is commonly referred to as the *gold standard* in quantum chemistry and is often used to obtain benchmark quality results for thermochemistry and NCIs.⁷⁴ However, CCSD(T) scales with N^7 number of basis functions, and is thus significantly more computationally expensive than HF or MP2, restricting its application to small systems of molecules. Quadratic configuration interaction (QCI) is closely related to CC, except that it uses quadratic operators in place of exponential ones. QCISD(T) and CCSD(T) gives very similar results.⁷⁵

2.1.7 The complete basis set limit

Complete basis set extrapolation

In accordance with the variational principle, the energy obtained by a particular method will always be greater than or equal to the exact energy. The exact energy can only be achieved with an infinite basis set, a value known as the *complete basis set* (CBS) limit.⁷⁶ Since this is computationally infeasible, specific tricks have been developed to approximate the CBS limit. Specifically, molecular properties calculated using the HF and post-HF methods have been shown to asymptotically approach the CBS limit in a smooth manner when appropriate basis sets are used. Therefore, to obtain results estimating a molecular property at the CBS limit ($Y(\infty)$), properties can be fit to three-parameter^{77,78} or two-parameter functions:^{79,80}

$$Y(x) = Y(\infty) + Ae^{-x/B} \quad (2.35)$$

$$Y(x) = Y(\infty) + A/x^3 \quad (2.36)$$

where the molecular property as a function of basis set cardinal number $Y(x)$ is fit using parameters A and B . Typically calculations of this nature are performed using the correlation consistent basis sets (cc-pVNZ), however there is evidence that the polarization consistent basis sets (pc- X) more rapidly approach the CBS limit for some molecular properties.⁸¹ The true *gold standard* in quantum chemistry is referred to as CCSD(T)/CBS, which typically means CCSD(T) with complete basis set extrapolation with aug-cc-pVNZ basis sets, where $N=D, T, Q$, or 5. Although extrapolation is useful for approximating highly accurate results, there is an inherent amount of uncertainty associated with the final fitted results, which may be unclear from the nomenclature.

Explicit correlation methods

A new technique which is gaining popularity among post-HF methods is the inclusion of so called *explicit correlation*.^{82,83} The introduction of additional functions dependent on inter-electronic distance coordinates allows for explicit correlation of electrons.⁸⁴ As a result, the dynamical correlation of electrons is treated more accurately with reduced basis sets, therefore accurate results can be achieved at a reduced computational cost. Basis set extrapolation can also be performed on explicitly correlated results: this is quickly become the standard approach.⁸⁵

2.1.8 Composite quantum chemistry methods

In order to calculate thermochemical and kinetic properties that are within a sub-kcal mol⁻¹ range of experiment, multistep *ab initio* procedures which are referred to as *composite methods* have been developed.⁸⁶ These procedures work by including important energy terms which contribute to molecular properties. Generally, composite methods make use of a combination of low correlation methods with large basis sets and high correlation methods with small basis sets, as is illustrated in Figure 2.1. Some of the relevant energy terms include: core-valence, relativistic, spin-orbital, Born-Oppenheimer, and zero-point vibrational energy corrections. There exist many composite methods, each of which makes use of a variety of quantum mechanical (QM) methods and different basis set extrapolation techniques in order to best approximate energy terms which are relevant, with the ultimate goal of achieving the exact energy of a system. In our work, we have made use of several composite methods including: the G4 and G4(MP2) methods,^{87,88} CBS-QB3 and CBS-APNO methods,^{89–91} and the W1BD method.⁹² A description of these methods will be provided in Chapter 4.

2.1.9 Density-functional theory

Density-functional theory (DFT) is the most popular quantum chemical method applied to date. It relies on the two Hohenberg-Kohn theorems, the first of which states that there exists a unique electron density ρ that defines the properties of a many-electron system. The second theorem defines an energy functional of the electron density and demonstrates that the correct ground state electron density minimizes the energy functional through the variational theorem.^{93,94} These theorems alone do not provide the solutions to the Schrödinger equation.

2.1. The quantum mechanical approach

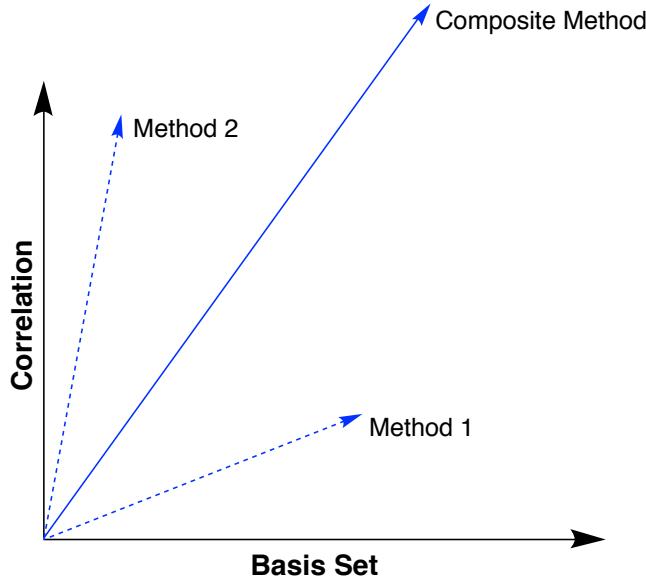


Figure 2.1: Schematic representation of a quantum mechanical composite method. The exact energy can only be achieved at the limits of an infinite basis set and complete correlation. Using a combination of Method 1 (low correlation/large basis set) and Method 2 (high correlation/small basis set), the Composite method approaches the exact energy.

It wasn't until the formulation of Kohn-Sham DFT⁹⁵ that the theory began gaining ground as a useful quantum theory. Kohn-Sham DFT scales formally with N^3 number of electrons⁷¹ which is better than HF by a factor of N . In addition, DFT is a complete theory like FCI; however, there is no straightforward way to determine the correct functionals of the electron density as the exact form of the functionals is unknown. Nonetheless, the drive for the development of the correct density-functional has been one of the main endeavours in quantum chemistry in the last two decades.

The framework behind conventional DFT is built into the description of the full energy functional E :

$$E[\rho] = T_{ni}[\rho] + V_{ne}[\rho] + V_{ee}[\rho] + \Delta T[\rho] + \Delta V_{ee}[\rho] \quad (2.37)$$

where T_{ni} is the kinetic energy of non-interacting electrons, V_{ne} is the potential of nuclear-electron interactions, and V_{ee} is the classical electron-electron repulsion. The last two terms are collectively referred to as the exchange-correlation (XC) functionals, where ΔT is the dynamical correlation term,

2.1. The quantum mechanical approach

and ΔV_{ee} is the non-classical correction to electron-electron repulsion. All the functionals, except the XC functionals have an exact form. It is therefore the XC functionals in which there is currently empiricism.

The ultimate goal in describing XC functionals is to find the “correct” XF functional which gives the exact energy of a system from the electron density. At this point, this must be done using approximations, for which there are several degrees of complexity. These approaches follow a hierarchical scheme, commonly referred to as the “Jacob’s ladder” of DFT.⁹⁶ The first rung represents the simplest approximation which is known as local-density approximations (LDAs), which approximate the exchange-correlation density at a given point by the electron density at that same point. The form of these functionals is:

$$E_{XC}^{LDA} = \int \rho(\mathbf{r}) \varepsilon_{XC}(\rho(\mathbf{r})) d\mathbf{r} \quad (2.38)$$

where $\varepsilon_{XC}(\rho(\mathbf{r}))$ is the exchange-correlation energy per particle (energy density) of a uniform electron gas of density $\rho(\mathbf{r})$. This approximation is overly simple and applies only when the electron density is constant at all points, and are thus not generally applied in chemical problems. Nonetheless, LDA based approaches are commonly employed in solid state physics.

The second rung on the ladder corresponds to generalized-gradient approximation (GGA) based functionals, which are still amongst some of the most popular density-functionals. GGAs depend on both the electron density and the gradient of the electron density at a point:

$$E_{XC}^{GGA} = \int \rho(\mathbf{r}) \varepsilon_{XC}^{GGA}(\rho(\mathbf{r}), \nabla \rho(\mathbf{r})) d\mathbf{r} \quad (2.39)$$

where, $\varepsilon(\rho(\mathbf{r}), \nabla \rho(\mathbf{r})) d\mathbf{r}$ is the energy density associated with a given GGA. GGA functionals provide a substantial improvement over LDAs, and most are constructed so that they correct the LDA energy:

$$\varepsilon_{XC}^{GGA}(\rho(\mathbf{r}), \nabla \rho(\mathbf{r})) = \varepsilon_{XC}^{LDA}(\rho(\mathbf{r})) d\mathbf{r} + \Delta \varepsilon_{XC} \left(\frac{\nabla \rho(\mathbf{r})}{\rho^{4/3}(\mathbf{r})} \right) \quad (2.40)$$

A step above GGAs on the third rung of the ladder are meta-GGAs, which depend on the electron density, as well as the first derivative of electron density at a point, and the kinetic-energy density, $\tau(\mathbf{r})$, defined as:

$$\tau(\mathbf{r}) = \sum_i^{\text{occupied}} \frac{1}{2} |\nabla \chi_i(\mathbf{r})|^2 \quad (2.41)$$

2.1. The quantum mechanical approach

where $\chi_i(\mathbf{r})$ are the self-consistently determined Kohn-Sham orbitals. Meta-GGAs improve upon the accuracy of GGAs at a comparable cost.⁷¹

The XC functionals described up to this point (LDAs, GGAs, meta-GGAs) depend only on the electron density and derivatives of the electron density. The fourth and fifth rungs of the ladder improve upon the prior functionals by inclusion of terms dependent on additional properties. While this approach improves upon the accuracy of these functionals, it comes with an increase in computational cost. On the fourth rung sit functionals which depend to some percentage on the HF exact exchange. When the ratio of HF exchange is fixed, these functionals are termed hybrid functionals. Alternatively, functionals are said to be range-separated corrected if a different amount of exact-exchange to describe long and short-range behaviours. In the cases of hybrid and range-separated functionals, the added computational cost comes from the calculation of the HF exact exchange.

Alternatively, one can describe the fourth rung functionals as the depending upon the properties of the occupied molecular orbitals. The fifth rung then, is said to depend on the properties of unoccupied molecular orbitals. These functionals are typically referred to as double-hybrids, and incorporated correlation energy from a post-HF method, typically MP2.⁹⁷ Double-hybrid DFT methods are once again more accurate than the lower rung methods, however, calculating the MP2 correlation energy is considerably more computationally demanding than traditional DFT approaches. Therefore, double-hybrid DFT methods have not gained popularity in the literature.

There are many published XC functionals. Fortunately, there is a fairly standard system of nomenclature, such that density functionals are described as *exchange functional-correlation functional*. The most commonly used density functional is the B3-LYP, which uses the 3-parameter hybrid exchange functional of Becke,⁹⁸ and the correlation functional of Lee, Yang, and Parr.⁹⁹ There are also standalone functionals which have built in exchange and correlation functionals. A common example of these are the Minnesota family of functionals from the Truhlar group.^{100,101}

Aside from the problem of choosing density-functionals, solving DFT is computationally very similar to the HF method. Within Kohn-Sham (KS) DFT, we define a fictitious system of non-interacting electrons with the same electron density as the real system. This is achieved by the use of a Hamiltonian in which there is an effective local potential, $V_s(\mathbf{r})$:

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$$\hat{H}_s = -\frac{1}{2} \sum_i^N \nabla_i^2 | \sum_i^N V_S(\mathbf{r}_i) \quad (2.42)$$

The ground state wave function of this non-interacting Hamiltonian is represented by a single Slater determinant with spin orbitals (χ), completely analogous to the HF problem. These spin orbitals, referred to as *Kohn-Sham orbitals* are determined by

$$\hat{h}_i^{KS} \chi_i = \varepsilon_i \chi_i \quad (2.43)$$

where the one-electron Kohn-Sham operator \hat{h}^{KS} is defined as

$$\hat{h}_i^{KS} = -\frac{1}{2} \nabla^2 + V_s(\mathbf{r}) \quad (2.44)$$

It is crucial to realize that this procedure does not give us the exact energy of a system, but rather is used to determine an electron density which represents our real system. The connection between this fictitious system comes from the choice of the effective potential such that the density of our real system is a result of summing over the squared moduli of the KS orbitals:

$$\rho(\mathbf{r}) = \sum_i |\chi_i|^2 \quad (2.45)$$

Once again in analogy to HF theory, one applies the variational principle to minimize the total energy functional in Equation 2.37 with respect to χ . The effective potential which variationally minimizes the energy is given by¹⁰²

$$\begin{aligned} V_s(\mathbf{r}) &= \frac{\delta J[\rho]}{\rho(\mathbf{r})} + \frac{\delta E_{XC}[\rho]}{\delta \rho(\mathbf{r})} + \sum_A^M \frac{Z_A}{r_{iA}} \\ &= \int \frac{\rho(\mathbf{r}_2)}{r_{12}} + V_{XC} + \sum_A^M \frac{Z_A}{r_{iA}} \end{aligned} \quad (2.46)$$

where the first term describes the Coulombic potential between two electrons, the last term is the potential between the electron and each nucleus. The middle term is once again the unknown XC potential. The electron density obtained from the fictitious system of non-interacting particles is finally used in Equation 2.37 to find the total energy of the system. Since

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$V_s(\mathbf{r})$ depends on the electron density, these equation must be solved iteratively, as with HF theory. Note however, that if the exact form of $E_{XC}[\rho]$ was known, this method would give the exact ground state electron density of the system, and thus the exact energy.

Challenges for density-functional theory methods

Pure DFT has low computational cost and potentially good accuracy, hence its popularity as a quantum chemical treatment. However, there are several problems which common DFT methods experience that lead to erroneous results in many cases.¹⁰³ It is well established that traditional DFT methods completely fail at describing non-covalent interactions.^{104,105} This shortcoming leads to poor descriptions of chemistry beyond equilibrium geometries, including transition states. Fortunately, there are several methods which can correct for this problem, commonly through the addition of an energy correction term E_{disp} to the DFT energy E_{DFT} , as

$$E_{tot} = E_{DFT} + E_{disp} \quad (2.47)$$

It is common to employ the empirical D3 pair-wise correction of Grimme,¹⁰⁶ paired with the Becke-Johnson damping functions,¹⁰⁷ denoted as D3(BJ). This correction works by calculating the dispersion interactions between all pairs of atoms A and B separated by distance R_{AB} , with the following equation:

$$E_{disp} = \sum_{A>B} \frac{C_6^{AB}}{R_{AB}^6} f_6(R_{AB}) + s_8 \frac{C_8^{AB}}{R_{AB}^8} f_8(R_{AB}) \quad (2.48)$$

where C_6 and C_8 are dispersion coefficients, s_8 is an empirically determined scaling parameter, and f_n are the damping functions which limit the range of dispersion correction, avoiding near singularities at small R_{AB} . Another approach to correcting for dispersion is to add parameters directly to the functional, as is the case in the Minnesota functionals.^{100,100} Both of these empirical corrections have the benefit of adding negligible computational time, but must be parametrized for each DFT method with which they are employed.

Another striking issue with DFT is the unphysical ability of an electron to interact with itself, termed *self-interaction error*. This is most obvious in what is known as *delocalization error*, which is a result of many-electrons interacting with themselves, or many-electron self-interaction error. In HF theory, self-interaction error is exactly cancelled, thus DFT methods which

have a high portion of HF exchange in their formulation are able to account for this issue. Consider for a moment a one electron system: there should be exactly zero electron correlation. In terms of the energy functionals shown in Equation 2.37, the electronic repulsion term $V_{ee}[\rho]$ should cancel exactly with the XC term ($V_{ee}[\rho] = -E_{XC}[\rho]$).⁷¹ Unfortunately, all pure DFT methods fail to reproduce this expected behaviour. An obvious manifestation of delocalization error is the incorrect treatment of charge-transfer in intramolecular interactions,^{108,109} as well as in transition state complexes. Even for the simplest HAT reaction $\text{H}_2 + \text{H}^\bullet \longrightarrow \text{H}^\bullet + \text{H}_2$, the calculated barrier height is underestimated by 8–9 kcal mol⁻¹ using a GGA functional.¹¹⁰ Charge-transfer occurs when a fraction of an electron is transferred between molecular entities. Specifically, charge-transfer is mistreated at longer ranges, thus either high percentage exact exchange hybrid functionals, or range-separated functionals are suggested for systems in which charge-transfer may occur.

As is the case for most experimental methods, identifying the correct theoretical methods requires the careful consideration of the problem at hand. Choosing a DFT based method requires calibration, however, once a method has been tested and is known to provide reasonably accurate results, DFT methods have the ability to help understand chemical problem with relatively low computational costs.

2.2 Applying theory to chemical problems

2.2.1 Geometry optimization

All QM methods depend parametrically on the geometry of a molecular system. That is the electronic energy of a system depends on the positions of the nuclei. While the wave functions can describe any arbitrary geometry, we are typically only interested in certain geometries of a molecule. These geometries of interest are normally stationary states along a the potential energy surface (PES) of a system, that is, points where the gradient of energy with respect to nuclear coordinates is zero. Therefore, we perform *geometry optimization* calculations to determine these points.

Molecular systems have complex PESs. For a non-linear molecule, the nuclear PES has $3N-6$ dimensions, where N is the number of nuclei present.¹¹¹ In geometry optimization, we seek the local minima (reactants, products, or intermediates) and local maxima (TS complexes). Consider only local minima for a moment. Often complex molecules have more than one possible conformation, and each conformation represents a different local minimum

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along the PES. It is therefore important to ensure the correct conformation, typically the lowest energy structure (global minimum), is used when approaching chemical problems.

In order to efficiently perform geometry optimization, numerical analysis techniques are employed. All geometry optimization methods follow the same general framework.¹¹² First, energy and necessary derivatives are computed from an initial geometry. Second, the geometry is modified to step towards the nearest stationary state. And last, some test is performed to determine if the new geometry is near enough to the stationary state along the PES. The most efficient method to do this is the *Newton method*, in which the energy is expanded in a Taylor series (truncated at the second order point) about the current point, \mathbf{x}_0 :

$$E(\mathbf{x}) = E_0 + \mathbf{g}_0 \Delta \mathbf{x} + \frac{1}{2} \Delta \mathbf{x} \mathbf{H}_0 \Delta \mathbf{x} \quad (2.49)$$

where E_0 , \mathbf{g}_0 , and \mathbf{H}_0 are the energy, gradient (Jacobian), and second derivative (Hessian) at point \mathbf{x}_0 , and $\Delta \mathbf{x} = \mathbf{x}_i - \mathbf{x}_0$. The aim of the Newton method is to minimize the gradient of the Taylor expansion, $\mathbf{g}(\mathbf{x})$, such that

$$\mathbf{g}(\mathbf{x}) = \mathbf{g}_0 + \mathbf{H}_0 \Delta \mathbf{x} \quad (2.50)$$

Solving for $\Delta \mathbf{x}$ gives the so-called Newton step that leads to minimization:

$$\Delta \mathbf{x} = -\mathbf{H}_0^{-1} \mathbf{g}_0 \quad (2.51)$$

The analytic computation of the Hessian is very expensive, especially for large systems. Therefore, to simplify the problem at the beginning of geometry optimization, the Hessian matrix is approximated and updated at each step in the optimization, using clever algorithms.¹¹² This is called the *quasi-Newton method*, and is the default optimization routine in the Gaussian¹¹³ quantum chemistry package, as well as many other quantum chemistry packages.

Some additional caution must be taken in optimising molecular structures. Normal algorithms which optimize structures stop when the gradient of energy is sufficiently close to zero; however, often PES can be flat or very shallow in regions and structures that are not fully optimized can be obtained. To avoid this, geometries are always subject to molecular vibration analysis.

2.2.2 Molecular vibrations

The computation of molecular vibrations can be performed simply given a set of molecular coordinates.¹¹⁴ Assuming a non-linear molecule, we start with $3N-6$ internal coordinates which are non-coupled (orthogonal). We then apply the *harmonic approximation*, in which we assume each normal mode follows Hooke's Law

$$F = kx \quad (2.52)$$

where F is the force, k is the force constant, and x is the displacement along one normal mode's coordinates. This approximation assumes the PES along the normal mode is parabolic, which in general is not true, but is a good approximation near the minima. Deviations from this approximation are known as *anharmonicity*. In practise, however, at normal temperatures ($\sim 298\text{K}$) the harmonic approximation is sufficient to describe molecular vibrations as displacements are assumed to be small.

Typically to obtain molecular frequencies, one computes the mass-weighted Hessian matrix elements F_{ij}

$$F_{ij} = \frac{1}{\sqrt{m_i m_j}} \mathbf{H}_{ij} \quad (2.53)$$

where the partial derivatives of internal coordinates x_i of the potential energy U are taken for $3N$ atoms with mass m . One then seeks to diagonalize this $3N \times 3N$ matrix to obtain eigenvalues λ_i , which describe the force constant of each normal mode. The harmonic frequencies ν_i are then obtained by

$$\nu_i = \frac{\sqrt{\lambda_i}}{2\pi} \quad (2.54)$$

and the lowest 6 modes are then discarded to account for $3N-6$ normal modes. These lowest energy modes generally correspond the internal rotations, and thus must be discarded to correctly obtain thermochemical corrections.

From these frequencies, the *zero-point vibrational energy* (ZPE, E_{ZPE}) is calculated:

$$E_{ZPE} = \sum_{i=1}^{3N-6} \frac{h\nu_i}{2} \quad (2.55)$$

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The ZPE is an important quantum correction to the classical potential, giving the electronic potential energy

$$U = E_{elec} + E_{ZPE} \quad (2.56)$$

where E_{elec} is the QM electronic energy.

If a normal mode describes a non-minimum along the PES, the energy gradient will be negative (imaginary) instead of positive. Only energy maxima or saddle-points (TS structures) should have a single imaginary mode. Therefore, if a non-TS molecular structure calculation yields one or more imaginary modes, the geometry optimization has yielded a structure which is not at minimum on the PES. In this situation additional steps must be taken to find a corrected structure.

2.2.3 Thermochemistry

Up until this point we have been viewing molecules from a microscopic perspective; however, this is not useful for describing properties of bulk systems. Fortunately, fundamental statistical thermodynamics can be used to approximately describe a system in bulk.^{115,116} We approximate our system as an ensemble of non-interacting particles: the ideal gas. Within statistical thermodynamics, the fundamental starting point is the partition function Q ,¹¹⁷ from which all thermodynamic properties can be calculated. For our ensemble, the molecular partition function is

$$Q = \sum_j e^{\varepsilon_j / k_B T} \quad (2.57)$$

where a Boltzmann distribution of j energy states ε is taken at temperature T , and k_B is the Boltzmann constant. All calculations herein are defined under conditions of temperature $T = 298.15$ K and pressure $P = 1$ atm.

Normally, the molecular partition function is decomposed into contributions from translational, vibrational, rotational, and electronic motion:

$$Q = q_{trans} q_{vib} q_{rot} q_{elec} \quad (2.58)$$

The equation describing the translational partition function q_{trans} is

$$q_{trans} = \left(\frac{2\pi m k_B T}{h^2} \right)^{3/2} \frac{k_B T}{P} \quad (2.59)$$

where m is the mass of the molecule, h is Planck's constants.

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The vibrational partition function q_{vib} depends on the contributions of each of K vibrational modes. Only the $3N-6$ (or $3N-5$ for linear molecules) real vibrational modes of a molecule are considered, and imaginary frequencies are ignored. Therefore, for molecules which posses an imaginary frequency this thermodynamic analysis is invalid. TS complexes do posses a single imaginary frequency which is ignored, as it is assumed to not contribute to the overall vibrational partition function as no formal bond is said to be formed in the acceptor-donor system. Each vibrational mode has a characteristic vibrational electronic temperature, $\Theta_{\nu,K} = h\nu/k_B$, and the partition function is

$$q_{vib} = \prod_K \frac{e^{-\Theta_{\nu,K}/2T}}{1 - e^{-\Theta_{\nu,K}/T}} \quad (2.60)$$

The rotational partition function depends on the geometry of a system. For a single molecule $q_{rot}=1$. For a linear molecule, the rotational partition function is

$$q_{rot} = \frac{1}{\sigma_r} \left(\frac{T}{\Theta_r} \right) \quad (2.61)$$

where σ_r is the symmetry number for rotation which depends on the molecular symmetry, and $\Theta_r = h^2/8\pi^2Ik_B$. I is the moment of inertia. Finally, for a non-linear polyatomic molecule, the rotational partition function is

$$q_{rot} = \frac{\sqrt{\pi}}{\sigma_r} \left(\frac{T^{3/2}}{\sqrt{\Theta_{r,x}\Theta_{r,y}\Theta_{r,z}}} \right) \quad (2.62)$$

where $\Theta_{r,x}$, $\Theta_{r,y}$, and $\Theta_{r,z}$ describe contributions of the moment of inertia in each of the x, y, and z-planes.

Finally, we make an important assumption that electronic contributions are assumed to exist in only the ground state, as excited states are generally safely assumed to be much larger than k_BT in energy. The full electronic partition function is

$$q_{elec} = \sum_{i=0} \omega_i e^{-\epsilon_i/k_BT} \quad (2.63)$$

where ω is the degeneracy of an energy level with energy ϵ . Applying our assumption, and by setting the ground state energy $\epsilon_0 = 0$, our problem simplifies dramatically, such that $q_{elec} = \omega_0$, which is simply the spin multiplicity of the molecule.

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We now have all the information needed to calculate the thermodynamic quantities we are interested in. In chemistry we are concerned with the Gibbs free energy G , which is defined by the entropy S and enthalpy H as

$$G = H - TS \quad (2.64)$$

From each of the partition functions, the entropy of a system with N moles, $S_{tot} = S_{trans} + S_{vib} + S_{rot} + S_{elec}$, is calculated using the relation

$$S = Nk_B + Nk_B \ln \left(\frac{Q}{N} \right) + Nk_B T \left(\frac{\partial \ln Q}{\partial T} \right)_V \quad (2.65)$$

Similarly, the internal energy of a system, $E_{int,tot} = E_{int,trans} + E_{int,vib} + E_{int,rot} + E_{int,elec}$, is given by the relation

$$E_{int} = Nk_B T^2 \left(\frac{\partial \ln Q}{\partial T} \right)_V \quad (2.66)$$

Finally, the enthalpy is obtained from

$$H_{tot} = E_{int,tot} + k_B T \quad (2.67)$$

Using very simple statistical thermodynamic arguments, the properties of a bulk system are easily computed. It is important to emphasize that these results are for particles in the gas phase, thus additional steps must be taken if one desires to compare results to experiments performed in solvent.

2.2.4 Modelling solvent

It is in principle possible to include solvent molecules explicitly in QM calculations: this is in practise, extremely cost prohibitive. In order to approximate the important contributions of solvation, so-called *implicit continuum solvent models* are generally employed.^{71,118} Mathematically, one describes this as

$$\hat{H}^{tot}(\mathbf{r}_m) = \hat{H}^{mol}(\mathbf{r}_m) + \hat{V}^{mol+sol}(\mathbf{r}_m) \quad (2.68)$$

where a perturbation $\hat{V}^{mol+sol}$ dependent only on the coordinates of the solute (\mathbf{r}_m ; thus implicit) is applied to the Hamiltonian of the solute. The perturbation term is composed of interaction operators which contribute to the net free energy:

$$G_{solv} = G_{cavity} + G_{electrostatic} + G_{dispersion} + G_{repulsion} + G_{solv \ kinetic} \quad (2.69)$$

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where the total solvation free energy G_{solv} contains terms from: the formation of a solvation cavity G_{cavity} , the electrostatic interactions between solvent and solute $G_{electrostatic}$, the dispersion interactions between solvent and solute $G_{dispersion}$, the QM exchange repulsion between solvent and solute $G_{repulsion}$, and the movement of solvent molecules $G_{solv\ kinetic}$.

A widely used model for solvation comes from the Truhlar group, and is known as SMD.¹¹⁹ The main parameter in implicit solvent models is the solvent dielectric constant (ϵ) with contributions from surface tension and the solvent-solute interface. SMD also includes terms which depend on the electron density of the solute. While many other implicit solvent models require the use of the same QM method as they were parametrized,¹²⁰ SMD is a *universal* model which was parametrized using several QM methods. Therefore, it does not require the use of a specific QM method and can be applied broadly in both single point energy and geometry optimization calculations.

2.2.5 Rate constants and transition state theory

In the discussion of chemical kinetics, the rate (r) of a bimolecular reaction



is determined by the *rate law*, which can generally be described as

$$r = \frac{dC}{dt} = \frac{dD}{dt} = k[A]^a[B]^b \quad (2.71)$$

where k is the rate constant, t is time, A, B, C , and D are chemical species with stoichiometric coefficients a, b, c , and d , and k is the rate constant. Computational chemistry is in general, not useful for determining rate laws: this must be done experimentally. Where computational studies can be useful, is in determining reaction mechanisms, and how the reaction barrier height can be altered. In doing so, we focus entirely on k .

Most chemists are intimately familiar with the phenomenological *Arrhenius equation*

$$k_{Arr} = Ae^{-E_a/RT} \quad (2.72)$$

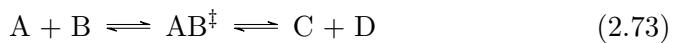
where A is a constant, R is the gas constant, and E_a is the *activation energy*, which is an experimental measure of the reaction barrier height. This equation dates back to the 1880s, when Arrhenius noticed that the

2.2. Applying theory to chemical problems

reactions depended more heavily on temperature than was intuitive, and thus introduced the A constant, known often as the Arrhenius pre-factor.¹²¹ The Arrhenius pre-factor is an empirical measure of how factors other than kinetic energy affect the rate constant. From the perspective of theory, Equation 2.72 has little meaning as the parameters are empirical. Thus, to study rate constants theoretically we must turn to *transition state theory*.

Transition state theory

The study of transition state theory (TST) originates in the 1930s, and was developed primarily by Eyring.^{121,122} In TST we focus on the TS complex, which is defined as a transient species which exists at the top of the energy barrier of a reaction. If we consider the same reaction in Equation 2.70, and set all the coefficients to 1, then TST states the reaction proceeds in two steps, the first of which includes a quasi-equilibrium between the reactants and TS complex



with an equilibrium constant (K_c^\ddagger) expression

$$K_c^\ddagger = \frac{[AB^\ddagger]/c^0}{[A]/c^0[B]/c^0} \quad (2.74)$$

where c^0 is the standard-state concentration (normally taken to be 1 M).

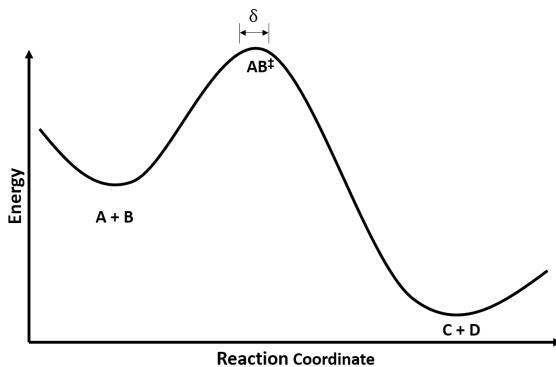


Figure 2.2: A reaction coordinate diagram for the reaction of Equation 2.73. The TS complex is defined to exist in the small region δ above the reaction barrier.

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In TST, we define the TS complex to exist throughout a small region of width δ above the reaction barrier (Figure 2.2). From the second step of the reaction in Equation 2.73, we can define a reaction rate dependent on the concentration $[AB^\ddagger]$ and v_c , a factor which defines the frequency with which the complexes proceed over the barrier:

$$r = v_c[AB^\ddagger] \quad (2.75)$$

From Equations 2.70 and 2.73, we now have two equivalent expressions for the reaction rate, which allows us to derive the following

$$r = k[A][B] = v_c[AB^\ddagger] \quad (2.76)$$

and solving Equation 2.74 for $[AB^\ddagger]$ results in

$$r = v_c \frac{[A][B]K_c^\ddagger}{c^0} \quad (2.77)$$

or

$$k = \frac{v_c K_c^\ddagger}{c^0} \quad (2.78)$$

We must now invoke the statistical thermodynamics to make sense of Equation 2.78. We can rewrite the equilibrium expression K_c^\ddagger in terms of partition functions of each molecular species:

$$K_c^\ddagger = \frac{[AB^\ddagger]/c^0}{[A]/c^0[B]/c^0} = \frac{(q^\ddagger/V)c^0}{(q_A/V)(q_b/V)} \quad (2.79)$$

where V is the volume, and q_A , q_B , and q^\ddagger are the partition functions of A, B, and AB^\ddagger , respectively.

Since we have defined the reaction to be occurring with one degree of freedom, the translational partition function q_{trans} can be defined as

$$q_{trans} = \frac{\sqrt{2\pi m^\ddagger k_B T}}{h} \delta \quad (2.80)$$

where m^\ddagger is the mass of the TS complex. The partition function of the TS complex can be written as the product $q^\ddagger = q_{trans}q_{int}^\ddagger$, where the second term accounts for all remaining degrees of freedom of the TS complex. We can use this and rewrite Equations 2.79 and 2.78 as

$$K_c^\ddagger = \frac{\sqrt{2\pi m^\ddagger k_B T}}{h} \delta \frac{(q_{int}^\ddagger/V)c^0}{(q_A/V)(q_b/V)} \quad (2.81)$$

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and

$$k = v_c \frac{\sqrt{2\pi m^\ddagger k_B T}}{hc^0} \delta \frac{(q_{int}^\ddagger/V)c^0}{(q_A/V)(q_b/V)} \quad (2.82)$$

We are now left with the two terms v_c and δ which are ill-defined. However, the product of these two terms is the average speed at which the TS complex crosses the barrier, $\langle u_{TS} \rangle = v_c \delta$. A Maxwell-Boltzmann distribution is used to calculate the value of $\langle u_{TS} \rangle$:

$$\langle u_{TS} \rangle = \left(\frac{m^\ddagger}{2\pi k_B T} \right)^{1/2} \int_0^\infty ue^{-m^\ddagger u^2/2k_B T} du = \left(\frac{m^\ddagger}{2\pi k_B T m^\ddagger} \right)^{1/2} \quad (2.83)$$

Substituting Equation 2.83 into Equation 2.82 for $v_c \delta$ yields

$$k = \frac{\sqrt{k_B T}}{hc^0} \frac{(q_{int}^\ddagger/V)c^0}{(q_A/V)(q_b/V)} = \frac{k_B T}{hc^0} K_c^\ddagger \quad (2.84)$$

Now, define the standard Gibbs free energy of activation ($\Delta^\ddagger G^0$) to be the change in Gibbs free energy in going from reactants to TS. The thermodynamical expression is

$$\Delta^\ddagger G^0 = -RT \ln K_c^\ddagger \quad (2.85)$$

which can be substituted into Equation 2.84

$$k = \frac{k_B T}{hc^0} e^{-\Delta^\ddagger G^0 / RT} \quad (2.86)$$

The standard Gibbs free energy of activation can be expressed in terms of enthalpy and entropy as

$$\Delta^\ddagger G^0 = \Delta^\ddagger H^0 - T\Delta^\ddagger S^0 \quad (2.87)$$

which, upon substitution gives the equation

$$k = \frac{k_B T}{hc^0} e^{-\Delta^\ddagger S^0 / R} e^{-\Delta^\ddagger H^0 / RT} \quad (2.88)$$

At this point, we can draw a direct comparison to the Arrhenius equation (Equation 2.72) by expressing E_a in terms of $\Delta^\ddagger H^0$ and A in terms of $\Delta^\ddagger S^0$. We must differentiate the natural logarithm of Equation 2.84, as well as Equation 2.72 (assuming that A is independent of temperature):

$$\frac{d \ln k}{dT} = \frac{1}{T} + \frac{d \ln K_c^\ddagger}{dT} \quad (2.89)$$

$$\frac{d \ln k_{Arr}}{dT} = \frac{E_a}{RT^2} \quad (2.90)$$

Next, we use the fact that $d \ln K_c/dT = \Delta U^0/RT^2$ for an ideal gas, then Equation 2.89 becomes

$$\frac{d \ln k}{dT} = \frac{1}{T} + \frac{\Delta^\ddagger U^0}{RT^2} \quad (2.91)$$

Additionally, $\Delta^\ddagger H^0 = \Delta^\ddagger U^0 + RT\Delta^\ddagger n$ ($\Delta^\ddagger n = 1$), as so Equation 2.91 can be rewritten as

$$\frac{d \ln k}{dT} = \frac{\Delta^\ddagger H^0 + 2RT}{RT^2} \quad (2.92)$$

Therefore, by comparison of Equation 2.92 and 2.90, we get

$$E_a = \Delta^\ddagger H^0 + 2RT \quad (2.93)$$

which then converts Equation 2.88 into the form

$$k = \frac{e^2 k_B T}{hc^0} e^{\Delta^\ddagger S^0 / R} e^{-E_a / RT} \quad (2.94)$$

Therefore, a statistical thermodynamical picture of the Arrhenius equation arises from TST, and the Arrhenius pre-factor A can be expressed as

$$A = \frac{e^2 k_B T}{hc^0} e^{\Delta^\ddagger S^0 / R} \quad (2.95)$$

In practise, we use the form of Equation 2.86 to compute the rate constant of a reaction, which we shall denote as k_{TST} . The conventional TST makes an assumption that the reaction coordinate is static along the lowest energy pathway. This can be corrected by the use of *variational transition state theory*.¹²³ We shall not consider variational TST in this work, as with careful application, conventional TST does a remarkably good job at accounting for the magnitude and temperature dependence of a wide range of reactions.¹²² Additionally, if one makes corrections for *QM tunnelling*, conventional TST can easily give a more complete description of the rate constant.

Quantum mechanical tunnelling

Atoms are quantum mechanical particles, and are thus subject to the strange probabilistic behaviours observed at the microscopic level. QM tunnelling refers to the ability of particles to penetrate the reaction barrier, rather than surmounting it classically (Figure 2.3). While all reactions are subject to QM tunnelling, we will show that due to the low mass of the hydrogen atom, QM tunnelling can play a significant role in HAT reactions.

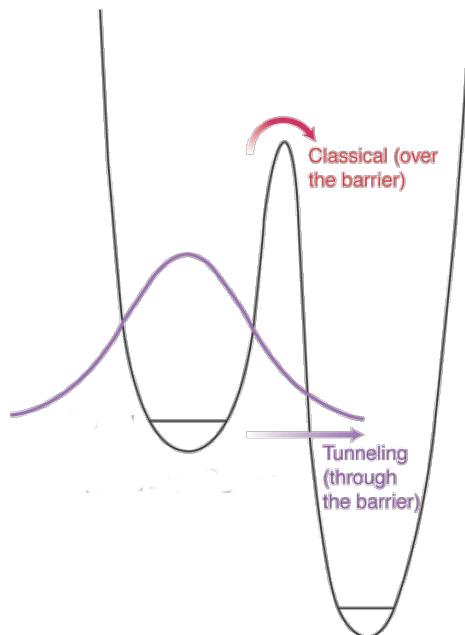


Figure 2.3: Quantum mechanical tunnelling occurs when a particle penetrates a reaction barrier, rather than surmounting it. Figure adapted from Reference 124.

In order to determine the effects of scattering, one must find transmission coefficients (κ) by solving the Schrödinger equation.⁴⁹ This is done by approximating the reaction barrier with an analytical potential, thus simplifying the problem mathematically. The earliest model potentials were introduced by Bell, who used a parabolic function to approximate the reaction barrier.¹²⁵ To obtain κ , and thus the observed rate constant (k_{obs}), the following equations were used:

$$k_{obs} = \kappa A e^{-E_a/RT} \quad (2.96)$$

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$$\kappa = \frac{e^\alpha}{\beta - \alpha} (\beta e^{-\alpha} - \alpha e^{-\beta}) \quad (2.97)$$

$$\alpha = E_a/RT \quad (2.98)$$

$$\beta = \frac{2a\pi^2(2mE_a)^{1/2}}{h} \quad (2.99)$$

where the Arrhenius equation was used to estimate the rate constant, m is the mass of the tunnelling particle, and $2a$ is the width of the barrier. Since the equation is dependent on the mass of the particle, tunnelling occurs more often when lighter particles are involved. As a consequence, tunnelling is more common in HAT reactions than other atom transfer reactions. Also, the height and width of the barrier are important factors in determining the contributions to tunnelling: reactions with small barriers have low tunnelling contributions; narrow barriers result in higher tunnelling contributions.

The Bell model is a poor representation of an actual reaction barrier. One which is a much better approximation is the *Eckart potential*.¹²⁶ The form of this potential is

$$V = -\frac{Ay}{1-y} - \frac{By}{1-y^2} \quad (2.100)$$

$$y = -e^{2\pi x/L} \quad (2.101)$$

where x is the variable along the reaction coordinate and L is called the characteristic length. If $A = 0$ the potential becomes a symmetric function, further simplifying the problem; however, most reactions do not have a symmetric potential. A , B and L are related to the change in barrier height in the forward and reverse direction, ΔV_1 and ΔV_2 , respectively:

$$A = \Delta V_1 - \Delta V_2 \quad (2.102)$$

$$B = ((\Delta V_1)^{1/2} + (\Delta V_2)^{1/2})^2 \quad (2.103)$$

$$\frac{L}{2\pi} = (-\frac{2}{F^*})^{1/2} [\frac{1}{(\Delta V_1)^{1/2}} + \frac{1}{(\Delta V_2)^{1/2}}]^{-1} \quad (2.104)$$

where $F^* = d^2V/dx^2$ evaluated at the maximum of the potential. In this formulation, V is a placeholder energy. Note that if a reaction is endoergic, tunnelling does not occur. Alternatively, one says tunnelling only occurs in exoergic or energy-neutral reactions.

The solutions to the Schrödinger equation for the Eckart potential are analytical, thus that transmission coefficient κ can easily be computed using

2.2. Applying theory to chemical problems

standard numerical techniques. These tunnelling corrections will be applied, where applicable as

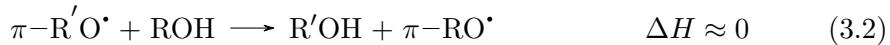
$$k_{calc} = \kappa k_{TST} = \kappa \frac{k_B T}{hc^0} e^{-\Delta^\ddagger G^0} \quad (2.105)$$

Chapter 3

The Relationship Between Arrhenius Pre-factors with Non-Covalent Binding

3.1 Introduction

DiLabio and Ingold⁴⁰ previously investigated the formal HAT reaction of the iminoxyl/oxime self-exchange reaction. In that paper, they compiled a table of parameters from the phenomenological Arrhenius equation for a series of interesting reactions, which appear here in Table 3.1.^{38,127–133} These are thermoneutral self-exchange reactions of oxygen-centred π -radicals,ⁱ and other nearly thermoneutral reactions involving the destruction and formation of oxygen-centred π -radicals, reactions 3.1 and 3.2, respectively:

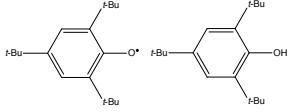
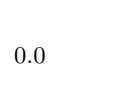
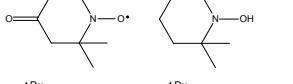
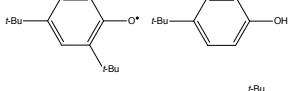
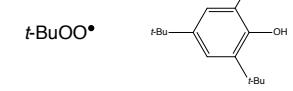
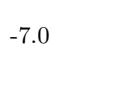
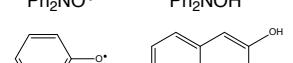
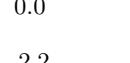
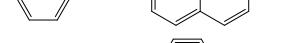
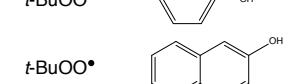
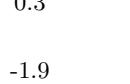
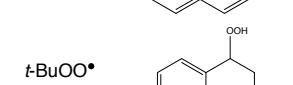
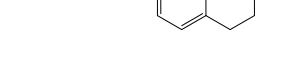


Although it is well known that reactions of this nature involve remarkably low activation energies (E_a),^{134–137} they also have unusually low Arrhenius pre-exponential factors (A), or as they shall be referred to herein, *A-factors*. As a result, these reactions are generally slower than expected, evidence for which is summarized in Table 3.1: The measured A-factors are small, and range from $10^{3.5}\text{--}10^{8.3}$ M⁻¹s⁻¹. In the past, this has been attributed to steric shielding around the oxygen atoms, resulting in a large entropic barrier.⁴⁰ Importantly, it was noted that the degree of steric shielding on

ⁱA π -radical is one in which the SOMO is orthogonal to the plane of the molecular framework, i.e. of π -symmetry. Note that free alkoxyl radicals cannot be distinguished as either σ or π -radicals, as the SOMO is degenerate, or free to rotate with respect to the rest of the molecular framework. Therefore, only the geometry of the radical-molecule complex can resolve the symmetry of the SOMO.

3.1. Introduction

Table 3.1: Table of results for (nearly) thermoneutral reactions studied. Units for ΔH , E_a , and calculated binding energy (BE) are kcal mol⁻¹, and log A and k are M⁻¹s⁻¹. References to the original literature are included with the Complex ID number. †Calculated binding energies involve non-minimum structure containing one or more small imaginary frequencies. Adapted with permission from Reference 40. Copyright (2005) American Chemical Society.

ID	$\text{RO}^\bullet/\text{R}'\text{O}^\bullet$	ROH	ΔH	$\log A$	E_a	k	BE
1 ³⁸			0.0	3.7	1.2	3.3×10^2	-10.8
2 ¹²⁷			-2.0	3.8	3.8	10	-14.8
3 ^{38†}			0.0	5.1	3.5	3.3×10^2	-10.1
4 ^{128,129†}			4.2	5.5	4.8	93	-10.0
5 ¹³⁰			-7.0	4.2	0.5	7×10^3	-6.8
6 ^{38†}			0.0	>7	-	$>10^7$	-13.6
7 ¹³¹			-2.2	8.3	2.3	4×10^6	-8.6
8 ^{132†}			0.3	7.2	5.2	3×10^3	-5.5
9 ^{132†}			-1.9	6.4	2.6	3×10^4	-5.6
10 ^{133†}			1.4	6.0	4.5	7×10^2	-8.0

the oxygen atom appears to play an important role in the order of the A-factor; systems with greater bulk have lower A-factors, while non-shielded systems have larger A-factors.

Stereo-electronic effects are known to play an important role in HAT, and have been studied extensively.^{36,138–144} Although the abstraction of a

3.1. Introduction

specific hydrogen atom may be more thermodynamically favourable than others on a given substrate, if it is not accessible due to steric constraints, abstraction will not occur at this site. Otherwise, additional steric bulk can lead to significant reductions in reactivity, through destabilization of the TS complex, or by forcing additional processes involving conformational changes in order to reach the appropriate TS structure. For example, in reactions of tertiary acetamides with CumO[•],¹⁴⁴ where abstraction occurs mainly from C-H bonds α to the nitrogen atom, a two-fold decrease in the rate constant (normalized for the number of equivalent hydrogen atoms) is observed in going from *N,N*-dimethylacetamide to *N,N*-diisobutylacetamide ($k_H = 2.0 \times 10^5$ and $7.8 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$, respectively). The decrease in rate constant is attributed to the steric clash between the methyl groups of CumO[•] and the isobutyl groups of *N,N*-diisobutylacetamide.

Upon first inspection, all of the reactions in Table 3.1 appear to be of a similar nature. Each reaction involves the breaking and formation of O-H bonds as the thermodynamic driving force. All of these bonds are expected to be of comparable strength, therefore, differences should not contribute significantly to reaction barriers in a Bell-Evans-Polanyi principle fashion. Hence, the large degree of variance in their rate constants (k) is somewhat surprising. These reactions are closely related to the self-exchange reaction between phenol and phenoxyl,²³ in which a strong molecule-radical pre-reaction complex is formed, ca. 10 kcal mol⁻¹ below the separated reactants. It is therefore expected that most, if not all, of the systems in Table 3.1 should exhibit a similar molecule-radical complex; granted, the strength of the interaction will vary because of steric repulsion.

Currently, there has been no comprehensive investigation of the relationship between the pre-reaction complex and the kinetics of a reaction. Using the reactions and data in Table 3.1, we ask the question: *Do A-factors have a correlation with non-covalent binding energies of the pre-reaction complex?* This is a reasonable question as non-covalent binding and steric hinderance represent a loss of degrees of freedom and therefore entropy,ⁱⁱ which ultimately determines the A-factor magnitude. If the answer to the question is yes, then non-covalent binding may be useful as a diagnostic for the “looseness” or “tightness” of a TS complex, in addition to providing an important link between theory and experiment.

ⁱⁱRecall from Equation 2.95 that the A-factor can be related to TST such that the primary variable is entropy ($\Delta^\ddagger S^0$).

3.2. Computational methods and details

3.2 Computational methods and details

Density-functional theory (DFT) calculations were carried out using the Gaussian-09 software package.¹¹³ Care was taken to obtain minimum energy structures through detailed conformational analysis. For this, the BLYP density-functional^{99,145} was utilized, paired with the empirical D3 dispersion correction¹⁰⁶ with the recommended Becke-Johnson damping functions,¹⁰⁷ as well as our groups' own basis set incompleteness potentials (BSIPs),*[\(update citation\)](#) and minimal MINIs basis sets.¹⁴⁶ The use of minimal basis sets corrected for basis set incompleteness allows DFT-based methods (as opposed to semi-empirical or force-field based approaches) to be used efficiently in performing a large number of calculations. Minimum energy conformers of the monomers (substrates and radicals) were first obtained by manual manipulation of the necessary dihedral bond angles, followed by geometry optimization and vibrational analysis.

The lowest energy radicals and substrates were combined to generate the appropriate pre-reaction complexes. These pre-reaction complexes were subject to conformational analysis using the same BLYP-D3(BJ)-BSIP/MINIs method. Geometries were initially manipulated by hand. It became apparent that manual manipulation resulted in an unsatisfactory exploration of the conformational space. To solve this, all the necessary dihedral angles were scanned systematically using a combination of scripts.¹⁴⁷ All manipulated geometries were subject to optimization. For each complex, the top 5–10 complex geometries were subject to further optimization using a higher level of theory (BLYP-D3(BJ)-BSIP/pc-1) to obtain the final minimum energy pre-reaction complex structures. Due to the free rotation of groups such as *t*-butyl and methyl, some of the optimized pre-reaction complex structures contain small imaginary frequencies, and thus do not represent proper stationary states. Several measures were taken to resolve this, however, no resolution was obtained in many cases. Regardless, the complexes adequately represent the pre-reaction complex and differences in “true” binding energies can likely be ignored.

To obtain accurate pre-reaction complex binding energies, the substrates and complexes were subject to single-point energy calculations using the LC- ω PBE long-range corrected density functional^{148,149} with D3(BJ) dispersion corrections and pc-2 basis sets with truncated *f*-type functions (pc-2-spd).¹⁵⁰ This method was selected on the recommendation of work by Johnson et al.¹⁵⁰, which demonstrated the accuracy of this method for the calculation of NCIs. On the basis of the reported mean absolute error in Reference 150 for the S66 benchmark set of sixty-six different non-covalently

3.3. Results and discussion

interacting dimers,¹⁵¹ the calculated binding energies reported herein from the LC- ω PBE-D3(BJ)/pc-2-spd level of theory carry an estimated 0.2 kcal mol⁻¹ margin of error.

3.3 Results and discussion

The theoretically determined electronic binding energies calculated for the lowest energy pre-reaction complex of each system are listed in Table 3.1. The logarithm of A-factor against binding energy was plotted, as shown in Figure 3.1. The overall correlation is quite poor ($R^2 = 0.33$), however much of the data is grouped about a single, well correlated line ($R^2 = 0.95$). The intercept of the fitted line which corresponds to zero binding energy is 8.63, a value which is in line with what has been cited as the expected A-factor for HAT reactions, *viz.* $10^{8.5 \pm 0.5} \text{ M}^{-1}\text{s}^{-1}$.¹⁵² These results suggest that the observed correlation is genuine, that is, NCIs may have an impact on A-factors. I shall demonstrate that the data which do not correlate are reasonable outliers. In fact, using simple rationale I shall demonstrate that different regimes of steric bulk results in different processes leading to the TS complex. As a result, deviations from the relationship between A-factor and binding energy are observed.

In order to illustrate this, consider the fundamental properties of the HAT reactions involved herein. There are two important concerted reaction mechanisms that are possible, namely direct HAT or PCET. Specifically, we must consider the geometric constraints in which these reaction mechanisms occur. For direct HAT to occur, the SOMO of the radical must overlap with the O-H σ^* anti-bonding orbital. This may require the rotation of the hydrogen atom donating hydroxyl group out of the plane. The rotation of a phenolic hydroxyl group has an energy barrier that follows a $\cos^2 \theta$ relationship, and can be as high as 3.1 kcal mol⁻¹ on the basis of the rotational barrier in phenol.¹⁵³ For a PCET mechanism to occur, there are two possible geometries: Either the SOMO of the radical overlaps can overlap with the corresponding oxygen lone pair p -orbital, as seen in the work of Mayer et al.²³; or a lone pair- π or π - π bonding overlap between the radical and substrate can occur, as seen in the work of DiLabio and Johnson²⁶. Due to time constraints, I did not seek to obtain TS complex structures. Nonetheless, from the pre-reaction complex one can surmise the most likely TS complex. Thus, by applying these basic principles, it is possible to rationalize deviations from the trend observed in Figure 3.1.

We shall begin by examining the points which fall on the expected line,

3.3. Results and discussion

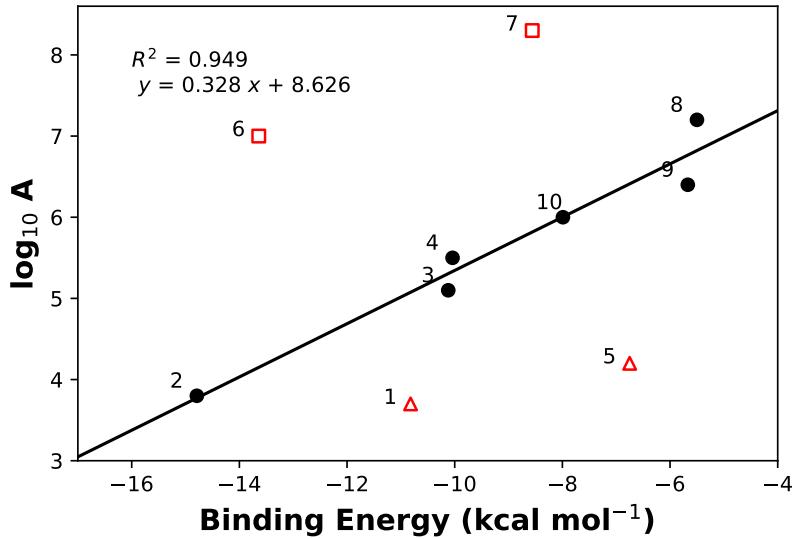


Figure 3.1: Plot of logarithm of A-factor against binding energy. Only the black points were included in the line fitting (slope = $0.328 \text{ kcal mol}^{-1}$, intercept = $8.626 \text{ kcal mol}^{-1}$, and $R^2 = 0.949$). Red points with open faced markers indicate outliers, *vide infra*. The inclusion of complexes 1, 5, and 7 result in an $R^2=0.334$. Complex 6 is always omitted from line fitting as the experimental A-factor is approximate.

3.3. Results and discussion

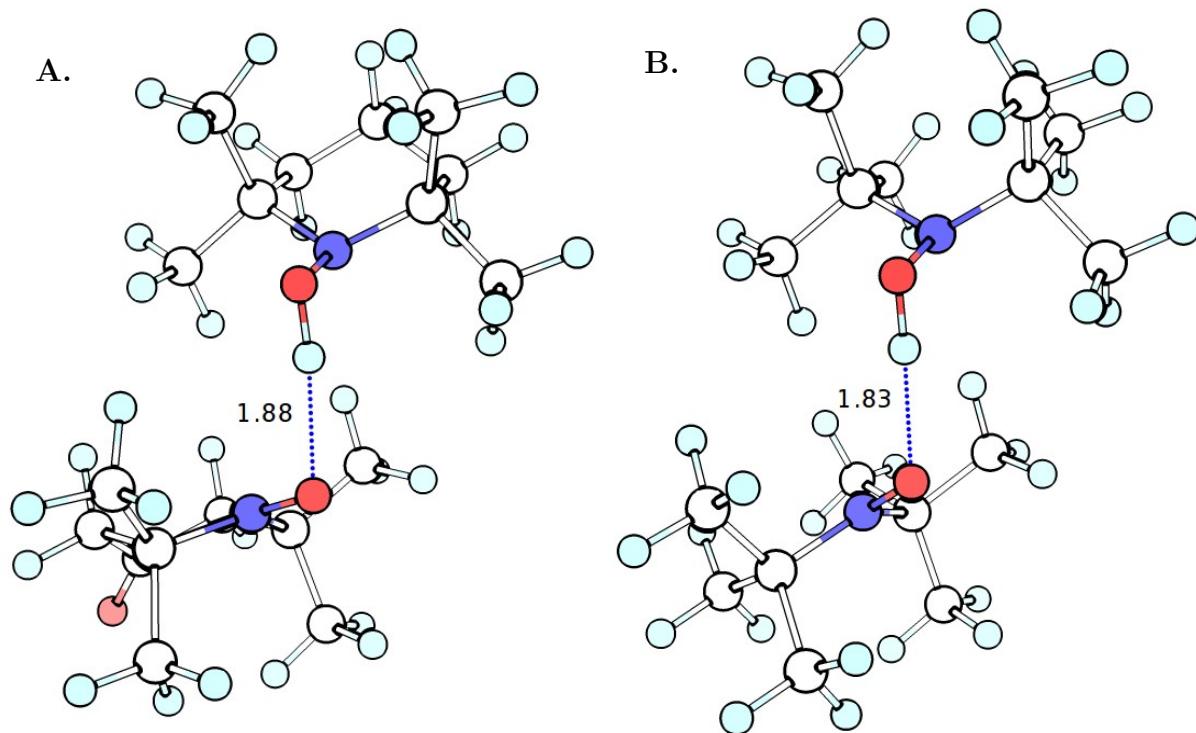


Figure 3.2: Three-dimensional structures of **A** complex 2, and **B** complex 3. Hydrogen bond distances are shown in units of Å. The elements are coloured as white for carbon, light blue for hydrogen, red for oxygen, and blue for nitrogen.

3.3. Results and discussion

complexes 2–4 and 8–10. The examination of all these pre-reaction complexes reveals that an additional process that has a moderate energetic barrier is required in order for formal HAT reactions to proceed. Complexes 2 and 3 are shown in Figure 3.2, and are very similar in structure. Both are hydroxylamine-nitroxyl couples with similar degrees of steric bulk adjacent to the reacting centres. The *t*-butyl groups of 3, and the methyl groups of 2 prevent the alignment of the NO-H-ON frameworks in a PCET manner. In order to reach the TS complex, both 2 and 3 must bring methyl groups within close proximity for direct HAT to occur. In the most stable stacked conformation, complex 4, as seen in Figure 3.3, cannot undergo PCET as the steric clash of the para-position *t*-butyl groups prevent π - π overlap. In order to react via direct HAT, the hydroxyl group must rotate further out of the aromatic plane, or the bulky para-position *t*-butyl groups must come into close proximity. Alternatively, an open conformation for complex 4 is possible, which lies ca. 2 kcal mol⁻¹ higher in energy than the stacked complex, a result which is also consistent with the observed trend-line. From the open conformation, PCET is still not possible due to the steric bulk of the ortho-position *t*-butyl groups of the radical, thus this reaction likely proceeds through a direct HAT mechanism.

Complexes 8 and 9 are similar systems, in which *t*-BuOO[•] reacts with unhindered phenolic substrates. As seen by the structures in Figure 3.4, the bound complexes are somewhat dissimilar. The hydroxyl group of complex 8 is rotated out of the plane 24°, while in complex 9 the hydroxyl group lies entirely in the plane. It is likely that the larger aromatic system of 2-naphthol results in a larger OH rotational barrier, and thus the most favourable conformation is entirely in the plane. Complex 8 was previously studied by DiLabio and Johnson²⁶, where it was demonstrated that a partial bonding interaction exists between the peroxy radical lone-pair and phenolic π -system, and thus formal HAT proceeds through a PCET mechanism. Although the pre-reaction complexes are somewhat dissimilar, the conformational changes necessary to reach a PCET TS complex, similar to that reported in reference 26, are likely not dramatically different in terms of energetic barriers. Any small differences result in noise in the observed trend.

Complex 10 is unique in that it is the only reaction between a peroxide and a peroxy radical. The self-exchange reaction between HOO[•] and HOOH can be considered the simplest reference for the reaction of α -tetralin peroxide with *t*-butylperoxy. To the best of my knowledge, the mechanism of the hydroperoxyhydrogen peroxide couple has not been characterized as either PCET or direct HAT previously in the literature, although the TS structure has been previously reported.¹⁵⁴ Using this structure, calcu-

3.3. Results and discussion

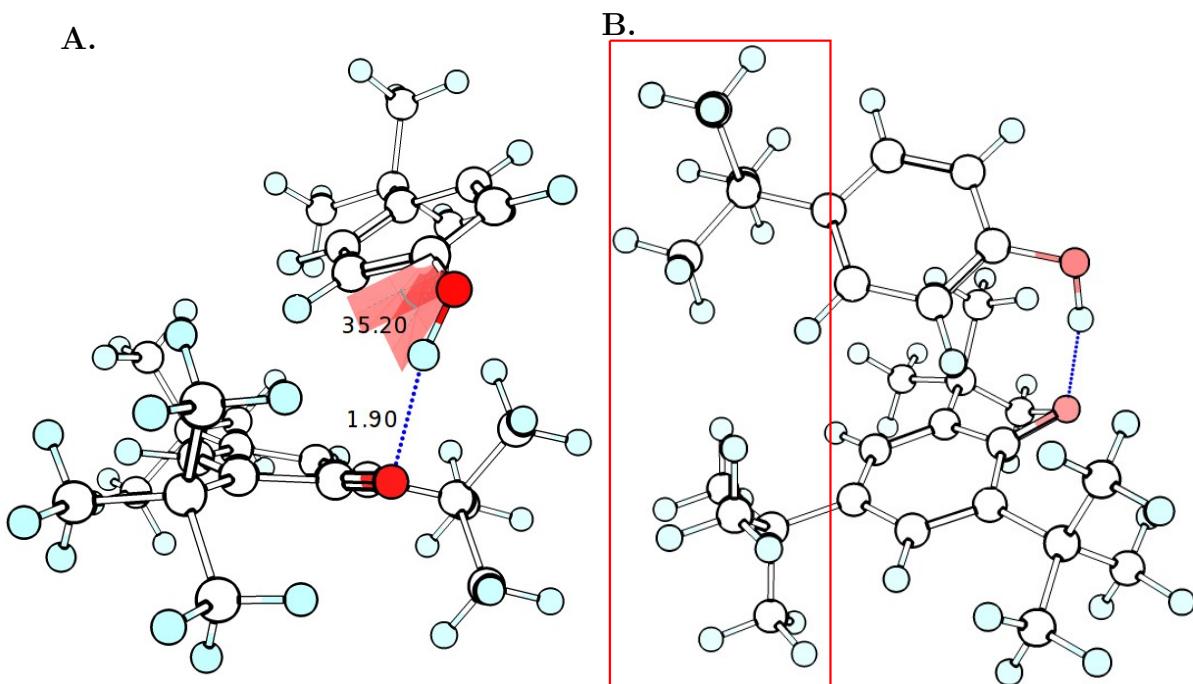


Figure 3.3: Three-dimensional structure of pre-reaction complex 4 between 2,4,6-tri-*t*-butylphenol and 4-*t*-butylphenoxy. **A** demonstrates the hydrogen bond distances in units of Å, and the out-of-plane rotation by 35.2° of the phenolic hydroxyl group. **B** demonstrates the steric clash (highlighted by red box) between the para-position *t*-butyl groups. The elements are coloured as white for carbon, light blue for hydrogen, and red for oxygen.

3.3. Results and discussion

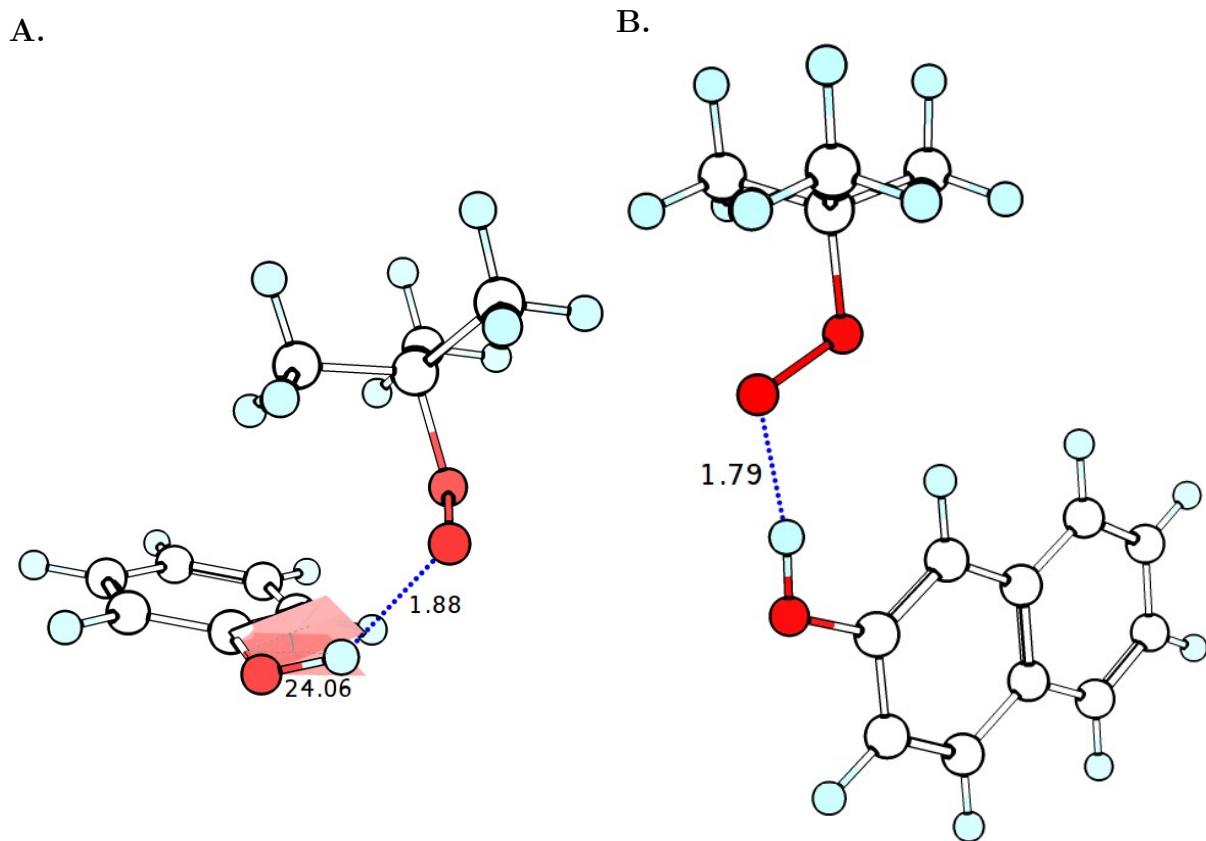


Figure 3.4: Three-dimensional structures of pre-reaction complexes **A.** 8 (*t*-butylperoxyl and phenol) and **B.** 9 (*t*-butylperoxyl and 2-naphthol). Hydrogen bond distances are shown in units of Å. Complex 8 has an out of plane rotation of the phenolic hydroxyl group of 24.1° . The elements are coloured as white for carbon, light blue for hydrogen, and red for oxygen.

3.3. Results and discussion

lations reveal a lone pair-lone pair interaction leading to partial bonding in the TS, i.e. a PCET mechanism. (See Appendix A, Figure A.2). Also the hydroperoxyl-hydrogen peroxide couple appears to prefer an H–O–O–H dihedral angle of 90° , so that the two non-reacting hydrogen atoms oriented 180° away from one another. Orienting substituents directly away from one another is likely the most stable TS structure for all peroxyl-peroxide formal HAT reactions. In order for complex 10 to achieve a similar TS structure, *t*-butylperoxy and α -tetralin peroxide must reorganize to avoid steric clash, likely through a rotation of the HOO moiety of α -tetralin peroxide.

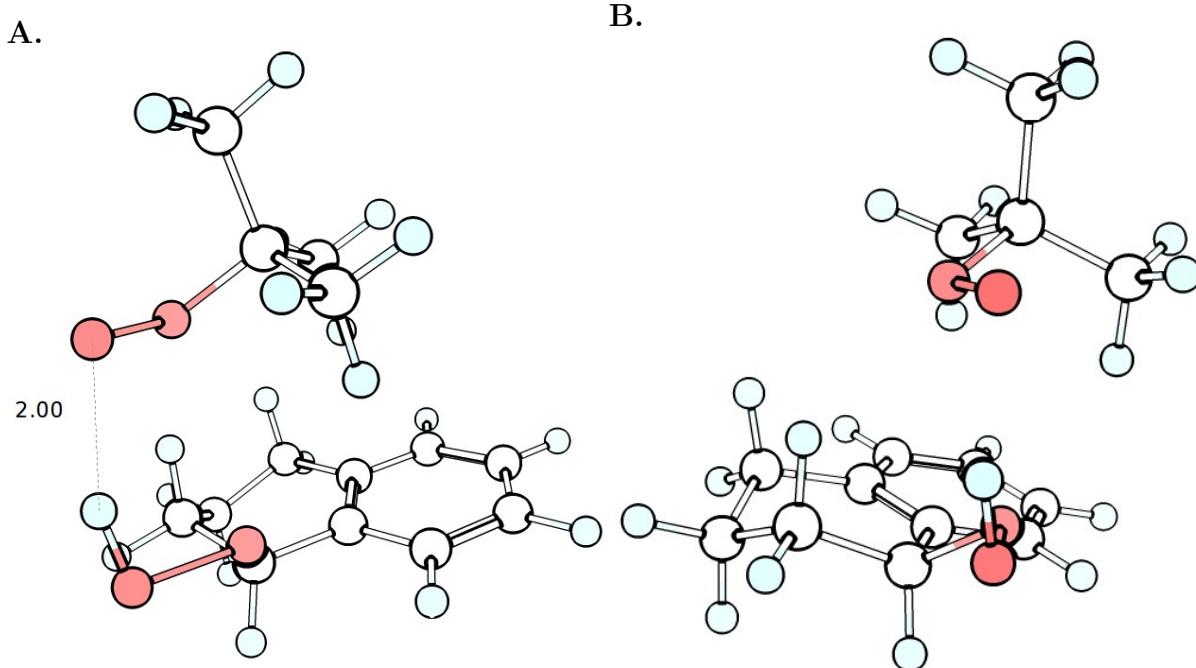


Figure 3.5: Three-dimensional structure of pre-reaction complex 10 between *t*-butylperoxy and α -tetralin peroxide. **A** demonstrates the hydrogen bond distances in units of Å. **B** demonstrates the incorrect orientation of the peroxyl-peroxide units for a PCET TS complex to occur. The elements are coloured as white for carbon, light blue for hydrogen, and red for oxygen.

Once again, complexes 2–4 and 9–10 follow the observed trend. In all cases, these complexes must undergo an additional conformational change with a small energy barrier in order to reach the pre-reaction complex which leads directly to the TS complex. This is illustrated in Figure 3.6,

Consider next the points which sit above the trendline, complexes 6 and

3.3. Results and discussion

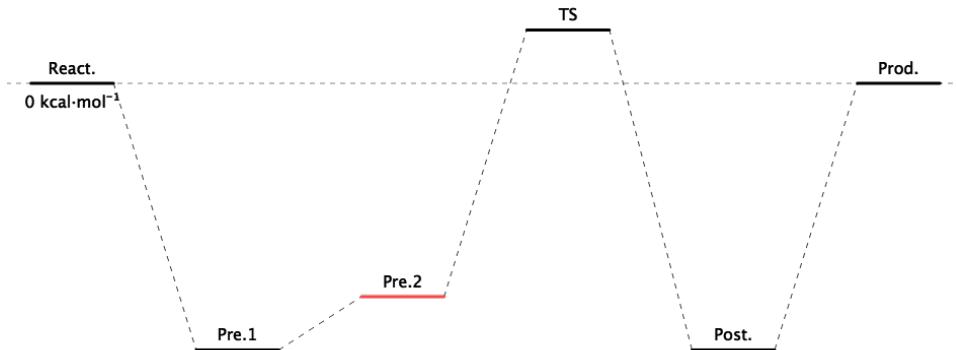


Figure 3.6: Reaction coordinate illustrating a conformational change to a second pre-reaction complex prior to transition state formation. Energies are estimated for a self-exchange reaction. React. = reactants, Pre.1 = lowest energy pre-reaction complex, Pre.2 = postulated higher energy pre-reaction complex involving conformational change, TS = transition state, Post. = post-reaction complex, Prod. = products.

7. The A-factor for complex 6 is approximate and thus does not get factored into the line fitting. In both cases, the non-covalently bound complexes are in a slipped-parallel π -stacked conformation. Complex 7 in particular is very similar to the phenol-phenoxy couple, except with 2-naphthol instead of phenol. Therefore, it is possible to infer that both of these reactions take place through a PCET mechanism. In fact, these pre-reaction complexes are optimally aligned to achieve the appropriate TS complexes. Therefore, in contrast to the observed trend, complexes 6 and 7 do not require an additional conformational change to approach the TS complexes, as illustrated in Figure 3.7.

Lastly, consider the points which fall below the trendline, complexes 1 and 5. In both cases, a high degree of steric repulsion likely does not allow for a PCET mechanism. Complex 1 is the self-exchange reaction between the very bulky 2,4,6-tri-*t*-butylphenol-2,4,6-tri-*t*-butylphenoxy couple, as seen in Figure 3.8 A. As a result of steric shielding around the reaction centres, the most stable pre-reaction complex is stacked to maximize dispersion interactions, but does not have a hydrogen bond, which is unique among the ten reaction couples studied herein. Therefore, these must be a higher-energy hydrogen-bonded pre-reaction couple that leads to the HAT transfer. Note however, that there is a barrier to rotation of the hydroxyl group to 90° out of the plane for direct HAT to occur.

3.3. Results and discussion

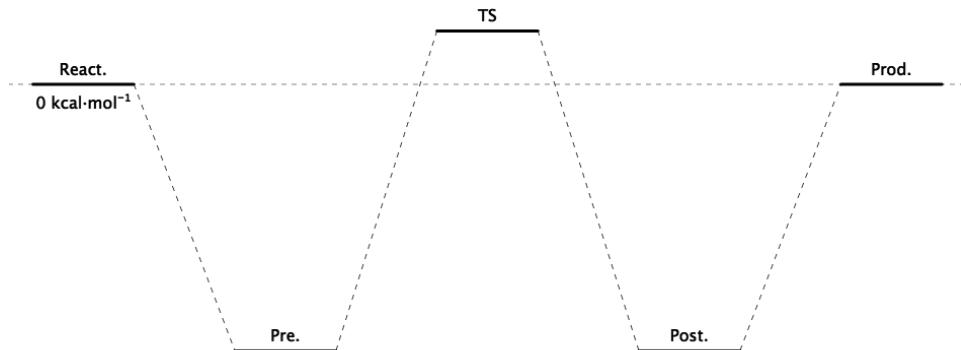


Figure 3.7: Reaction coordinate illustrating no conformational change before moving from pre-reaction complex to the transition state. Energies are estimated based on a self-exchange reaction. React. = reactants, Pre. = lowest energy pre-reaction complex, TS = transition state, Post. = post-reaction complex, Prod. = products.

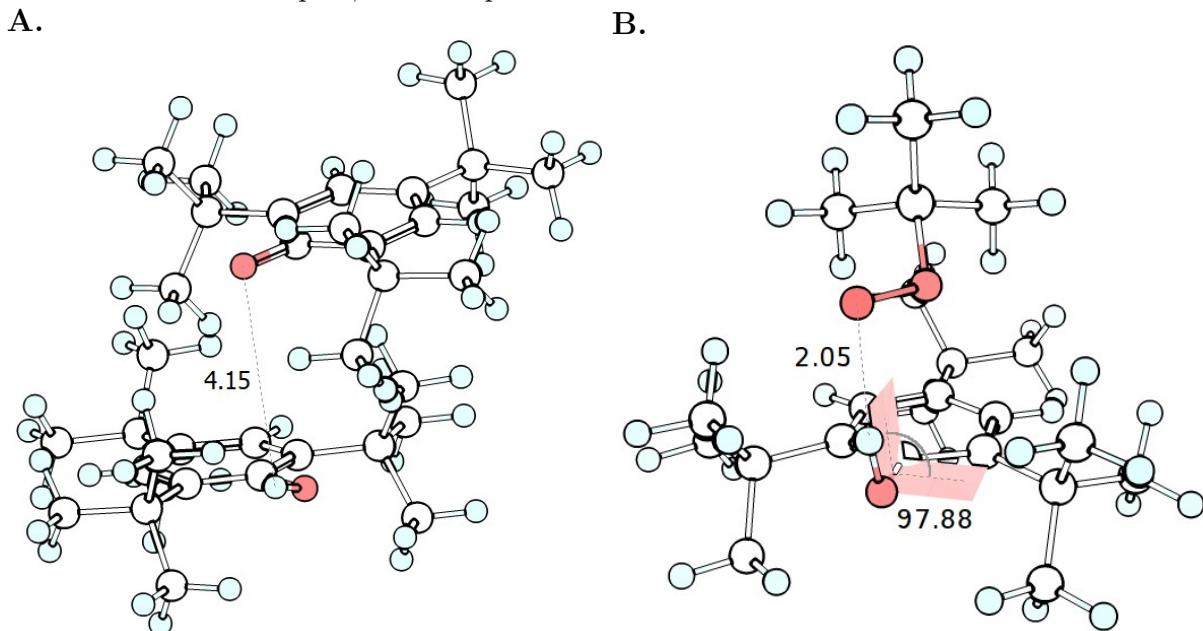


Figure 3.8: Three-dimensional structures of pre-reaction complexes **A.** 1 (2,4,6-tri-*t*-butylphenoxyl and 2,4,6-tri-*t*-butylphenol) and **B.** 5 (2,4,6-tri-*t*-butylphenol and *t*-butyperoxy). Distances in unit of Å and angles are shown in degrees. The elements are coloured as white for carbon, light blue for hydrogen, and red for oxygen.

3.4. Summary

Complex 5 is the 2,4,6-tri-*t*-butylphenol-*t*-butylperoxyl reaction couple. The lowest-energy pre-reaction complex contains a hydrogen bond, however the hydroxyl group is rotated 90° out of the plane. It is likely that as with complex 1, a pre-reaction complex without a hydrogen bond forms first. However, in complex 1 there is less steric clashing, thus the formation of a hydrogen bond is favourable. There is a barrier to rotationⁱⁱⁱ of the hydroxyl group that is about 4.1 kcal mol⁻¹. Note the unusual character of the hydrogen bond formed. Optimal hydrogen bonds are nearly linear so that there is both a dipole-dipole interaction and an orbital interaction such that the lone pair of the acceptor donates electron density into the OH σ^* anti-bonding orbital.¹⁵⁵ In the case of complex 5, the hydrogen bond is nearly perpendicular, resulting in only an orbital interaction.^{iv} The lowest energy pre-reaction complex 5 is comparable to that of complex 8, the TS of which as published in reference 26. Formal HAT in complex 8 takes place through a PCET mechanism, however due to steric shielding it is unlikely that the correct $\pi - \pi$ orbital overlap can occur for PCET to occur. Therefore, this reaction can also be described as taking place through a direct HAT mechanism.

Complexes 1 and 5 fall below the trendline of log *A* vs calculated binding energy. Because of the steric bulk of 2,4,5-tri-*t*-butylphenol, the hydroxyl group must rotate 90° out of plane from the minimum energy structure, in order for HAT to occur. This process has an energy barrier of about 4.1 kcal mol⁻¹. For complex 1, this results in a higher energy pre-reaction complex, while for complex 5 this results in a lower energy pre-reaction complex. However, because the formation of a non-hydrogen bonded complex must necessarily come first, the experimental A-factor does not correlate with the calculated binding energy as observed for complexes 2–4 and 8–10, which undergo a conformational change with little or no barrier. That is to say, the rotation of the phenol hydroxyl group is an additional process with a significant energy barrier, and thus explains the difference in trends.

3.4 Summary

In this investigation, I report the lowest energy pre-reaction complexes for a series of thermoneutral or nearly thermoneutral HAT reactions. I have

^{iv}Calculated as the difference in energy between the in-plane and out-of-plane structures of 2,4,6-tri-*t*-butylphenol at the LC- ω PBE-D3/6-311+G(2d,2p) level of theory.

^{iv}The hydrogen bonding nature of this interaction has been verified using the NCIplot software.^{156,157} These results can be found in Appendix A, Figure A.1.

3.4. Summary

plotted the theoretically determined electronic binding energies against the logarithm of experimentally determined A-factors. These results demonstrate that the A-factor is correlated to some extent with the binding energy, given that the reactions proceed through energetically similar pathways. The results herein can be sorted into three bins:

1. Complexes which require a small conformational with no barrier to approach the TS structure fall onto the observed trendline. This appears to be the most likely case for formal HAT reactions.
2. Complexes which are optimally aligned to approach the TS structure. This was the case for complexes 6 and 7.
3. Complexes which the full 90° rotation of the phenolic hydroxyl group is required for formal HAT to occur. This is the case when the phenol is highly sterically shielded.

These results indicate that different regimes of steric interactions lead to different chemical processes in seemingly similar reactions. As a result, non-covalent binding can be used as a metric for kinetics parameters, however, it cannot fully describe the entropic factors which contribute to the A-factor. One must first determine the relationship between the pre-reaction and TS complex.

Additional work is necessary to extend these results. In particular, a larger sample of data points should be used. Regardless, the results herein represent a novel attempt to link theory and experiment. Given that obtaining the full PES for large molecules is currently computationally impractical, these results serve as a seed for developing a fundamental understanding of complex formal HAT reactions.

Chapter 4

Interrogation of the Bell-Evans-Polanyi Principle: Investigation of the Bond Dissociation Enthalpies Correlated with Hydrogen Atom Transfer Rate Constants

4.1 Introduction

The Bell-Evans-Polanyi (BEP) principle is a conceptual framework that states, for two closely related reactions, the difference in activation energy is proportional to the difference in their enthalpy of reaction.^{44,45,158} This is commonly expressed as the linear free energy relationship (LFER): $E_a = E_0 + \alpha\Delta H$ (Equation 1.1). Initially, the BEP principle was used as a simple model to explain the Brønsted catalysis law, which states that the stronger an acid is, the faster the catalyzed reaction will proceed.¹⁵⁹ A key assumption is made for the BEP principle: the position of the TS along the reaction coordinate is the same for all reactions. The relationship can be described schematically: the more stable the product, the lower the reaction barrier, as seen in Figure 4.1.

A modern utilization of the BEP principle is to estimate rate constants of related reactions. This is a desirable, because as system size increases, ab initio computational modelling becomes computationally challenging, or even infeasible due to the exponential scaling of computational cost with system size. Therefore, the main purpose of LFERs is to apply previous

4.1. Introduction

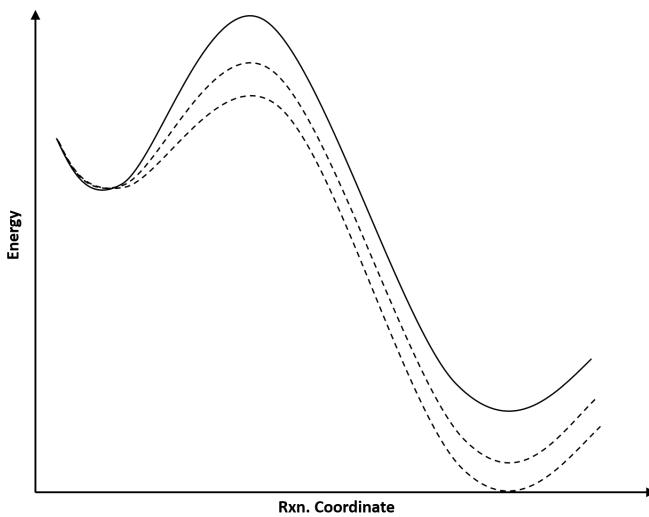


Figure 4.1: Energy profiles for a series of related exothermic reactions illustrating the Bell-Evans-Polanyi principle.

knowledge to new systems and help develop insights. For example, much of our groups' work focuses on studying simple protein models. By thoroughly investigating small systems with ab initio approaches, it is possible to extrapolate the fundamental concepts to large-scale systems. Furthermore, if one can establish that there exists a LFER between activation energy and bond strength for a specific model, then the difference in bond dissociation enthalpy (BDE) can be used to estimate HAT reaction rates in a large-scale protein system.

In application of the BEP principle in HAT reactions, plots of the logarithm of the rate constant (k_H) against BDEs are commonly used: $\log(k_H) = \alpha\Delta H + \text{constant}$. For HAT reactions involving abstraction by CumO[•], the enthalpy of reaction (ΔH) is directly related to the strength of the breaking bond: $\Delta H = \text{BDE}(\text{C}-\text{H}) - \text{BDE}(\text{CumO}-\text{H})$. If the relationship holds for a series of related HAT reactions, then BDEs should correlate with the activation energy. It would then stand that an increase in bond strength represents a destabilization in the TS complex, and thus a decrease in reaction rate. This concept is also important for the work in Chapter 5, where the interaction of non-redox active metal cations results in an increase in effective bond strength, and decrease in rate constant. It is also important to note that if the BEP principle breaks down for reactions that appear related, then additional physico-chemical factors, such as non-covalent binding (*viz.*

4.1. Introduction

Chapter 3), or stereo-electronics may be influencing the reaction barrier.

An interesting application of the BEP principle is the work of Pratt et al.¹⁶⁰, in which the free radical oxidation of unsaturated lipids was examined. They studied the correlation of theoretically determined allylic or benzylic C–H and C–OO[•] bond strengths with experimentally-measured HAT rate constants and O₂ addition rate constants, respectively. BEP plots (log k vs. BDE) for a large range of polyunsaturated fatty acid models show good correlation for C–OO[•] bonds examined, and reasonable correlation for C–H bonds. This demonstrates that BDEs may directly impact the reaction barrier height, in line with the BEP principle. Additionally, these results provide the important ability of predicting rate constants for HAT and oxygen addition reactions related to unsaturated lipid models, by means of calculating BDEs. Another area of research in which the BEP principle is often applied is heterogenous catalysis.¹⁶¹

There is a significant gap in the literature on the BEP principle: there are no criteria for how broadly the BEP principle can be utilized. In fact, the theoretical validity of the BEP relationship has come into question, and a call has been made to theoreticians for a detailed analysis of the BEP principle.¹⁶² In this work, I explore this issue. In order to achieve this, I have studied HAT reactions involving the abstraction of C–H bonds by CumO[•] under the same experimental conditions, for which many rate constants have been published.^{46,138,139,141,142,163–165} Additional unpublished rate constants have been provided by our experimental colleagues in Rome. The above studies, as well as many others, have used CumO[•] and the closely related *t*-butoxyl radical (*t*–BuO[•]) as models for reactive oxygen-centred radicals in studying oxidative damage of biomaterials,^{166–168} as well as in studying the mechanism and efficiency of antioxidants.^{169–173} Using these radicals to study biomolecular oxidation has an important caveat: The fundamental chemistry of these radicals is less well understood than often assumed.^{36,37,174}

The BDE^v of CumO–H is 106.7 kcal mol^{−1}, a value that is larger than all the C–H bonds studied herein. Therefore, these reactions are all exothermic on the order of 5–32 kcal mol^{−1}. The transition states can then be described as early, by the Hammond Postulate, and the BEP α values should all be less than 0.5.¹⁷⁵ Now, if the BEP principle holds as a LFER, the substrates should be considered as if the BDEs were controlled by substituent effects. For example, if one considers methane as the reference C–H bond model, the BDE of toluene should reflect the effect of replacing one hydrogen with a phenyl group. This is also the basis for schemes that utilize group additivity

4.1. Introduction

to predict molecular heats of formation.¹⁵²

Considering this group additivity-like approach, I have hypothesized that there should exist two general BEP relations for C–H bond: one in which the incipient radical is delocalized into a π -system (benzylic or allylic), and one in which the remaining alkyl radicals are largely localized. Plotting the experimental rate constants against literature BDEs (Figure 4.2) there appears to be evidence for the two BEP relations.

There is a considerable amount of scatter in Figure 4.2, which may be due to differences in experimental procedures. BDEs are measurable using a large number of different experimental techniques, and a great deal of data exists in the literature. Much of this data has conveniently been compiled in the *de facto* reference for BDEs: the *CRC Handbook of Bond Dissociation Enthalpies*.¹⁷⁶ However, caution must be taken with experimentally determined BDEs, as not all experimental methods give reliable data. For example, BDEs from the Bordwell¹⁷⁷ thermochemical cycle are possibly unreliable.^{142,178} This was demonstrated for the BDE of dimethyl sulfoxide (DMSO), for which the experimentally determined BDE is about 8 kcal mol⁻¹ lower than the best computational estimate.¹⁴² Therefore, quantum chemistry is a useful tool for studying BDEs, as it is relatively simple to compute BDEs. An arbitrary X–H bond dissociation enthalpy is given by:

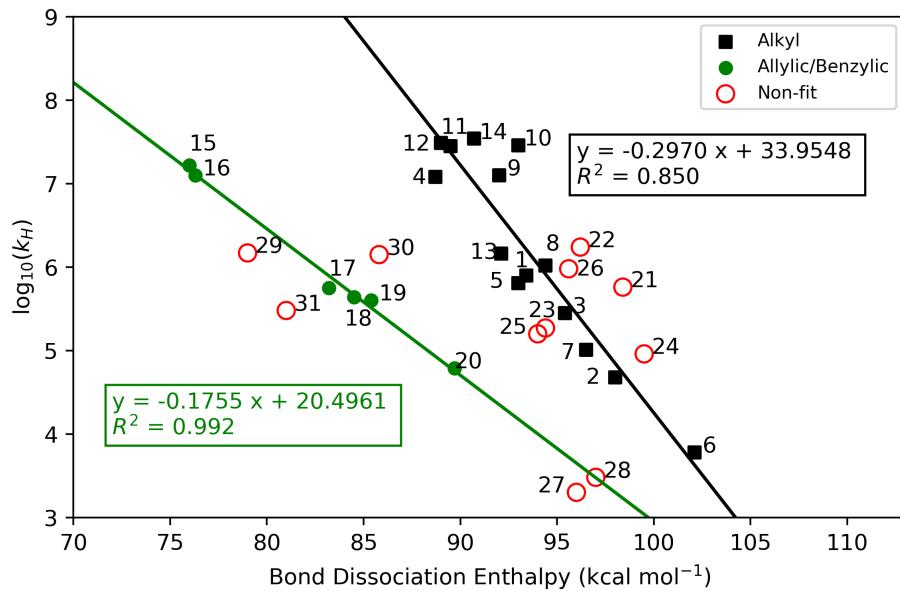
$$\Delta H(BDE) = H(X^\bullet) + H(H^\bullet) - H(X-H) \quad (4.1)$$

where $\Delta H(BDE)$ is the BDE, and the right-hand terms are the enthalpies of the radical product, the hydrogen atom, and the substrate, respectively. By computing the most accurate BDEs possible, we are able to discern if the BEP principle holds for C–H bond hydrogen abstraction by CumO[•].

DFT-based methods have been shown to give reliable relative BDEs, however, highly correlated wave function based methods are required to predict chemically accurate (sub-kcal mol⁻¹) BDEs.^{179–181} For this purpose, we shall use composite quantum chemical procedures. Unfortunately, due to the computational cost of some of these procedures, calculations are often limited to small molecules. Additionally, there is currently no literature that compares the ability of common composite methods to predict accurate BDEs. Therefore, another aim of the work is to determine which composite procedure can be used to calculate accurate BDEs for relatively large molecules.

^vCalculated using the ROCBS-QB3 composite method, *vide infra*.

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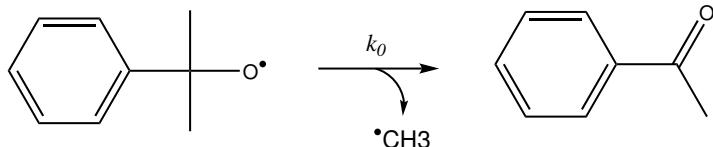
1	1,4-diazobicyclo[2.2.2]octane	2	2,2-dimethylbutane
3	2,2-dimethylbutane	4	Benzaldehyde
5	Diethyl ether	6	Dimethyl sulfoxide
7	Dioxane	8	Hexamethylphosphoramide
9	Morpholine	10	Piperazine
11	Piperidine	12	Pyrroldiine
13	Tetrahydrofuran	14	Triethylamine
15	1,4-cyclohexadiene	16	9,10-dihydroanthracene
17	Cumene	18	Diphenylmethane
19	Ethylbenzen	20	Toluene
21	Adamantane (2°)	22	Adamantane (3°)
23	Cycloheptane	24	Cyclohexane
25	Cyclooctane	26	Cyclopentane
27	Acetone	28	Acetonitrile
29	Benzyl alcohol	30	Dibenzyl ether
31	Triphenylmethane		

Figure 4.2: Bell-Evans-Polanyi plot of experimental rate constants (normalized for the number of equivalent hydrogen atoms) for HAT between CumO \cdot and substrates against literature BDEs. BDEs for dimethyl sulfoxide and hexamethylphosphoramide are from Ref. 142, while all other BDEs are from Ref. 176.

4.2. Methods

Experimental rate constants were either provided from unpublished results from our colleagues in Rome, or come from literature sources.^{46,138,139,141,142,163–165} All rate constants come from laser flash photolysis (LFP) experiments of CumO[•] with the substrates of interest. Nitrogen or argon saturated acetonitrile solvent and ambient conditions (298 K and 1 atm) were used in all cases. For those results that are unpublished, CumO[•] is generated by laser pulses at either 266 nm or 355 nm in solutions of excess dicumyl peroxide. Many of the literature results are also from the Bietti group, where the same procedure is used. Other results may have small variations in experimental details, however, all results are well time-resolved.

Observed rate constants (k_{obs}) are generally obtained from 2–8 averaged trials, which are reproducible to within 5%. Transient absorption decay traces of CumO[•] monitored at 485 nm are used to determine k_{obs} . The observed rate constant is plotted against concentration of substrate to provide the bimolecular HAT rate constant (k_H) as the slope ($k_{obs} = k_0 + k_H[\text{substrate}]$). The CumO[•] radical decays unimolecularly through the β -scission of a methyl group, giving acetophenone and a methyl radical, as shown in Scheme 4.1. The unimolecular decay rate constant^{182,183} for CumO[•](k_0) in acetonitrile is on the order of $6.3 \times 10^5 \text{ s}^{-1}$ at 298 K.



Scheme 4.1: Unimolecular decay of the cumyloxy radical.

All quantum chemical calculations were performed using the Gaussian 09 software package.¹¹³ Several composite quantum chemical methods that are implemented in Gaussian 09 were used in this work: W1BD, CBS-QB3 and the restricted open-shell variant ROCBS-QB3, CBS-APNO, G4 and the MP2 variant G4(MP2). An approach using ROCCSD(T) with locally-dense basis sets^{184,185} (LDBS) was also utilized in order to approximate W1BD results. Each of these methods is briefly described below.

4.2.1 Quantum chemical composite procedures

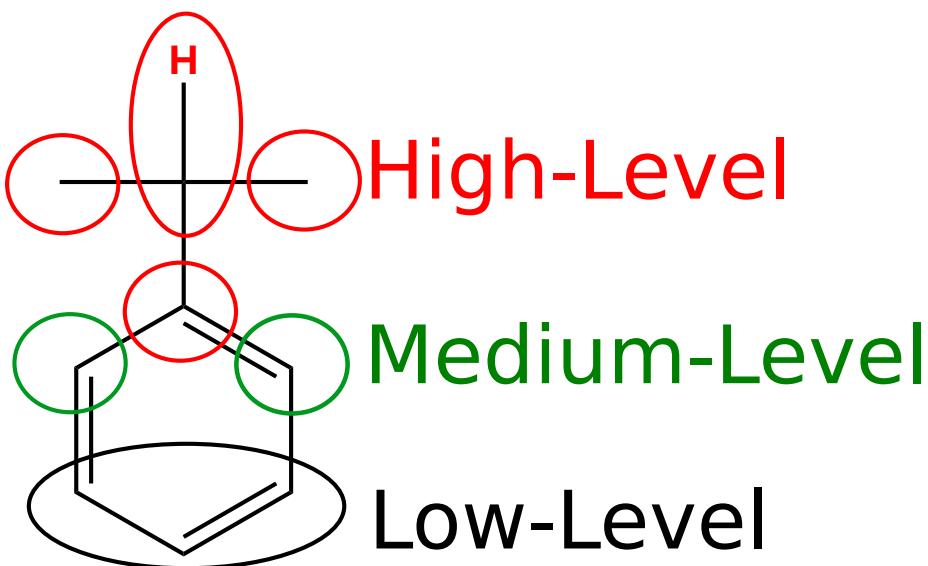
W1BD

4.2. Methods

The highest-accuracy method used is W1BD, which employs seven different calculations to obtain highly-correlated electronic energies, as well as thermochemically corrected quantities. This method is very computationally expensive, and thus cannot be applied to the larger species of interest in this work. Geometries and thermochemical corrections come from DFT-based B3LYP calculations with nearly complete cc-pVTZ+d basis sets. A frequency scaling factor of 0.985 is used to obtain thermochemical corrections. The electronic energy comes from several additive corrections involving the Brueckner Doubles⁹² (BD) variation of coupled cluster and large basis sets extrapolated to the complete basis set limit. Corrections for core-electron correlation and relativistic contributions are computed using an uncontracted variant of the cc-pVTZ+2df basis sets, known as MTsmall.¹⁸⁶

LDBS approach

Locally-dense basis sets have been used in the past to calculated BDEs for relatively large molecules.^{184,185,187} The principle behind LDBS is to use large basis sets to treat the atomic centres that are directly involved in the chemistry taking place, and use progressively smaller basis sets for “remote” portions of the molecule, thus taking advantage of error cancellation. We chose a method that best approximates W1BD results for a small subset of molecules. The scheme utilized herein involves geometry optimization and scaled frequency calculations from DFT-based B3LYP/cc-pVTZ+d, as used in the W1BD procedure. Single-point energy calculations are then performed using ROCCSD(T) and an LDBS partitioning scheme we denote as pc-3/3/2/1, demonstrated in Scheme 4.2, using the polarization consistent basis sets.⁶⁴



Scheme 4.2: Locally-dense basis set partitioning used in the calculation of BDEs. The scheme is referred to as pc-3/3/2/1, where for the shown cumene molecule, the centre of C–H cleavage and the immediately adjacent groups are treated with high-level pc-3 basis sets. The next groups are treated with medium-level pc-2 basis sets, and all other atoms/groups are treated with low-level pc-1 basis sets.

CBS methods

The Complete Basis Set (CBS) methods of Petersson and colleagues^{89–91,188} are widely used because of the relatively low computational cost (compared to other composite procedures), and well-established accuracy.^{189,190} CBS-QB3^{89,90} utilizes DFT-based B3LYP optimization and scaled frequencies (factor = 0.990) with modified triple-zeta Pople style basis sets. Electronic energies are obtained by extrapolation of medium basis set CCSD(T) and MP4SDQ. Small empirical corrections are added to achieve more accurate results compared to the parametrization sets.¹⁹¹ ROCBS-QB3 is a similar procedure to CBS-QB3, except spin-restricted wave functions are used in place of unrestricted wave functions. This is done to eliminate spin contamination, and the use of a restricted open-shell definition has been shown to produce more accurate BDEs.¹⁷⁹ The (RO)CBS-QB3 methods have been implemented for the first, second, and third periods of elements.

Atomic pair natural orbital (APNO) expansions are a method used for

4.2. Methods

averaging over multiple Slater determinants. The use of APNOs allows for small basis set extrapolation of higher order correlation energies to converge more rapidly to the complete basis set limit. This approach is used in the CBS-APNO method.⁹¹ Geometries and scaled frequencies (factor = 0.989) are obtained at the QCISD/6-311G(d,p) level of theory. Similar to CBS-QB3, the extrapolation of moderate basis set MP4SDQ and QCISD(T) results gives the electronic energy. An empirical correction is also used in CBS-APNO. Although CBS-APNO is more accurate, the expansion of APNOs makes CBS-APNO more computationally demanding than CBS-QB3. As a result, CBS-APNO has only been implemented for first and second row periods, and is thus less commonly used in the literature.

G_n methods

The Gaussian-*n* (G_n) series of methods originates from the Pople group,¹⁹² and G4 is the fourth generation. G4 utilizes moderately large basis sets and extrapolation techniques with CCSD(T) calculations to obtain highly correlated electronic energies. G4(MP2) uses MP2 in place of CCSD(T) and is thus less computationally expensive, but also gives a less complete description of electron correlation. Both methods use the B3LYP/6-31(2df,p) level of theory for optimization and frequency calculations with a frequency scaling factor of 0.9854. G4 results have been described as generally on par with CBS-QB3 results,^{189,190} but calculations are more computationally expensive.

4.2.2 Transition state calculations

Calculations were performed to identify the lowest energy TS complex of several reactions between CumO[•] and organic substrates. In all cases cisoid and transoid conformations were explored. All optimization calculations were performed at the B3LYP-D3(BJ)/6-31+G* level of theory, followed by single-point energy calculations at the LC- ω PBE-D3(BJ)/6-311+G** level of theory. The latter DFT-based method was selected to minimize delocalization error in the TS complex.¹⁰⁹ Transition states were visualized using the Chemcraft program¹⁹³ to confirm a single imaginary frequency connecting reactants to products. In some cases, a small secondary imaginary frequency was observed, indicating a TS complex that is not fully optimized. Necessary steps were taken to re-optimize the structures and eliminate the small imaginary frequencies, however, this was not always successful. Nonetheless, I am confident the structures reported herein sufficiently represent the true TS complex geometries and relative energies. Results from structures that

4.3. Comparison of composite method for the prediction of BDEs

are not fully optimized are indicated appropriately as such.

4.3 Comparison of composite method for the prediction of BDEs

In order to determine the best method for BEP principle analysis, and to investigate which is the most efficient yet accurate composite method, the BDEs of 50 species have been calculated. This set of species contains a wide variety of chemical functionalities with BDEs ranging from 75–113 kcal mol⁻¹, thus this set may be described as a comprehensive test of these methods for C-H BDEs. Given that W1BD is the most accurate method used, these results have been used for comparison to other composite methods. However, BDEs for only 33 out of the 50 species studied were able to be calculated using W1BD due to computational cost restrictions: hard disk capacity was insufficient for large systems. Therefore, literature BDEs from Luo¹⁷⁶ for the 49 species that have literature values in the set are also used for comparison. The literature and calculated BDEs are listed in Table 4.1.

4.3. Comparison of composite method for the prediction of BDEs

Table 4.1: Bond dissociation enthalpies of the species used to investigate the accuracy of composite methods. All values are in kcal mol⁻¹. Statistics are listed at the bottom of the table.

Molecule	Lit. ¹⁷⁶	W1BD	LDBS	CBS-QB3	ROCBS-QB3	CBS-APNO	G4	G4(MP2)
1,3-pentadiene	83.0	82.9	82.2	80.9	81.7	81.8	81.6	82.1
1,4-diazabicyclo[2.2.2]-octane	93.4	98.9	98.9	98.8	98.5	96.7	95.6	
1,4-pentadiene	76.6	76.2	76.0	74.2	75.0	75.2	75.1	75.7
2,2-dimethylbutane	98.0	99.3	99.1	99.4	99.3	99.7	97.5	96.7
2,3-dimethylbutane	95.4	97.8	97.7	97.9	97.8	98.0	96.2	95.5
2-methylbutane	95.8	97.3	97.2	97.3	97.1	97.3	95.9	95.5
Acetaldehyde	94.3	95.9	95.3	95.3	95.7	95.5	94.9	94.8
Acetone	96.0	96.9	96.4	96.2	96.7	97.1	95.4	95.0
Acetonitrile	97.0	96.9	96.6	96.2	96.6	96.5	96.3	96.3
Adamantane (2°)	98.4		100.9	100.5	100.4	100.9	97.8	96.3
Adamantane (3°)	96.2		100.3	99.9	99.9	100.3	95.7	
Benzaldehyde	88.7		90.9	91.5	91.4	91.0	89.3	88.2
Benzene	112.9	113.1	112.7	115.4	113.0			113.0
Benzyl Alcohol	79.0		84.4	84.3	83.2	83.9	83.4	83.6
Cumene	83.2		87.9	87.9	86.9		86.9	86.7
Cycloheptane	94.0		96.0	96.0	95.8	96.1	93.9	92.9
Cyclohexadiene	76.0	76.3	76.2	74.3	75.0	75.2	75.5	
Cyclohexane	99.5	99.2	99.1	99.4	99.3	99.6	97.5	96.8

4.3. Comparison of composite method for the prediction of BDEs

Molecule	Lit. ¹⁷⁶	W1BD	LDBS	CBS-QB3	ROCBS-QB3	CBS-APNO	G4	G4(MP2)
Cyclooctane	94.4	92.6	92.6	92.4	92.8	90.2	89.1	
Cyclopentane	95.6	96.3	96.1	96.5	96.3	95.6	95.0	
Cyclopropane	106.3	109.0	108.5	109.3	109.2	109.5	108.2	108.0
Dibenzyl ether	85.8		83.6	84.3	82.7			79.6
Diethyl ether	93.0	95.3	95.1	95.6	95.5	95.4	93.8	93.1
Dihydroanthracene	76.3		80.4	80.9	78.1			79.9
Dimethylamine	94.2	92.6	92.4	92.9	92.8	92.7	92.0	91.9
Dimethylsulfoxide	94.0	102.0	101.7	102.3	102.3		100.9	100.6
Dioxane	96.5	97.3	97.3	97.7	97.6	97.4	95.7	94.9
Diphenylmethane	84.5		84.1	85.3	82.8			84.5
Ethane	100.5	101.3	99.3	101.7	101.5	101.8	100.7	100.7
Ethylbenzene	85.4		88.3	88.6	87.6	89.3	87.6	87.7
Ethylene	110.9	110.8	110.3	110.6	110.9	111.1	109.9	110.2
Fluorene	82.0		82.4	83.6	81.9			81.2
Formaldehyde	88.0	88.6	88.0	89.1	88.9	88.2	88.2	87.9
Hexamethyl-phosphoramide		93.8	94.1	93.9				88.5
Indene	83.0		80.6	80.4	80.1	81.2	79.0	78.3
Methane	105.0	105.0	104.4	105.4	105.2	105.4	104.5	104.6
Methanol	96.1	96.4	96.0	96.9	96.8	96.6	96.0	95.8
Methylamine	93.9	93.1	92.8	93.4	93.3	93.3	92.7	92.8
Morpholine	92.0		93.4	93.4	93.3	93.3	91.8	91.1
N,N-dimethylacetamide (acetyl)	91.4	99.6	99.4	99.5	99.5	100.1	97.6	96.8

4.3. Comparison of composite method for the prediction of BDEs

Molecule	Lit. ¹⁷⁶	W1BD	LDBS	CBS-QB3	ROCBS-QB3	CBS-APNO	G4	G4(MP2)
Piperazine	93.0	93.4	93.5	93.6	93.5	93.4	91.9	91.2
Piperidine	89.5	92.1	92.2	92.3	92.2	92.1	90.7	90.0
Propane	100.9	101.6	101.3	102.0	101.8	102.1	100.7	100.4
Pyrrolidine	89.0	90.8	90.6	90.8	90.7	90.7	89.5	89.0
Tetrahydro-2H-pyran	96.0	96.3	96.2	96.6	96.5	96.3	94.7	93.9
Tetrahydrofuran	92.1	93.7	93.3	93.9	93.8	93.6	92.2	91.6
Toluene	89.7	90.5	90.1	90.6	89.7	91.9	89.8	90.2
Trichloromethane	93.8	93.5	93.4	93.8	93.7	92.4	92.0	92.0
Triethylamine	90.7	—	91.4	91.3	91.2	91.4	89.4	88.4
Trifluormethane	106.4	107.2	106.6	107.4	107.4	106.8	105.8	105.0
Statistics	Lit.	W1BD	LDBS	CBS-QB3	ROCBS-QB3	CBS-APNO	G4	G4(MP2)
Number of BDEs (N)	49	33	50	50	50	40	43	50
MAE (Lit.)	0.82	1.60	1.88	1.64	1.35	1.21	1.57	
Max. Error	1.59	2.41	2.63	3.15	1.85	4.19	6.23	
Min. Error	-8.22	-8.04	-8.26	-8.25	-8.74	-6.86	-6.58	
MAE (W1BD)	0.22	0.32	0.18	0.20	0.70	0.70	0.88	
Max. Error	2.00	2.01	1.26	1.08	2.05	2.05	2.84	
Min. Error	-0.09	-2.37	-0.35	-1.39	0.37	0.37	0.02	

4.3. Comparison of composite method for the prediction of BDEs

Mean absolute error (MAE) is used to assess the quality of computational methods, where errors are calculated with respect to benchmark values for a given data set.¹⁹⁴ The MAE is calculated as

$$\text{MAE} = \frac{1}{N} \sum |E_{ref} - E_{calc}| \quad (4.2)$$

where, for a set of N reference values, the MAE is the average of the mean differences of the reference energy (E_{ref}) and the calculated value (E_{calc}). The MAE with respect to W1BD and literature shall be reported herein as “MAEW1BD (MAELit.)”. An additional semi-quantitative metric which I used to evaluate the accuracy of composite procedures to reproduce experimental results is a bar chart that summarizes the number of deviations from literature within given error ranges. This bar chart is reported in Figure 4.3. Note that calculations for some species with some methods failed to converge, thus number of BDEs out of 49 are also shown in Figure 4.3. Also, an alternative method that I shall utilize for reporting these data is through the use of one-to-one plots, in which BDEs from two methods are directly compared. An ideal plot should have a slope = 1 and y-intercept = 0.

Comparing W1BD results to literature, the MAE is 0.82 kcal mol⁻¹, and the majority of the data match to within 1–2 kcal mol⁻¹ of literature. Thus, W1BD is largely consistent with the literature values. Additionally, the one-to-one plots comparing W1BD to literature in Figure 4.4 show reasonable agreement with slope of 0.98 and a y-intercept of 2.35. There are, however, two notable outliers: DMSO^{vi} and *N,N*-dimethylacetamide, for which experiment underestimates the BDEs by -8.0 and -8.2 kcal mol⁻¹, respectively. DMSO and *N,N*-dimethylacetamide are consistently outliers amongst all composite methods, suggesting the literature BDEs are incorrect.

^{vi}The experimental BDE for dimethyl sulfoxide was previously identified as being inaccurate by Salamone et al.¹⁴²

4.3. Comparison of composite method for the prediction of BDEs

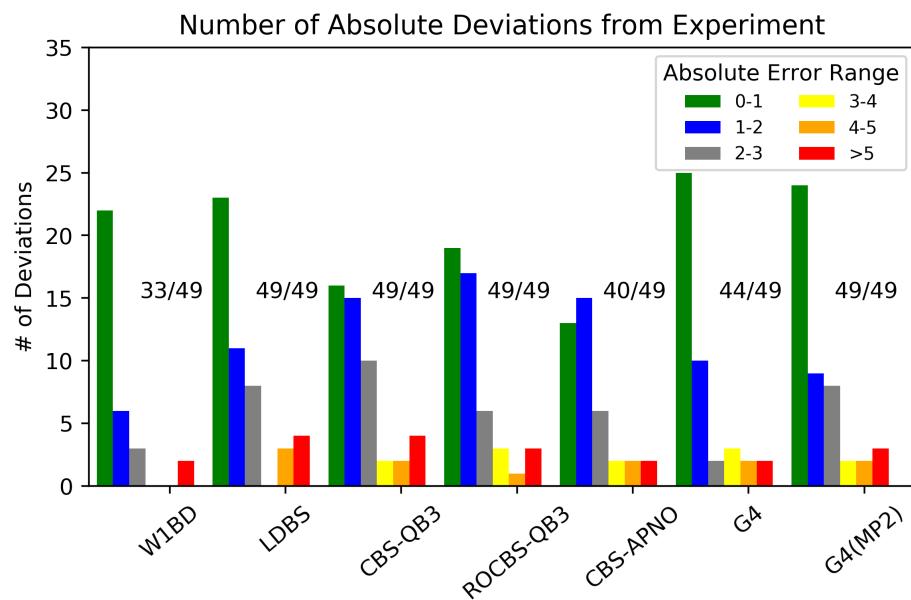


Figure 4.3: Summary of deviations of BDEs from literature or composite quantum chemical methods. Errors are units of kcal mol^{-1} and are relative to Ref. 176. Numbers out of 49 represent the total number of data points that were computed for the given method.

4.3. Comparison of composite method for the prediction of BDEs

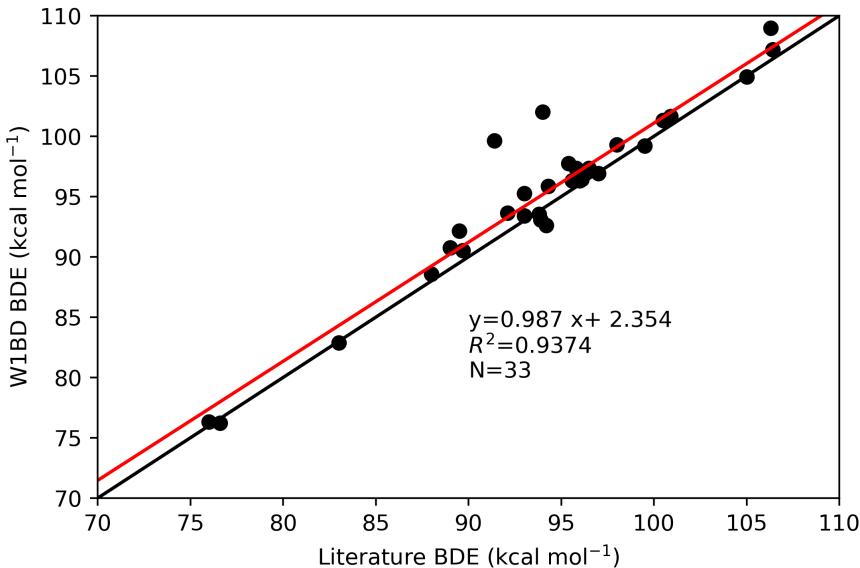


Figure 4.4: One-to-one plot of BDEs from literature¹⁷⁶ and as calculated by the W1BD composite method. The red line represents the least squares line of best fit, while black line represents a perfect one-to-one correlation.

The method that gives the best combined agreement with W1BD and literature is ROCBS-QB3 with an MAE = 0.18 (1.64) kcal mol⁻¹. It is also apparent, from the one-to-one plots in Figure 4.5, that ROCBS-QB3 matches well with literature and experiment. In comparison, CBS-QB3 has an MAE = 0.32 (1.88) kcal mol⁻¹, while CBS-APNO has an MAE = 0.20 (1.40) kcal mol⁻¹. The LDBS approach also performs well with an MAE = 0.22 (1.60) kcal mol⁻¹. The G4 method deviates from the W1BD reference by about 0.5 kcal mol⁻¹ more, however, it appears to give reasonable agreement with experimental results (MAE = 0.70 (1.21) mol). The use of the MP2 variant of G4 gives somewhat questionable results, with an MAE of 0.88 (1.60) kcal mol⁻¹, as well as a large outlier of 6.2 kcal mol⁻¹ that is not present in the other data from composite methods. One-to-one plots of all other methods are presented in Appendix B.

4.4. Analysis of the Bell-Evans-Polanyi principle

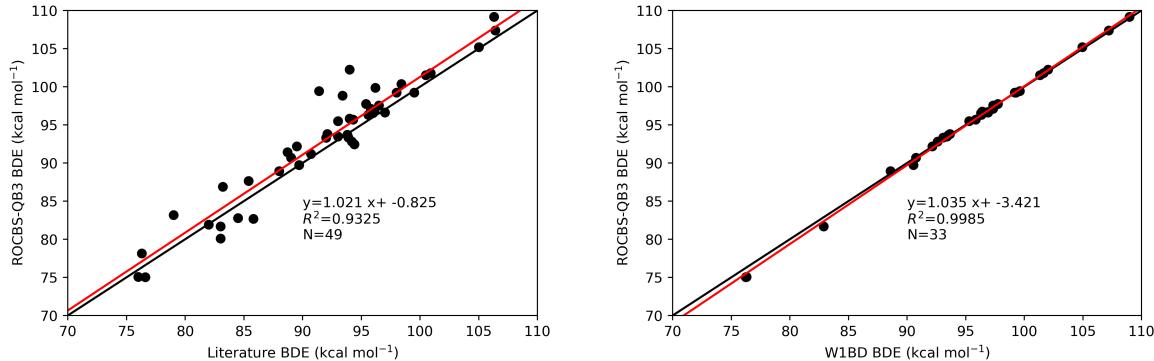


Figure 4.5: One-to-one plot comparing calculated BDEs calculated by the ROCBS-QB3 to reference literature¹⁷⁶ and W1BD BDE values, respectively. The red line represents the least squares line of best fit, while black line represents a perfect one-to-one correlation.

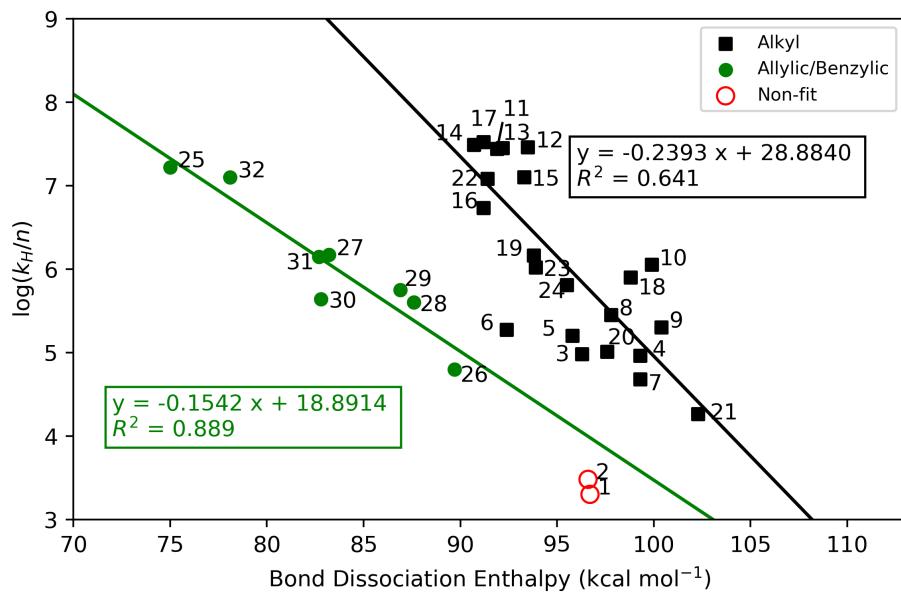
In summary, ROCBS-QB3 performs best for the calculation of C–H BDEs while G4(MP2) performs worst. Given these data, and considering the relative computational cost, I recommend the ROCBS-QB3 for the calculation of accurate BDEs, particularly for large molecules for which more expensive computational methods are not possible. Importantly, we can now confidently continue investigating the BEP relationships using reliably calculated BDE data from the ROCBS-QB3 method. Furthermore, these results can be extended to even larger systems as the ROCBS-QB3 approach is one of the least computationally-expensive composite methods. For example, calculations on the cyclohexane molecule, which take about 20 minutes using ROCBS-QB3 on SGI Altix compute nodes with 6 processors and 8 GB RAM, while G4 takes approximately 27 times longer, the LDBS approach takes about 500 times longer, and W1BD takes about 1100 times longer.

4.4 Analysis of the Bell-Evans-Polanyi principle

We turn now to the application of accurate BDEs to the BEP principle. Experimental HAT rate constants have been collected for 32 reactions involving CumO[·] and organic substrates. The BEP plot of the logarithm of rate constants divided by the number of equivalent H atoms (i.e., normalized) against BDEs is shown in Figure 4.6.

As with the experimental results in Figure 4.2, there clearly exists two

4.4. Analysis of the Bell-Evans-Polanyi principle



1	Acetone	2	Acetonitrile
3	Cyclopentane	4	Cyclohexane
5	Cycloheptane	6	Cyclooctane
7	2,2-dimethylbutane	8	2,3-dimethylbutane
9	Adamantane (2°)	10	Adamantane (3°)
11	Diethyl amine	12	Piperazine
13	Piperidine	14	Pyrrolidine
15	Morpholine	16	Propylamine
17	Triethylamine	18	1,4-diazobicyclo[2.2.2]octane
19	Tetrahydrofuran	20	Dioxane
21	Dimethyl sulfoxide	22	Benzaldehyde
23	Hexamethylphosphoramide	24	Diethyl ether
25	1,4-cyclohexadiene	26	Toluene
27	Benzyl alcohol	28	Ethylbenzene
29	Cumene	30	Diphenylmethane
31	Dibenzyl ether	32	9,10-dihydroanthracene

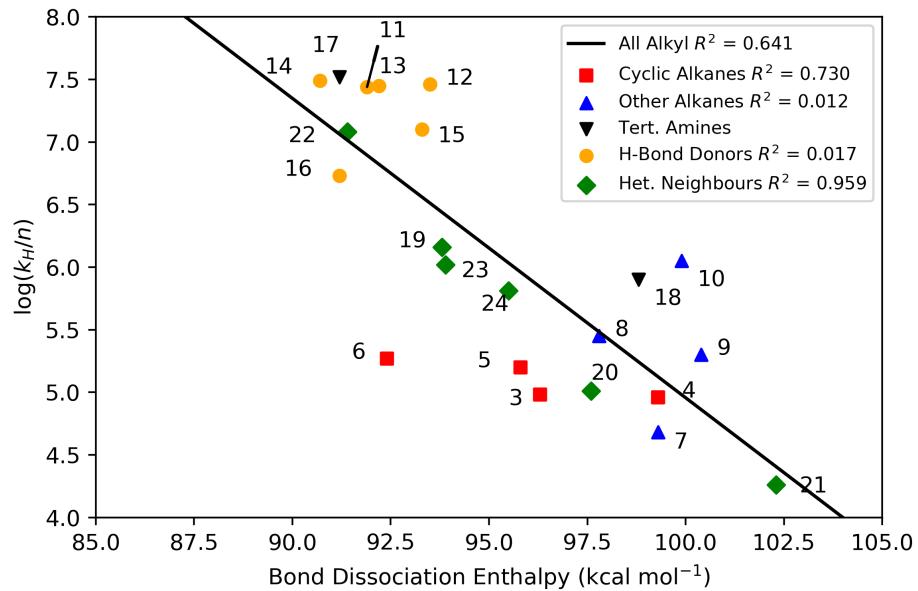
Figure 4.6: Bell-Evans-Polanyi plot of experimental rate constants (normalized for the number of equivalent hydrogen atoms) for HAT between CumO[•] and substrates against BDEs calculated using the ROCBS-QB3 method.. Acetone and acetonitrile are note included in fitting as the experimental rate constants are approximate.

4.4. Analysis of the Bell-Evans-Polanyi principle

distinct regions in Figure 4.6. This is congruent with our initial hypothesis that there should exist two linear relations: one for allylic/benzylic C–H bonds, and another for alkyl C–H bonds. However, there remains a considerable amount of scatter in the data, thus correlation of the expected BEP relations is poor. For the allylic/benzylic series of C–H BDEs which result in a radical which is delocalized, the correlation coefficient is 0.89. This result is consistent with work of Pratt et al.,¹⁶⁰ which found a BEP plot correlation coefficient of 0.82 for the abstraction of C–H bonds from models for unsaturated fatty acids. Most of the rate constants used in the work of Pratt et al. are for the abstraction of C–H by peroxy radicals, which were obtained through an experimental method that gives estimated HAT rate constants with large associated errors. Thus, they suggested that the degree of scatter is associated with experimental errors. The same however cannot be said for the rate constants associated with this work. Therefore, there must be additional physico-chemical factors at play.

The alkyl C–H BDEs show very weak correlation with CumO[•] HAT rate constants, with a correlation coefficient of 0.63. One possibility is that applying the BEP principle to such a large grouping of substrates is inappropriate. Thus, I have re-plotted this data in Figure 4.7, breaking the data into several smaller chemical groupings: cyclic alkanes, other alkanes, tertiary amines (Tert. Amines), hydrogen bond donating (H-Bond Donors) species, and other C–H bonds with heteroatom neighbours (Het. Neighbours). Doing so appears to reveal one well-correlated trend for C–H bonds with heteroatom neighbours ($R^2 = 0.96$). There are two data points for the tertiary amines, thus the points should not be fit to a line, however it is unclear why they do not fit into the other heteratomic neighbours trend. The cyclic alkanes are poorly correlated ($R^2 = 0.73$). Extremely poor correlation is observed for both the hydrogen bond donating species ($R^2 = 0.02$) and other alkanes ($R^2 = 0.01$). There are no evident reasons on the basis of group-additivity based arguments that explain the poor correlations observed. Thus, the lack of simple relationships is perhaps evidence against the validity of the BEP principle. However, before making any conclusions, we must consider if there are any explanations that arise from examining the transition state structures.

4.4. Analysis of the Bell-Evans-Polanyi principle



3	Cyclopentane	4	Cyclohexane
5	Cycloheptane	6	Cyclooctane
7	2,2-dimethylbutane	8	2,3-dimethylbutane
9	Adamantane (2°)	10	Adamantane (3°)
11	Diethyl amine	12	Piperazine
13	Piperidine	14	Pyrrolidine
15	Morpholine	16	Propylamine
17	Triethylamine	18	1,4-diazobicyclo[2.2.2]octane
19	Tetrahydrofuran	20	Dioxane
21	Dimethyl sulfoxide	22	Benzaldehyde
23	Hexamethylphosphoramide	24	Diethyl ether

Figure 4.7: Further breakdown of Bell-Evans-Polanyi plot of experimental rate constants (normalized for the number of equivalent hydrogen atoms) for HAT between CumO[•] and substrates.

4.5. Transition state analysis

4.5 Transition state analysis

In order to determine if there are any reasons for the breakdown of the BEP principle, I have calculated TS structures for 20 of the reactions at the LC- ω PBE-D3(BJ)/6-311+G(2d,2p)//B3LYP-D3(BJ)/6-31+G* level of theory. The calculated reaction free-energy barrier heights (ΔG^\ddagger) are listed in Table 4.2, along with the decomposition into enthalpic and entropic terms: $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$.

First, consider some general features associated with the TS complexes listed in Table 4.2. One factor that may lead to deviations from the BEP principle is the possibility for different HAT reaction mechanisms, i.e. direct HAT or PCET. Consider first the reaction of toluene with CumO[•]. As this reaction is similar to the self-exchange reaction of the benzyl-toluene couple as described by DiLabio and Johnson,²⁶ one might expect the reaction to proceed via PCET. The lowest-energy TS complex has a partially π -stacked conformation with the rings oriented approximately 40° relative to one another. Examination of the SOMO and HOMO reveals no π - π partial bonding interaction, as can be seen in Figure 4.8. The electron density of the SOMO is largely localized on the toluene portion of the complex. This is likely due to the additional non-conjugated carbon centre of CumO[•], which prevents an additional electron channel for PCET to occur. Therefore, this reaction takes place through direct HAT, as has been previously described.¹³⁸ This behaviour is specific to the CumO[•] radical, thus all the reactions likely also take place through a direct HAT mechanism, and this should not factor into the deviations in the observed BEP principle relationships.

For all of the TS structures of the reactions in Table 4.2, a conformation that maximizes non-covalent interactions while minimizing steric repulsion is adopted. In the cases of acetone, acetonitrile, hexamethylphosphoramide (HMPA), and DMSO, a very weak hydrogen bonding interaction is formed between the X=O (or C≡N for acetonitrile) moieties and the C-H of the methyl of CumO[•]. In all but two cases, this involves a cisoid (partially-stacked) complex so that dispersion interactions are maximized. The two outliers are benzaldehyde and cyclooctane. In order for benzaldehyde to adopt a cisoid TS structure, there are two possibilities. First, a T-shaped conformation could be adopted, rather than a slipped-parallel π -stacked conformation. On the basis of the benzene-benzene non-covalently bound dimer,¹⁹⁵ this conformation is very slightly favourable by circa 0.1 kcal mol⁻¹. However, this would require a rotation of nearly 90° of the C(CH₃)₂O[•] of CumO[•], which has an energetic cost^{vii} of 4.3 kcal mol⁻¹, and so this conformation is unlikely. On the other hand, the C(CH₃)₂O[•] of

4.5. Transition state analysis

Table 4.2: Reaction barrier heights for reactions of substrates with CumO[•] calculated in the gas phase at 298 K at the LC- ω PBE-D3(BJ)/6-311+G(2d,2p)//B3LYP-D3(BJ)/6-31+G* level of theory. All values are in units of kcal mol⁻¹. ID numbers match those in Figure 4.6 [†]TS structure contains small additional imaginary frequency.

ID	Substrate	ΔG^\ddagger	ΔH^\ddagger	$-T\Delta S^\ddagger$
Non-fit				
1	Acetone	17.6	3.6	14.0
2	Acetonitrile	18.3	6.8	11.5
Cyclic Alkanes				
3	Cyclopentane [†]	13.5	0.5	13.0
4	Cyclohexane	11.8	1.2	10.6
6	Cyclooctane [†]	13.6	-0.5	14.1
Other Alkanes				
7	2,2-dimethylbutane	11.2	-0.8	12.0
8	2,3-dimethylbutane	11.2	1.1	10.2
9	Adamantane (2°)	12.6	0.6	12.0
10	Adamantane (3°)	10.8	-1.0	11.8
Tert. Amine and H-Bond Donor				
11	Diethylamine	10.0	-3.0	13.0
18	1,4-diazobicyclo[2.2.2]octane	11.8	-0.5	12.3
Heteroatom Neighbours				
20	Dioxane	11.4	-0.4	11.8
21	Dimethyl sulfoxide	15.7	3.8	11.9
22	Benzaldehyde [†]	12.6	-0.3	12.9
23	Hexamethylphosphoramide	12.1	-2.3	14.4
24	Diethyl ether	7.6	-3.8	11.4
Allylic/Benzylic				
25	1,4-cyclohexadiene	12.0	-1.0	13.0
26	Toluene	14.7	0.9	13.7
29	Cumene	11.4	-1.9	13.3
30	Diphenylmethane [†]	13.6	-1.0	14.5
32	9,10-dihydroanthracene [†]	11.4	-3.2	14.6

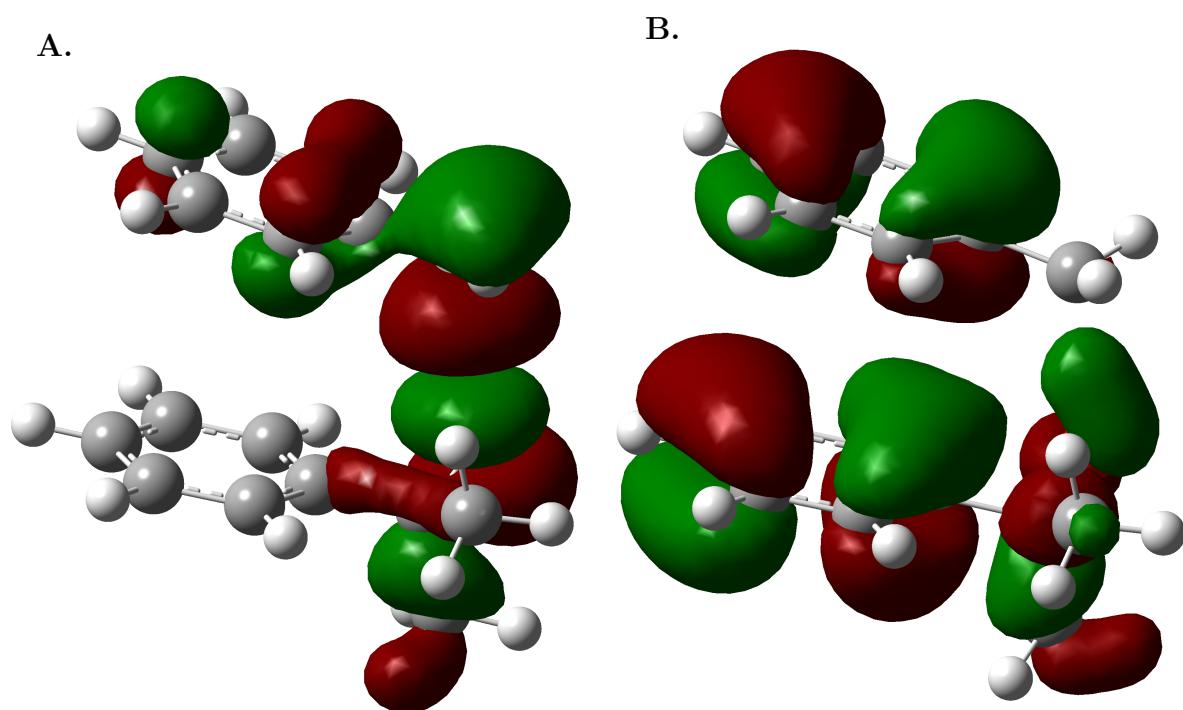


Figure 4.8: Structures of TS for HAT between CumO[•] and toluene with **A.** SOMO and **B.** HOMO. The elements are coloured as grey for carbon, white for hydrogen, and red for oxygen.

4.5. Transition state analysis

CumO[•] could rotate to accommodate a partially slipped-parallel π -stacking conformation in the TS complex. Note that I was unable to obtain TS structures for either of the described possible cisoid conformations for the benzaldehyde-CumO[•] TS complex, as geometry optimization calculations did not converge. For cyclooctane, the difference in free energy between the cisoid and transoid TS structures is 1.8 kcal mol⁻¹, however both structures were unable to be fully optimized and contain a secondary small imaginary frequency. The reason for the transoid TS structure being more stable is somewhat unclear, but it is possible that the non-optimal nature of the TS structures is the cause. Furthermore, it is possible that the cyclooctane molecule undergoes a conformational change in forming the TS complex which was not accounted for in these calculations. Cyclooctane has many conformations that are close in relative energy.¹⁹⁶

TS complex structures and mechanism aside, there is one striking feature in the reaction barriers calculated for HAT reactions involving CumO[•]: all the the reactions studied are entropy-controlled at 298 K. This means that the free-energy barrier, and thus rate constant, is controlled by the entropic contributions, rather than the enthalpic contributions, i.e., $-T\Delta S^\ddagger > \Delta H^\ddagger$. From the results in Table 4.2, it can be said that $-T\Delta S^\ddagger >> \Delta H^\ddagger$ for hydrogen abstraction by CumO[•]. One interpretation of these results is that CumO[•] is so highly reactive that HAT is governed by trajectory, orientation, and degrees of freedom, factors that are normally associated with the A-factor in Arrhenius theory. In fact, in many cases, ΔH^\ddagger is calculated to be negative with respect to the separated reactants. This implies that a pre-reaction complex is formed, which, as was demonstrated in Chapter 3, can have significance on HAT reactivity with respect to the magnitude of the A-factor. Pre-reaction complex structures were not calculated in this work, however in some cases the systems have been studied in combined experimental and theoretical work. Some examples of previously calculated CumO[•] + substrate pre-reaction complex binding enthalpies are: HMPA^{viii} $\Delta H \approx -6$ kcal mol⁻¹, DMSO $\Delta H \approx -5$ kcal mol⁻¹, and 1,4-diazobicyclo[2.2.2]octane (DABCO)³⁷ $\Delta H \approx -0.1$ kcal mol⁻¹. Note that the calculated enthalpic barrier herein is -0.5 kcal mol⁻¹ for DABCO, a result that can be ascribed to differences in computational methods. In Ref. 37, no dispersion correction was used, thus accounting for a less stable TS complex and pre-reaction complex. The calculated difference in enthalpy from pre-reaction complex to TS complex for DABCO was found to be only

^{vii}Calculated at the LC- ω PBE-D3(BJ)/6-311+G(2d,2p) level of theory.

4.6. Is the Bell-Evans-Polanyi principle valid?

1.0 kcal mol⁻¹.

The fact that hydrogen abstraction by CumO[•] is entropy-controlled is perhaps unsurprising, given the work of Finn et al.³⁶, which demonstrated that HAT reactions involving various organic substrates and the closely related radical *t*-BuO[•] are also entropy-controlled at room temperature. Furthermore, it has been shown that CumO[•] and *t*-BuO[•] display very similar hydrogen atom abstraction reactivities.^{138,198–200} It is surprising then that these radicals remain so often applied as proxies for reactive oxygen species in kinetic studies. Future work should use extreme caution in applying CumO[•] and *t*-BuO[•] as chemical probes, as been noted in the past.^{36,37,138} Note also that it is uncommon to encounter entropy-controlled reactions in organic chemistry, and they are often associated with non-Arrhenius behaviour. Other examples of reported entropy-controlled reactions include the addition of a carbene across a multiple bond,^{201,202} and radical-radical recombination reactions.²⁰³

Classical physical organic chemical literature can explain why the reactions which are entropy-controlled do not follow “normal” LFERs.²⁰⁴ Black-adder and Hinshelwood²⁰⁵ defined three classifications for different types of LFERs, the first of which applies to the BEP principle: A series of reactions with constant entropy are controlled by enthalpy changes that are based on electronic effects that do not affect the form of the TS. Therefore, reaction rates that involve non-isoentropic TS complex formation will not correlate with bond strengths, as is observed herein. It seems prudent at this point to suggest that expecting reactions to be isoentropic with respect to transition state formation is an over-simplification, especially given the number of factors that contribute to entropy in solvent phase chemistry.

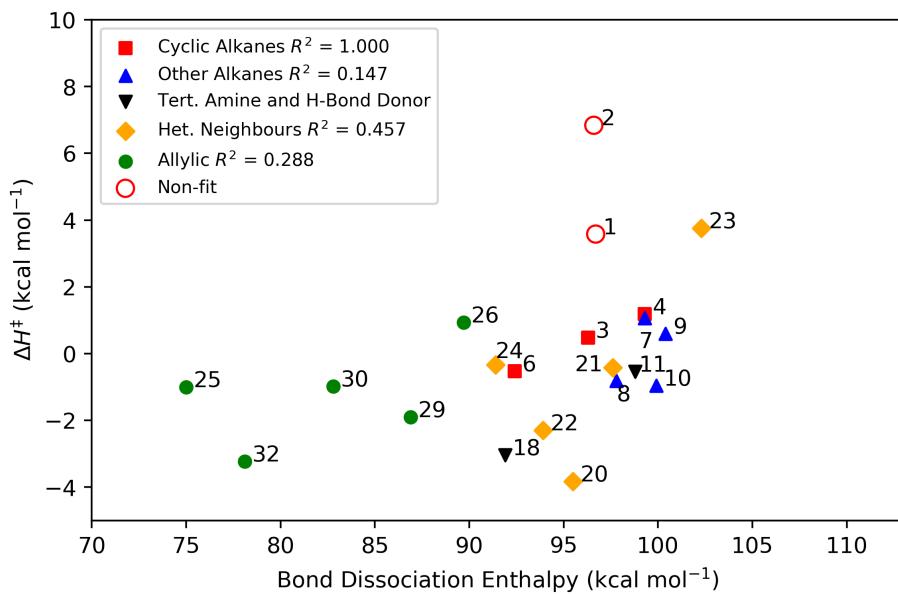
4.6 Is the Bell-Evans-Polanyi principle valid?

The question still remains whether the BEP principle is valid or not. Recall from Equation 2.93 that E_a is related directly to ΔH^\ddagger . Thus, if the BEP principle still holds for HAT reactions between CumO[•] and organic substrates, then the calculated values of ΔH^\ddagger should be a function of C–H BDE. These data are plotted in Figure 4.9.

Perhaps unsurprisingly at this point, there is once again a great deal of scatter in the data. The cyclic alkanes fit into a linear relationship with perfect correlation ($R^2=1.00$). However, all other chemical groupings show

^{viii}DMSO and HMPA were studied in Ref. 142 at the B3LYP-DCP¹⁹⁷/6-31+G(2d,2p) level of theory

4.6. Is the Bell-Evans-Polanyi principle valid?



1	Acetone	2	Acetonitrile
3	Cyclopentane	4	Cyclohexane
6	Cyclooctane	7	2,2-dimethylbutane
8	2,3-dimethylbutane	9	Adamantane (2°)
10	Adamantane (3°)	11	Diethyl amine
18	1,4-diazobicyclo[2.2.2]octane	20	Dioxane
21	Dimethyl sulfoxide	22	Benzaldehyde
23	Hexamethylphosphoramide	24	Diethyl ether
25	1,4-cyclohexadiene	26	Toluene
29	Cumene	30	Diphenylmethane
32	9,10-dihydroanthracene		

Figure 4.9: Bell-Evans-Polanyi plot of calculated enthalpic barriers for HAT between CumO[•] and substrates against BDEs calculated using the ROCBS-QB3 method.

4.6. Is the Bell-Evans-Polanyi principle valid?

almost no correlation. Therefore, the correlation seen for the cycloalkanes is an adventitious example of the BEP principle showing a linear relation between ΔH^\ddagger and BDE. Even the substrates with allylic/benzylic C–H bonds show only weak correlation in a BEP relation, although the experimental results show a reasonable correlation between $\log(k_H/n)$ and calculated BDEs. Therefore, the experimental results are likely serendipitous, especially considering the reactions are entropy-controlled and non-isoentropic.

Further analysis of the allylic/benzylic relation demonstrates a clear breakdown in the BEP principle. If one begins with toluene with a BDE of 89.7 kcal mol⁻¹ and ΔH^\ddagger of 0.9 kcal mol⁻¹, then the addition of two methyl substituents forms cumene, with a BDE of 86.9 kcal mol⁻¹ and ΔH^\ddagger of -1.9 kcal mol⁻¹, indicating the stabilization of the TS by substituents. However, if one adds another phenyl group instead of two methyl groups, diphenylmethane is obtained, which has a BDE of 82.8 kcal mol⁻¹. This indicates that phenyl is a better radical stabilizing group, however ΔH^\ddagger is -1.0 kcal mol⁻¹, which is higher than that of cumene. The difference can be partially attributed then to differences in progress along the reaction coordinate. Evidence of this difference is the spin density localized on the O-centre of CumO[•] in the TS complex, which should go to zero as the reactants move to products. The O[•] spin densities are 0.533 e⁻, 0.589 e⁻, and 0.600 e⁻ for toluene, cumene, and diphenylmethane, respectively. Therefore, the progress along the reaction coordinate is furthest for toluene, and progressively less far for cumene and diphenylmethane. Note, however, that the O[•] spin densities for cyclopentane, cyclohexane, and cyclooctane are 0.461 e⁻, 0.425 e⁻, and 0.420 e⁻, respectively. Therefore the progress along the reaction coordinate for the cycloalkanes is not the same, even though the enthalpic barriers do correlate with BDE.

Such contradictory data makes it very difficult to draw any conclusions. Instead, I shall make some suggestions as to why the BEP principle is an incomplete theoretical construct for studying HAT reaction of CumO[•] with organic substrates:

1. HAT reactions between CumO[•] and these organic substrates may be decidedly exothermic, resulting in reactions with no enthalpic barrier associated with the breaking of a C–H bonds and the formation of an O–H bond. This is supported by the fact that the calculated enthalpic barriers are all very low or even negative. Therefore, any remaining nominal activation energy is a result of stereo-electronic interactions between CumO[•] and the substrate. Also, the high reactivity of CumO[•] also suggests that abstraction from the weakest bond in a substrate

4.6. Is the Bell-Evans-Polanyi principle valid?

will not always occur. The site of abstraction will most likely be determined by the orientation of the substrate upon collision. This is likely an additional reason why $\log k_H/n$ does not correlate with the calculated C–H BDEs.

2. Polar effects have been shown to be extremely important in the stability of the TS complex.²⁰⁶ The species involved in HAT reactions are often neutral radicals, thus the influence of charge transfer in the TS complex can have important implications. Consider the TS of a generic HAT reaction in Scheme 4.3, there are four obvious resonance forms. Oxygen-centred radicals are electrophilic in nature, thus the importance of the third resonance structure increases. The BEP principle does not account for polarity in the TS complex, as these effects are not captured by the BDE of the substrate, thus ΔH^\ddagger does not correlate well with BDE. This issue was addressed by Roberts and Steel²⁰⁷, who suggested an extension of the BEP principle to include simple empirical parameters that capture the polar effects in the transition state.



Scheme 4.3: A generic HAT transition state structures and possible resonance forms.

3. The BEP principle is an over-simplification that does not capture nearly enough of the physics associated with the deceptively complex hydrogen abstraction reactivity of CumO[•] (or *t*-BuO[•]). Therefore, I suggest that the BEP principle should not be used as a tool for predicting activation energies or rate constants. One method that has been popularized by Mayer is the use of Marcus cross-relations.²⁹ This predictive method has also been used to explain reactions that have negative enthalpic barriers.¹²⁷ An alternative approach is that of Zavitsas, that predicts activation energies based on so-called “triplet repulsion”^{ix} and radical delocalization.^{208,209} It is clear from the analysis herein that the BEP principle is valid only as a conceptual framework, rather than a true linear relationship.

^{ix}Zavitsas uses the term “triplet repulsion” to describe repulsion between the parallel spins

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of the hydrogen atom acceptor and donor atoms ($\uparrow\downarrow\uparrow$ or $\downarrow\uparrow\downarrow$) in the TS complex.

Chapter 5

Do non-redox active metal cations have the potentials to behave as chemo-protective agents? The Effects on Metal Cations on HAT Reaction Barrier Heights

5.1 Introduction

Metal cations are ubiquitous in biological systems and play an important role in biological function. As such, there is a great deal of interest in studying metals in biological systems. Proteins in particular are often associated with metals, and in the worldwide Protein Data Bank,^{210,211} over one-third of crystal structures contain metals. Redox active metals, such as copper and iron, act as co-factors in metalloenzymes for important catalytic processes.²¹²

Non-redox active metal cations are equally as important in biological function as redox active metals, where they are essential to protein structure and function, along with cellular and neuronal signaling.²¹³ Sodium and calcium ions are most abundant extracellularly, while potassium and magnesium are dominant inside of cells. While specific ionic concentrations vary dramatically depending on physiological conditions, estimates for equilibrium concentrations in both mammalian heart cells²¹⁴ and blood plasma²¹⁵ are listed in Table 5.1. As sodium and magnesium are most abundant alkali and alkaline earth metals found in biologically relevant systems, they are of prime interest for investigation.

Extensive crystallographic surveys indicate that metals bind predominantly to oxygen centres in proteins.^{216–218} Divalent metals are most often

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Table 5.1: Ionic concentrations inside a mammalian heart cell and in the blood plasma. Concentrations are in units of mM. Values are rounded to one significant figure. Data are from Ref. 214 and 215.

Ion Conc.	Mammalian Cells	Blood Plasma
Na ⁺	10	100–200
Mg ²⁺	10	1
K ⁺	100	4
Ca ²⁺	0.1	2

found bound directly to proteins. Calcium binds anywhere from 4 to 6 binding sites in protein crystal structures, while magnesium binds only 1 or 2. Monovalent metals, on the other hand, are often heavily solvated and so they appear in solvent cavities of proteins, although sodium or potassium are sometimes found bound directly to carbonyl or carboxylate oxygen centres.²¹⁰

A great deal of research has focussed on Ca²⁺ in the context of reactive oxygen-centred radical production.²¹⁹ Specifically, Ca²⁺ ions are important in the mitochondria, where, depending on physiological conditions and concentrations, they can act as inhibitor or promoters of free-radical production in the electron transport chain.²²⁰ An explanation is that Ca²⁺ induce conformational changes of the proteins involved in the electron transport chain which are responsible for radical generation.²²¹ Mitochondrial free-radicals, when present in moderate amounts, can act as cell signalling molecules to activate pro-growth responses.²²² However, “dysfunctional” mitochondria can produce excess radicals leading to oxidative damage which has been linked to degenerative diseases.

Given the significant importance alkali and alkaline earth metals play in biological systems, their impact on protein oxidation must be considered. However, until recently, kinetic studies of protein oxidation have not investigated the mechanistic role of non-redox active metals. In a series of three papers,^{47,48,223} Bietti and colleagues have shown that alkali and alkaline earth metals have an inhibitory effect on HAT reactions involving CumO[•] and organic substrates. Some of the experimental rate constants from these papers are summarized in Table 5.2. All rate constants were obtained by time-resolved LFP in nitrogen or argon-saturated acetonitrile (MeCN) at 298 K, as was previously described in Section 4.2. All of the experimental results have been rationalized on the basis of Lewis acid metals cations interactions with Lewis basic substrates.

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Table 5.2: Table summary of experimental data - Needs completion

Substrate	Conditions	k_H ($M^{-1}s^{-1}$)	$k_H(\text{MeCN})/k_H(M^{n+})$
1,4-cyclohexadiene (CHD)		6.7×10^7	
	LiClO_4 1.0 M	7.5×10^7	0.89
	$\text{Mg}(\text{ClO}_4)_2$ 1.0 M	7.0×10^7	0.96
tetrahydrofuran (THF)		5.7×10^6	
	LiClO_4 1.0 M	2.9×10^6	1.7
	LiOTf 1.0 M	2.8×10^6	2.0
triethylamine (TEA)		1.8×10^6	3.2
		2.0×10^8	
	LiClO_4 1.0 M	9.4×10^7	2.1
<i>N,N</i> -dimethylformamide (DMF)		$<1 \times 10^6$	>200
		1.2×10^6	
	LiClO_4 0.5 M	$k_{H1} = 8.9 \times 10^5$ $k_{H2} = 1.5 \times 10^6$	1.3 0.80
<i>N,N</i> -dimethylacetamide (DMF)		$k_{H1} = 9.6 \times 10^5$ $k_{H2} = 1.4 \times 10^6$	1.3 0.86
		$k_{H1} = 5.8 \times 10^5$ $k_{H2} = 1.1 \times 10^6$	2.1 1.1
	$\text{Ca}(\text{ClO}_4)_2$ 0.2 M	$k_{H1} = 1.0 \times 10^6$ 1.2×10^6	0.83
		$k_{H1} = 8.5 \times 10^5$ $k_{H2} = 1.5 \times 10^6$	1.4 0.8
		$k_{H1} = 1.1 \times 10^6$ $k_{H2} = 1.3 \times 10^6$	1.1 0.92
		$k_{H1} = 4.7 \times 10^5$ $k_{H2} = 2.4 \times 10^5$ $k_{H3} = 1.1 \times 10^6$	2.6 5.0 1.1
	$\text{Ca}(\text{ClO}_4)_2$ 0.2 M	$k_{H1} = 1.2 \times 10^6$	1.0

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Firstly, for hydrocarbons, cyclic ethers, and tertiary amines, CumO[•] hydrogen abstraction rate constants in the presence of excess concentrations of lithium and magnesium salts were measured.²²³ In the presence of LiClO₄ and Mg(ClO₄)₂, the rate of abstraction by CumO[•] from 1,4-cyclohexadiene (CHD) increases very slightly. Since CHD has no Lewis basic centres, the increase in HAT rate constant was explained on the basis of metal cation interactions with CumO[•], very slightly increasing the hydrogen abstraction ability by withdrawing electron density from the aromatic ring. Metal cations were also shown to increase the unimolecular decay of CumO[•] by β -scission (See Section 4.2). The largest kinetic effect was observed with LiClO₄ with $k_{\beta} = 1.8 \times 10^6 \text{ s}^{-1}$, which is a roughly 3-fold increase as compared to the rate in MeCN at 298 K ($k_{\beta}^{183} = 6.3 \times 10^5 \text{ s}^{-1}$). This effect is significantly less than the observed kinetic solvent effect on CumO[•] β -scission measured in H₂O or 2,2,2-trifluoroethanol ($k_{\beta} = 1.0 \times 10^7$ and $6.1 \times 10^6 \text{ s}^{-1}$, respectively).^{224,225} Therefore, the kinetic effects of these alkali and alkaline metal salts interacting via Lewis acid-base interactions with the oxygen-centre of CumO[•] are less than the effects of hydrogen-bonding by solvents.

Next, the HAT rate constants for abstraction from tetrahydrofuran (THF) decrease in the presence of non-redox active metal salts. Both LiClO₄ and LiOTf decrease k_H by a factor of about 2, indicating the nature of the counter-anion plays a negligible role in the Lewis acid-base interactions between metal cations and substrates. The addition of Mg(ClO₄)₂ has a greater effect on HAT reactivity, decreasing k_H by a factor of 3. Magnesium ions are a stronger Lewis acid than lithium,²²⁶ supporting the notion of Lewis acid-base interactions between the oxygen lone-pair and the metal cations. The decrease in k_H has been partially attributed to the reduction in hyperconjugative overlap between the oxygen lone-pair and the neighbouring C–H σ^* anti-bonding orbital (See Scheme 1.3), as a consequence of the metal cation withdrawing electron density from the oxygen lone-pair.

A 2-fold decrease in k_H for the tertiary amine, triethylamine (TEA), is observed upon the addition of LiClO₄, for which an analogous orbital interaction explanation is also appropriate. Interestingly, the addition of 1.0 M Mg(ClO₄)₂ was reported to immediately form a precipitate to form. This precipitate was identified as the formation of a strong TEA-Mg²⁺ Lewis acid-base adduct. This observation is once again consistent with the stronger Lewis acidity of Mg²⁺ as compared to Li⁺, and also the significantly greater Lewis basicity of TEA vs THF.^{223,227} It was also pointed out that MeCN will competitively bind with metal cations, however it is a weaker Lewis base than both THF and TEA. Measurements of k_H for HAT between CumO[•] and TEA in the presence of 0.005 M Mg(ClO₄)₂ were successful only up until

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$[TEA] = 9.6 \text{ mM}$, at which point a precipitate began to form. Nonetheless, an upper limit to the hydrogen abstraction rate constant was estimated as $k_H < 1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, or at least a 200 fold decrease relative to no metal salt. Very similar results for bulkier tertiary amines were also obtained. Thus, the presence of strong Lewis acids in the presence of Lewis basic sites on hydrogen atom donors can deactivate C–H bonds.

Next, we turn to the more relevant models for the work of this thesis, the tertiary amides *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA). As with THF, normal hyperconjugative overlap between the conjugated amide π -system and the adjacent C–H σ^* anti-bonding orbitals weakens the C–H bonds. Therefore, metal binding to the amide oxygen-centre should result in a decrease in this orbital interaction, strengthen the C–H bonds, and decrease HAT reactivity. In their study, Salamone et al.⁴⁷ measured CumO $^\bullet$ abstraction rate constants from DMF and DMA in the presence of stoichiometric equivalents of LiClO₄, LiOTf, NaClO₄, Mg(ClO₄)₂, and Ca(ClO₄)₂ (in contrast to the excess used in Reference 223). Figure 5.1a,b shows the plots of k_{obs} against [substrate] for the reactions of CumO $^\bullet$ with DMF and DMA in MeCN containing 0.2 M Mg(ClO₄)₂, respectively. For both DMF and DMA, there are three distinct regions in the plots: weak C–H bond activation for $[\text{amide}]/[\text{Mg}^{2+}] \leq 2$, followed by strong C–H bond deactivation for $2 < [\text{amide}]/[\text{Mg}^{2+}] \leq 4$, and no deactivation for $[\text{amide}]/[\text{Mg}^{2+}] < 4$.

The addition of both LiClO₄ and LiOTf decrease to a similar extent the rate constants for abstraction from DMF and DMA by CumO $^\bullet$. However, in contrast to Mg(ClO₄)₂, the lithium salts strongly deactivate C–H bonds for 2 equivalents, followed by weak deactivation for another 2 equivalents, and no deactivation for $[\text{amide}]/[\text{Li}^+] < 4$. Salamone et al. were not able to give a clear cut explanation, but suggest that the different patterns are a result of differences in charge density, which is greater for Mg²⁺ than Li⁺, as well as different coordination geometries of the two ions. A coordination number of 4 is most common for Li⁺, while an octahedral geometry with the coordination of 6 ligands is almost always observed for Mg²⁺.^{228,229} As a result, interactions of the ions with solvent and counter-anions are suggested to be more important for Mg²⁺ than Li⁺.

NaClO₄ and Ca(ClO₄)₂ influence HAT between CumO $^\bullet$ and DMA to different extents than both LiClO₄ and Mg(ClO₄)₂. Figure 5.2a,b shows the plots of k_{obs} against [substrate] for the reactions of CumO $^\bullet$ with DMA in MeCN containing 0.2 M NaClO₄ and Mg(ClO₄)₂, respectively. For NaClO₄, an almost negligible deactivation of C–H bonds is observed for up

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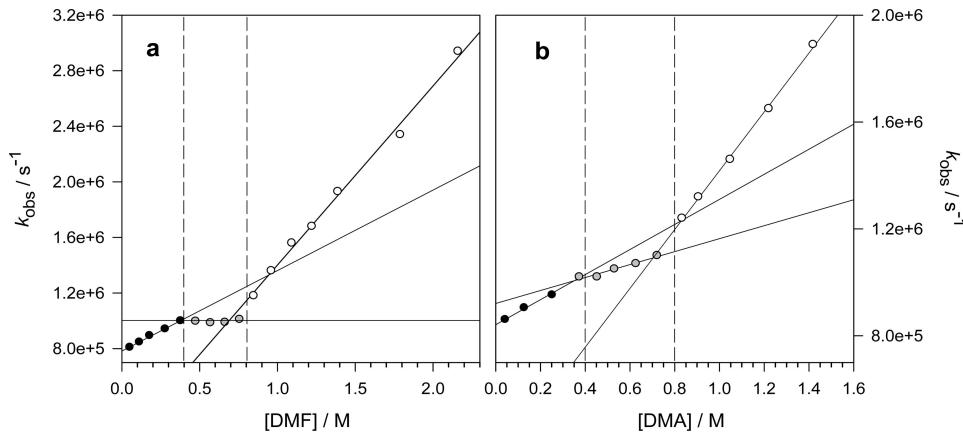


Figure 5.1: **a)** Plot of observed rate constant against concentration of DMF for reaction with CumO[•] at 298 K in the presence of 0.2 M Mg(ClO₄)₂. 0–0.4 M [DMF] range (black circles), $k_{H1} = 5.8 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$; 0.8–2.2 M [DMF] range (white circles), $k_{H2} = 1.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. **b)** Plot of observed rate constant against concentration of DMA for reaction with CumO[•] at 298 K in the presence of 0.2 M Mg(ClO₄)₂. 0–0.4 M [DMA] range (black circles), $k_{H1} = 4.7 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$; 0.4–0.8 M [DMA] range (grey circles), $k_{H2} = 2.4 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$; 0.8–2.2 M [DMA] range (white circles), $k_{H3} = 1.1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. Reprinted with permission from Reference 47. Copyright 2015 American Chemical Society.

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to 4 equivalents of DMA. This was explained on the basis of the weaker Lewis acidity of Na^+ as compared to Li^+ . With regards to $\text{Ca}(\text{ClO}_4)_2$, binding to DMA fully deactivates C–H bond abstraction up to 4 equivalents of DMA. The first region of Figure 5.2b ([DMA] = 0–0.2 M, black circles) represents the decrease in k_β of CumO^\cdot as Ca^{2+} preferentially binds to DMA over CumO^\cdot . Interestingly, for both DMF and DMA, the same experiments in dimethyl sulfoxide (DMSO) solvent show no inhibition of HAT reactivity by metal cations. This was rationalized on the basis of the stronger Lewis basicity of DMSO as compared to both MeCN and the amides, thus the metals preferentially bind solvent rather than amide substrate.

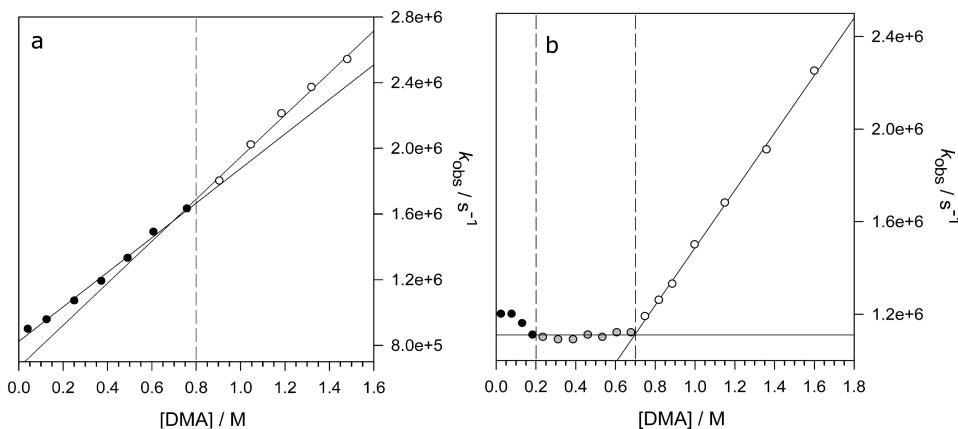


Figure 5.2: **a)** Plot of observed rate constant against concentration of DMA for reaction with CumO^\cdot at 298 K in the presence of 0.2 M NaClO_4 . 0–0.8 M [DMA] range (black circles), $k_{H1} = 9.6 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$; 0.8–1.4 M [DMA] range (white circles), $k_{H2} = 1.4 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. **b)** Plot of observed rate constant against concentration of DMA for reaction with CumO^\cdot at 298 K in the presence of 0.2 M $\text{Ca}(\text{ClO}_4)_2$. 0.8–1.7 M [DMA] range (white circles), $k_{H1} = 1.2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. Adapted with permission from Reference 47. Copyright 2015 American Chemical Society.

Finally, Salamone et al.⁴⁸ examined the effects of substrate structure on HAT reaction between CumO^\cdot and tertiary alkanamides in the presence of alkali and alkaline earth metal ions. For *N,N*-dialkylacetamides, the steric bulk of the *N*-alkyl groups was previously characterized.¹⁴⁴ Steric repulsion between CumO^\cdot and the *N*-alkyl groups can decreases the HAT rate constant, as evident by the 3-fold decrease in k_H in going from DMA to *N,N*-diisobutylacetamide (DIA; 1.2×10^6 and $3.1 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, respectively). For reactions of CumO^\cdot with DIA addition of 0.2 M LiClO_4 or $\text{Ca}(\text{ClO}_4)_2$ to re-

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sults in the same trends in C–H bond deactivation observed for DMA. This indicates that the influence of metal cation-substrate binding is not significantly influences by the steric bulk of *N*-alkyl groups. The same is true for the addition of 0.2 M Mg(ClO₄)₂ to abstraction from DIA by CumO[•], as shown in Figure 5.3. Once again, an slight decrease in reactivity is observed for the first 2 equivalents of DIA, followed by strong C-H bond deactivation for an additional two equivalents, and no deactivation beyond that. No additional insight was provided by Salamone et al. as to the reason for this reactivity. The plausible explanation provided was once again that Mg²⁺ has a high charge density. These results show that Lewis acid-base interactions between alkali or alkaline earth metal cations can greatly depress hydrogen abstraction by alkyoxyl radicals.

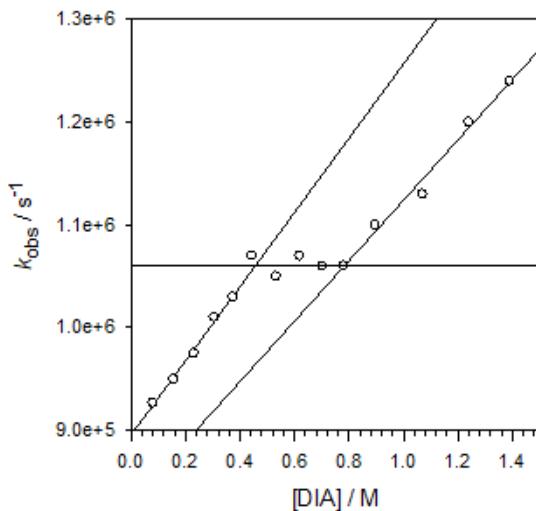


Figure 5.3: Plot of observed rate constant against concentration of DIA for reaction with CumO[•] at 298 K in the presence of 0.2 M Mg(ClO₄)₂. 0–0.4 M [DIA] range, $k_{H1} = 3.6 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$; 0.8–1.4 M [DIA] range, $k_{H2} = 2.9 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$. Reprinted from Tetrahedron, 72, Salamone et al., Hydrogen atom transfer from tertiary alkanamides to the cumyloxyl radical. The role of substrate structure on alkali and alkaline earth metal ion induced CH bond deactivation, 7757–7763, 2016, with permission from Elsevier.

With these results in mind, I am interested in the possibility that alkali and alkaline earth metal cations found in biological system can protect C–H bonds in proteins from HAT to reactive oxygen-centred radicals. However,

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the experimental results do not answer some of the key physico-chemical determinants which may make this possible. Specifically, I have composed several important research questions which remain unclear from the experimental results.

The first question which I have is one of methodology: Can DFT-based methods accurately treat alkali/alkaline metal cation binding to organic substrates or radicals? There exists limited ab initio data describing these interactions.^{230–233} Therefore, I have conducted a benchmark quality study involving Li^+ , Na^+ , Mg^{2+} , K^+ , and Ca^{2+} . to the best of my knowledge, this represents the first systematic benchmark study of these metal cations with both organic substrates, and radicals.

Secondly, the nature of the binding of metal ions to substrates is still poorly described, especially given the odd stoichiometric effects observed for $\text{Mg}(\text{ClO}_4)_2$ with alkanamides. Specifically, I wish to address the range of these interactions, and how much the metals do effect the C-H being broken. Throughout this investigation I have utilized both Na^+ and Mg^{2+} in my calculations. These metal ions were chosen to capture the large differences in Lewis acidity and ion size associated with these third-period ions, and because they are two of the most biologically relevant metal ions.

Thirdly, I address the effect that metal ions have on the HAT barrier heights. Experiments demonstrate that under certain conditions the presence of metal ions can decrease HAT reactivity. If metal ions do effectively increase C-H bond strengths, this will certainly be a contributing factor to the free energy barrier. There will likely be additional factors such as polarization in the TS complex, or other effects of possible charge transfer from the substrate to metal ions. To investigate this, I have primarily studied HAT reactions involving DMA and oxygen-centred radicals. I have also performed calculations with the bulkier DIA substrate to see if steric bulk does have an influence on the ability of a metal cation to effect HAT reactions. I was also interested in structural differences of the oxygen-centred radical, thus I have utilized the BnO^\bullet and CumO^\bullet , as well as the more biologically relevant HO^\bullet . These results

Finally, I wanted to address the effect of strong Lewis basicity in the hydrogen donating substrate. HAT reactions involving alkoxy radicals and strong Lewis bases have been previously studied.

5.2 Computational methods and details

All quantum mechanical calculations were performed using either the Gaussian 09 software package,¹¹³ or the TURBOMOLE software package.⁷⁰ Calculations for the benchmark quality data of metal binding to substrates were first optimized at the LC- ω PBE-D3(BJ)/6-31+G(2d,2p) level of theory, and later re-optimized with larger 6-311+G(3df,3pd) basis sets. Single-point energy calculations were then carried out using the coupled cluster methodology with single, double and perturbative triples with full core correlation, CCSD(T,Full), and various basis sets, as will be described in Section 5.3. Final benchmark quality binding energies have been calculated using the F12* explicitly correlated method with Def2-QZVPPD primary basis sets and Def2-QZVPP auxiliary basis sets required for the resolution-of-the-identity (RI) approximation as implemented in TURBOMOLE. The RI approximation is used to reduce the computational cost associated with calculating MO integrals.²³⁴ At total of 31 different DFT-based methods with nearly complete 6-311+G(3df,3pd) and moderate 6-31+G(2d,2p) basis sets were tested both by single-point energy calculations on the benchmark structures. Geometry optimization calculations starting from the benchmark structures were also performed for three of the best performing DFT-based method, in order to verify their ability to capture the minimum energy bound structures.

To test the effects of metal cations on HAT barrier heights, calculations were first performed for the reactions not involving metal cations. Geometry optimizations were performed at the M05-2X/6-31+G** level of theory. Transition state (TS) structures were obtained by first freezing the abstraction donor-hydrogen-acceptor bond lengths with multiple initial orientations. The frozen bonds were then relaxed to obtain the final TS structures, which were then used to identify the appropriate pre- and post-reaction complexes. All structures were subjected to harmonic vibrational frequency calculations, which were visualized using the Chemcraft program¹⁹³ to verify minima (or saddle-points with a single imaginary frequency connecting reactants to products for TS structures). Single-point energy calculations were performed at the M05-2X/6-311+G(2d,2p) level of theory. The effects of MeCN solvent were estimated by inclusion of the SMD continuum solvent model in single-point energy calculations.

The inclusion of metal cations into the TS structures proved to be technically challenging. It was my expectation that I could simply include metal cations and necessary counter-anions into the minimum energy complex structures and re-optimize, however this was not the case. TS structures

were once again obtained by constrained optimization with the inclusion of the metal cation and counter-anion and freezing the abstraction donor-hydrogen-acceptor bond lengths, providing a guess TS structure. However, in most cases the force constants (which are necessary for a TS optimization calculation) from the the guess TS structure were not representative of the true TS structure, thus force constants were recalculated for every step along the optimization, using the “CalcAll” keyword in Gaussian. The final TS structures were once again used to identify the appropriate pre- and post-reaction complexes.

5.3 Benchmarking DFT based methods for the binding of alkali and alkaline earth metals to organic substrates and oxygen centred radicals

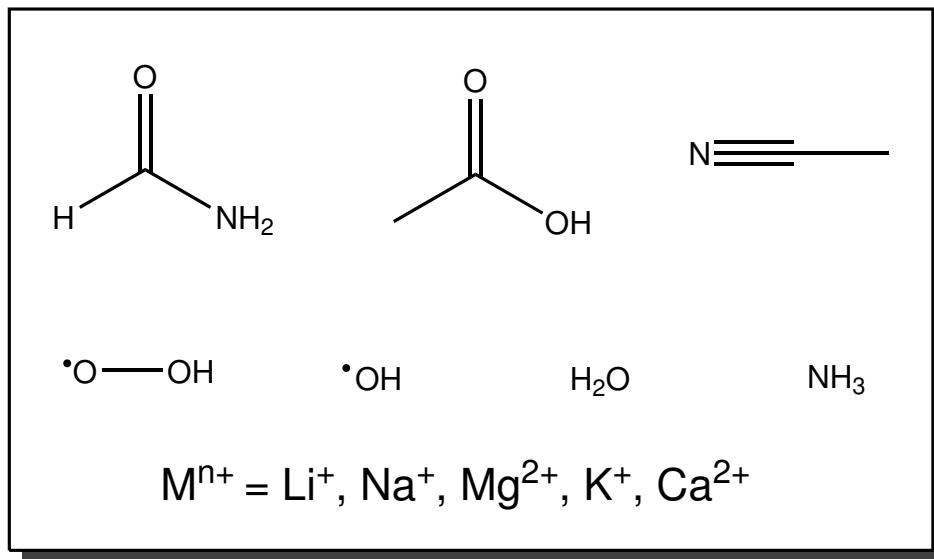
In order to confidently perform quantum mechanical mechanistic studies, the method of choice must be confidently calibrated. While DFT-based methods have been widely applied to these studied, few studies have previously investigated alkali and alkaline earth-metal cation binding to organic substrates.^{230–233} Most importantly, benchmark quality data for a wide variety of metals binding to biologically relevant substrates and oxygen-centred radicals does not exist to calibrate DFT-based methods. Therefore, I proposed a benchmark study which incorporated all the biologically relevant alkali and alkaline earth-metal cations, models for dipeptides including amino acid side chains, oxygen-centred radicals, and solvents which are utilized in the experimental mechanistic studies involved in probing these systems. Unfortunately, due to computational restrictions (*vide infra*), benchmark quality calculations on the originally proposed benchmark set were not possible. Full details of the originally proposed benchmark set are in Appendix C, Scheme C.1

Benchmark quality binding energies are generally calculated using the “gold standard” approach, CCSD(T)/CBS, where correlation consistent basis sets^{235,236} (cc-pV_XZ, X=T,Q,5) developed by Dunning and co-workers are used for complete basis set extrapolation. These basis sets have limited availability for the metals of interest. Specifically, basis sets for K are not available, and only non-augmented basis sets for Li, Na, Mg, and Ca. It is necessary to include core-correlation of at least the first core shell in alkali and alkaline earth metals, thus it would be appropriate to use core valence

5.3. Benchmarking DFT based methods

basis sets such as cc-pCVXZ.⁶³ However, these basis sets are even more limited. Therefore, I originally chose the augmented version of the polarization consistent basis sets of Jensen and co-workers^{64–67} (aug-*pc-N*, *N*=2,3,4), which have been shown to converge to the CBS limit systematically⁸¹ and are available for all the elements of interest.

While performing CCSD(T)/CBS calculations, I noticed that the metal cations (and neutral metal atoms), did not converge smoothly to the complete basis set limit. As a consequence, complete basis set extrapolation is not feasible. In light of this problem, I decided to re-evaluate the size scope of the benchmark set being used. In order to facilitate future DFT-based work and probe the issue of basis set convergence of alkali and alkaline earth metals, a benchmark set of small substrates was proposed. This new set is shown in Scheme 5.1. The new, small benchmark set was selected to include important functional groups and radicals found biological systems, and one of the most common solvents used in physical organic experiments, acetonitrile.



Scheme 5.1: Revised benchmark set of small substrates and cations. Note this set consists of all combinations of substrates and metal cations, i.e., there are 35 complexes in the set.

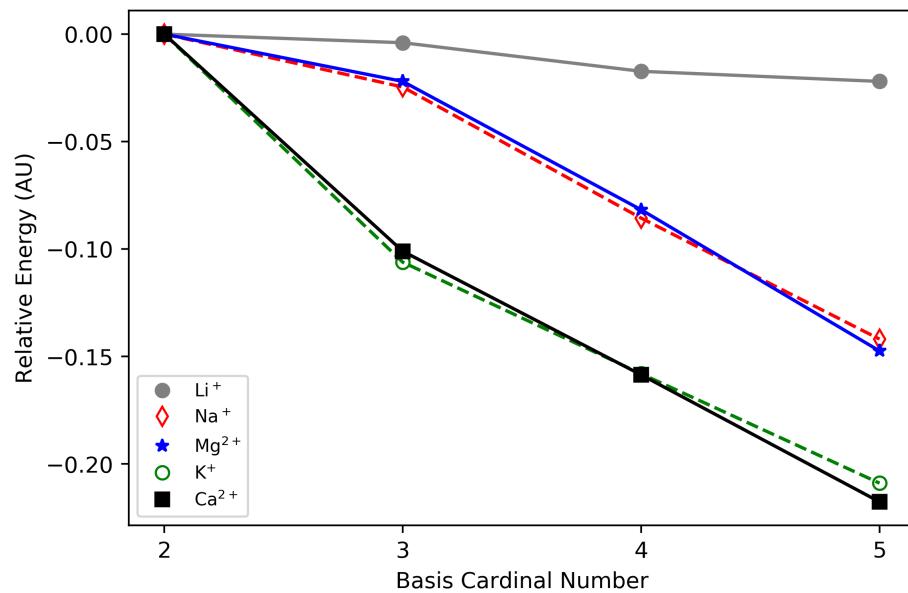


Figure 5.4: Basis set convergence of CCSD(T,Full)/aug-pc- N ($N=1,2,3,4$) for alkali and alkaline earth-metal cations. The relative energy of each basis set relative to the aug-pc-1 for each metal. The cardinal number of the aug-pc- N basis sets is $X = N + 1$.

5.3.1 Metal cation basis set convergence

In order to perform complete basis set (CBS) extrapolation, the total energy of a molecule/atom should converge smoothly to the CBS limit.⁷⁶ However, Figure 5.4 shows the poor basis set convergence of CCSD(T,Full)/aug-pcN ($N=1,2,3,4$) calculations for alkali and alkaline earth-metals. The energy of each ion relative to the smallest basis set is shown. For Li^+ the value appears to converge reasonably, however this is expected as there are only 2 electrons in this ion. For all of Na^+ , Mg^{2+} , K^+ , and Ca^{2+} , there appears to be no convergence to the CBS limit as each line continues down linearly. This is problematic as it means that CBS extrapolation would result in a significant degree of uncertainty in the estimated CBS limit total energy.

The poor convergence was thought to be a result of poorly suited basis sets to full core-correlation. However, the same CCSD(T,Full) calculations using the core-correlation (cc-pCVNZ) basis sets as show unsatisfactory convergence for Na^+ and Mg^{2+} (See Appendix C, Figure C.1). Therefore, I was tasked with finding a method which would give results which best approximate alkali and alkaline metal binding at the complete basis set limit. I decided to use an explicitly correlated CCSD(T) treatment known as “F12*” to more rapidly approach the CBS limit.⁸⁴ I tested both the core-correlation consistent basis set developed for used with explicitly correlation (cc-pCVXZ-F12),²³⁷ and the Ahlrich basis sets (Def2-SVP,-TZVPPD, and -QZVPPD).²³⁸ Both these basis sets combined with the CCSD(T,Full)-F12* methodology gave satisfactory convergence to the CBS limit for the sodium and magnesium ion (See Appendix C, Figure C.2) for the convergence of all metal ions calculated with the CCSD(T,Full)-F12*/Def2-QZVPPD method). Given that Def2-QZVPPD is available for almost every atom on the periodic table, and the observed convergence to the CBS limit, this basis set was selected for benchmark quality binding energies.

To the best of my knowledge, there is no precedent for extrapolating the Ahlrich basis sets, thus the final benchmark energies are at the CCSD(T)-F12*/Def2-QZVPPD level of theory without extrapolation. The convergence of the total energies of the cations can be estimated as the sum of the experimental ionization energies of the ions. These results are listed in Table 5.3. The calculated values are in too high (i.e., not at the CBS limit), and deviate from experiment from 0.16 and 0.66 AU (4.4–18 eV). Deviations of this magnitude are rather significant, but can likely be accounted for by cumulative experimental error, as the experimental ionization energies range from 4–5500 eV. Therefore, the calculated binding energies herein are likely the best available approximation to the gas-phase metal-substrate binding

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energy.

Table 5.3: Total energy of alkali and alkaline earth-metal cations from experimental ionization energies²³⁹ (Expt.) and calculated (Calc.) at the CCSD(T,Full)-F12*/Def2-QZVPPD level of theory. All values are in units of AU.

Ion	Expt.	Calc.
Li ⁺	-7.47798	-7.27983
Na ⁺	-162.43089	-162.24203
Mg ²⁺	-200.32523	-199.49171
K ⁺	-601.93332	-601.77381
Ca ²⁺	-680.19158	-679.53065

5.3.2 High level results and evaluation of various density-functional theory based methods

Table 5.4 lists the benchmark binding energy values calculated at the CCSD(T,Full)-F12*/Def2-QZVPPD//LC- ω PBE-D3(BJ)/6-311+G(3df,3pd) level of theory. Some general trends are that alkaline earth-metals bind more strongly than alkali earth-metals. In general the order of binding follows the Lewis acidity of the metal ions: Mg²⁺ > Ca²⁺ > Li⁺ > Na⁺ > K⁺. Also, the metals all appear to bind most strongly to the amidic oxygen-centre, reflecting the higher Lewis basicity. All the metals also bind weakest to the oxygen-centred radicals, with greater binding to HOO[·] as compared to HO[·].

Table 5.4: Benchmark gas-phase binding energies of alkali and alkaline earth-metals with small organic substrates and radicals. Values are calculated at the CCSD(T,Full)-F12*/Def2-QZVPPD//LC- ω PBE-D3(BJ)/6-311+G(3df,3pd) level of theory. All values are in kcal mol⁻¹.

	Li ⁺	Na ⁺	Mg ²⁺	K ⁺	Ca ²⁺
H ₂ O	-34.7	-24.4	-82.0	-17.8	-56.8
NH ₃	-39.9	-28.2	-98.1	-19.8	-65.3
MeCN	-44.4	-33.0	-113.1	-24.9	-80.7
Formamide	-50.7	-36.9	-128.2	-28.5	-96.1
Formic acid	-38.4	-27.0	-101.9	-20.0	-72.6
HO [·]	-21.3	-16.8	-57.0	-12.4	-40.7
HOO [·]	-27.1	-19.1	-72.2	-13.9	-49.0

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Next, 31 DFT-based methods combined with a moderate basis set (6-31+G(2d,2p)) and a large basis set (6-311+G(3df,3pd)) were tested for their ability to estimate the binding energy between metal cations and substrates. The mean absolute/signed errors (MAE/MSE) and maximum and minimum errors for each method are listed in Table 5.5.

Table 5.5: Evaluation of DFT-based methods for alkali and alkaline metal binding to organic substrates and radicals. All values are in kcal mol⁻¹. Negative values indicate under-binding.

Method	MAE/MSE	Max./Min	MAE/MSE	Max./Min.
	6-311+G(3df,3pd)		6-31+G(2d,2p)	
B3 ⁹⁸ LYP ⁹⁹	1.49/1.35	5.12/-0.57	1.59/-0.17	4.67/-7.28
B3P86 ²⁴⁰	0.94/0.47	3.87/-0.96	1.36/-1.08	1.99/-7.38
B3PW91 ²⁴¹	0.95/-0.14	2.74/-1.64	1.89/-1.70	1.47/-8.76
BH+H ²⁴² LYP	1.89/1.84	5.29/-0.59	1.93/0.63	4.65/-5.64
B ¹⁴⁵ LYP	1.60/1.07	5.56/-1.51	1.88/-0.75	5.30/-8.80
BMK ²⁴³	0.90/-0.70	1.13/-2.40	1.98/-1.93	0.86/-8.75
BP86	1.63/-0.25	4.61/-3.21	2.27/-2.14	1.55/-9.38
CAM-B3LYP ²⁴⁴	2.40/2.40	6.25/ 0.21	1.98/1.04	5.82/-5.25
LC- ω PBE ^{148,149}	0.78/0.58	2.95/-0.73	1.34/-0.74	2.19/-8.00
M05-2X ¹⁰⁰	1.11/1.11	3.21/ 0.15	1.24/-0.17	2.55/-5.75
M06 ²⁴⁵	1.05/-0.62	2.36/-4.83	1.83/-1.63	1.76/-9.03
M06-2X ²⁴⁵	1.13/1.13	3.68/ 0.11	1.26/-0.07	3.00/-6.63
M06L ²⁴⁶	1.52/-1.14	2.64/-6.94	2.55/-2.48	1.21/-11.2
MOHLYP ²⁴⁷	2.30/-2.02	1.52/-5.40	4.04/-3.96	0.89/-15.2
PBE0 ^{248,249}	1.22/1.18	4.19/-0.31	1.25/-0.34	3.30/-7.25
PBE ²⁵⁰	1.70/1.46	6.09/-0.87	1.58/-0.46	4.68/-8.15
TPSS ²⁵¹	1.38/0.95	4.88/-1.12	1.60/-0.98	2.91/-8.12
B97 ²⁵² D3 ¹⁰⁶	1.50/0.47	5.94/-2.19	1.69/-1.37	2.67/-8.41
ω B97 ²⁵³	0.61/0.23	2.13/-1.72	1.41/-0.97	1.78/-7.57
ω B97XD ²⁵⁴	1.12/-0.94	1.02/-4.52	2.24/-2.21	0.65/-8.64
HSEH1PBE ^{255,256}	1.30/1.29	4.28/-0.16	1.23/-0.23	3.45/-6.95
B3LYP-D3(BJ) ^{106,107}	2.86/2.86	7.50/ 0.34	1.92/1.34	7.05/-4.33
BLYP-D3(BJ)	2.89/2.88	8.40/-0.14	1.83/1.06	8.14/-5.30
B3PW91-D3(BJ)	1.47/1.40	5.81/-0.44	1.02/-0.14	3.88/-5.69
BMK-D3(BJ)	1.03/0.80	4.05/-1.06	1.02/-0.43	2.03/-5.49
BP86-D3(BJ)	1.77/1.29	7.78/-1.05	1.26/-0.60	3.96/-6.19

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CAM-B3LYP-D3(BJ)	3.19/3.19	7.50/ 0.78	2.27/1.82	7.07/-3.54
LC- ω PDE-D3(BJ)	1.47/1.46	4.07/-0.06	1.33/0.14	3.30/-6.15
PBE0-D3(BJ)	1.92/1.92	5.37/ 0.20	1.33/0.40	4.47/-5.74
PBE-D3(BJ)	2.24/2.23	7.57/-0.22	1.44/0.30	5.90/-6.67
TPSS-D3(BJ)	2.03/1.99	6.93/-0.30	1.25/0.06	4.56/-6.03

Given the magnitude of the binding energies, the overall agreement between the benchmark values and the DFT-based method values with both moderate and large basis sets is very good. Interestingly, the application of the empirical D3(BJ) dispersion correction systematically decreases agreement with benchmark values as it increases over-binding. Also, going from moderate to large basis sets systematically increases the predicted binding energies, as indicated by an increase in MSE across the board. I chose three of the best performing methods (BMK-D3(BJ), TPSS-D3(BJ), and M05-2X) and performed geometry optimizations with moderate basis sets on the benchmark structures to determine if the choice of method would significantly impact the minimum energy bound structure. These results are listed in Table 5.6.

Table 5.6: Comparison of single point (SP on benchmark structure) and relaxed (optimized with method) binding energies for alkali and alkaline metal binding with DFT-based methods and 6-31+G(2d,2p) basis sets. Mean absolute error (MAE) values are in kcal mol⁻¹ and average root mean squared deviation (RMSD)²⁵⁸ of geometry are in Å.

Method	MAE(SP)	MAE(Relaxed)	Average RMSD
BMK-D3(BJ)	1.02	1.24	0.012
M05-2X	1.24	1.17	0.020
TPSS-D3(BJ)	1.25	1.21	0.026

For all the three methods tested, the average of the root mean square deviations from benchmark structures are very small (0.012–0.026 Å). For BMK-D3(BJ), re-optimization of the structures results in a slight increase in MAE, while for TPSS-D3(BJ) and M05-2X, the opposite is true. As a whole, it seems that DFT-based methods are capable of capturing alkali and alkaline metal ion binding with organic substrates and molecules. M05-2X appears to be one of the best performing DFT-based methods. Additionally, M05-2X is recommended by the QM-ORSA²⁵⁹ method, which outlines best

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principles for calculating accurate HAT rate constants in solution. And finally, M05-2X was previously used by our group in the study of the HAT reaction between DMSO and BnO^\bullet ,²⁶⁰ thus I have selected this method for further study of the effects of alkali and alkaline earth metal cations on the barrier heights of HAT reactions. Note also that M05-2X is a hybrid density-functional with 56% HF-exchange, and thus should not suffer from delocalization error.

5.4 Exploring the nature of metal cation substrate interactions

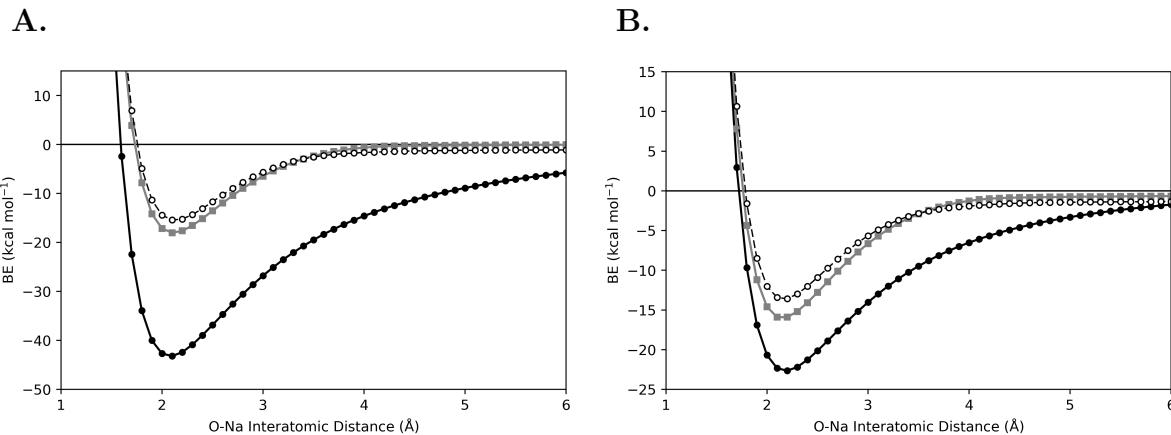


Figure 5.5: Potential energy surface of binding energy between DMA and **A** sodium cation and **B** sodium chloride as a function of O-Na interaction distance (Å). The black line and points represent gas-phase results, the grey squares and line is in continuum MeCN solvent, and white circles and dashed line is in continuum water solvent. Calculated as a rigid scan from the M05-2X/6-31+G** minimized complex structure at the M05-2X/6-311+G(2d,2p) level of theory with the SMD solvent model.

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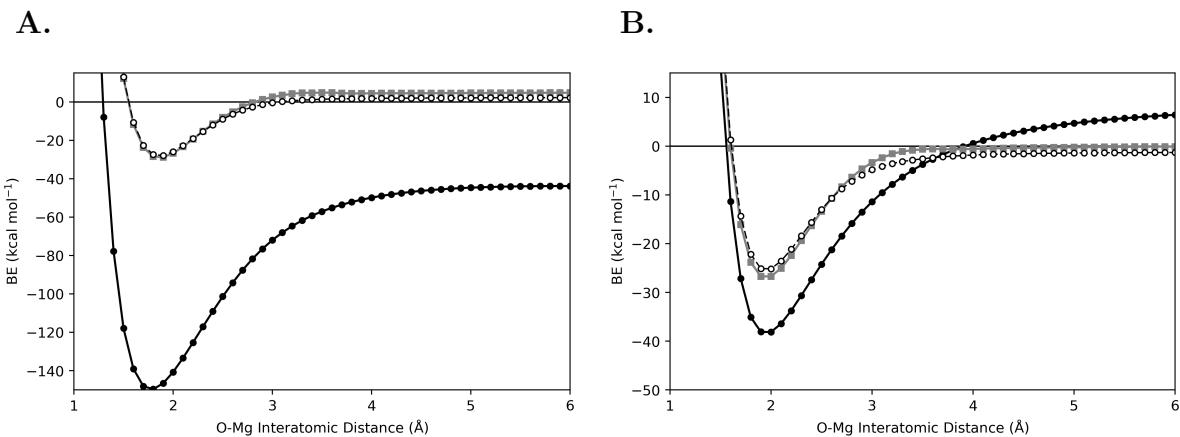


Figure 5.6: Potential energy surface of binding energy between DMA and **A** magnesium cation and **B** magnesium chloride as a function of O-Mg interaction distance (Å). The black line and points represent gas-phase results, the grey squares and line is in continuum MeCN solvent, and white circles and dashed line is in continuum water solvent. Calculated as a rigid scan from the M05-2X/6-31+G** minimized complex structure at the M05-2X/6-311+G(2d,2p) level of theory with the SMD solvent model.

Chapter 6

Conclusion

Here comes the conclusion.

Chapter 6. Conclusion

Your conclusion can go on for several pages.

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Appendix

Appendix A

Chapter 3 Additional Data

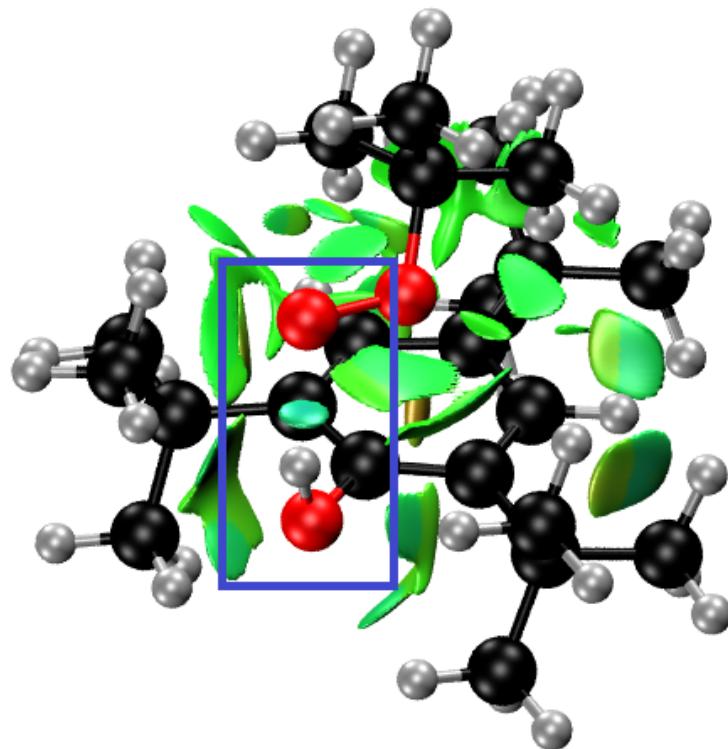


Figure A.1: NCIplot^{156,157} of complex 5. The blue spheroid (highlighted in the blue box) between the *t*-butylperoxy oxygen centred radical and the 2,4,6-tri-*t*-butylphenol hydroxyl indicates a hydrogen bonding interaction. The additional green surfaces represent stereo-electronic and weak dispersion interactions.

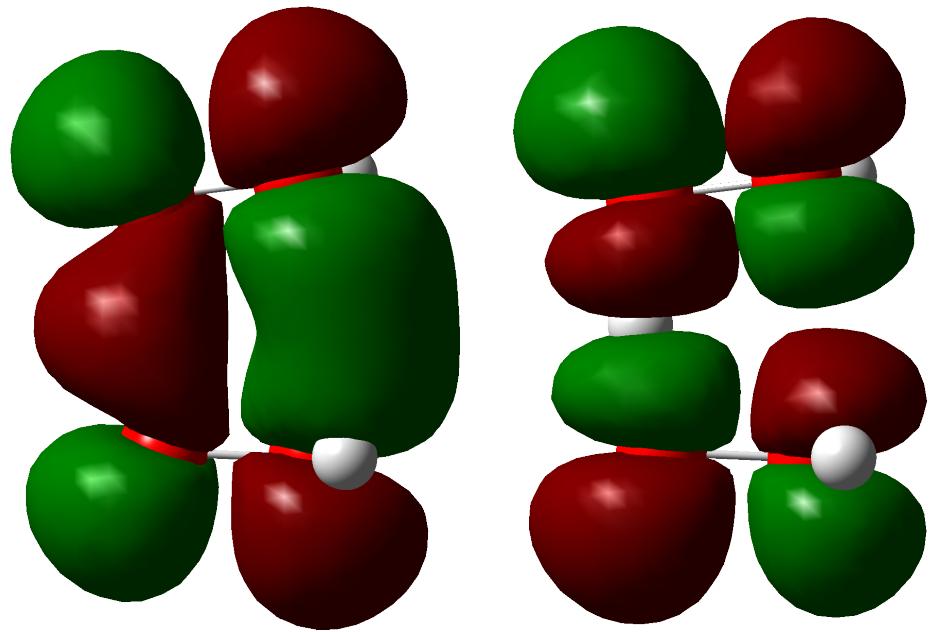


Figure A.2: Molecular orbitals of hydrogen peroxide-peroxyxyl self-exchange reaction TS complex, demonstrating a PCET mechanism. Left is the HOMO-1 and right is the SOMO. Together they demonstrate a lone pair-lone pair net half bonding interactions, consistent with PCET.

Appendix B

Chapter 4 Additional Data

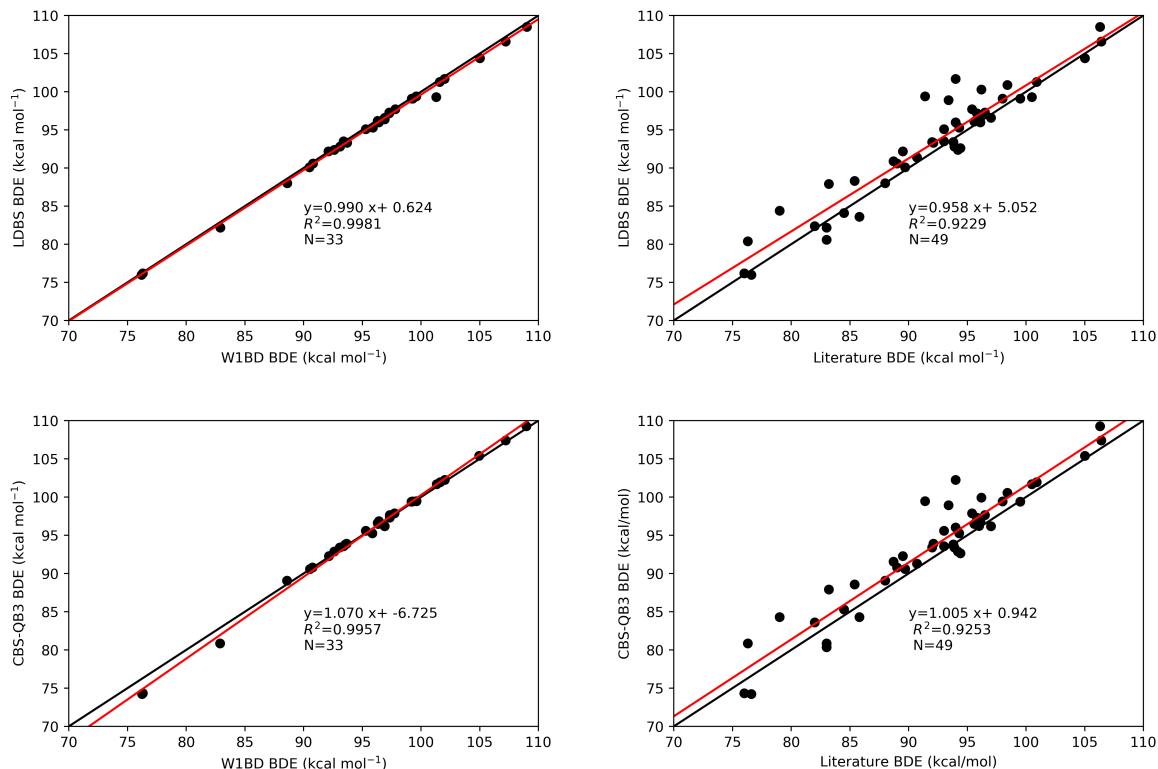


Figure B.1: One-to-one plots of composite methods compared to literature and W1BD.

Appendix B. Chapter 4 Additional Data

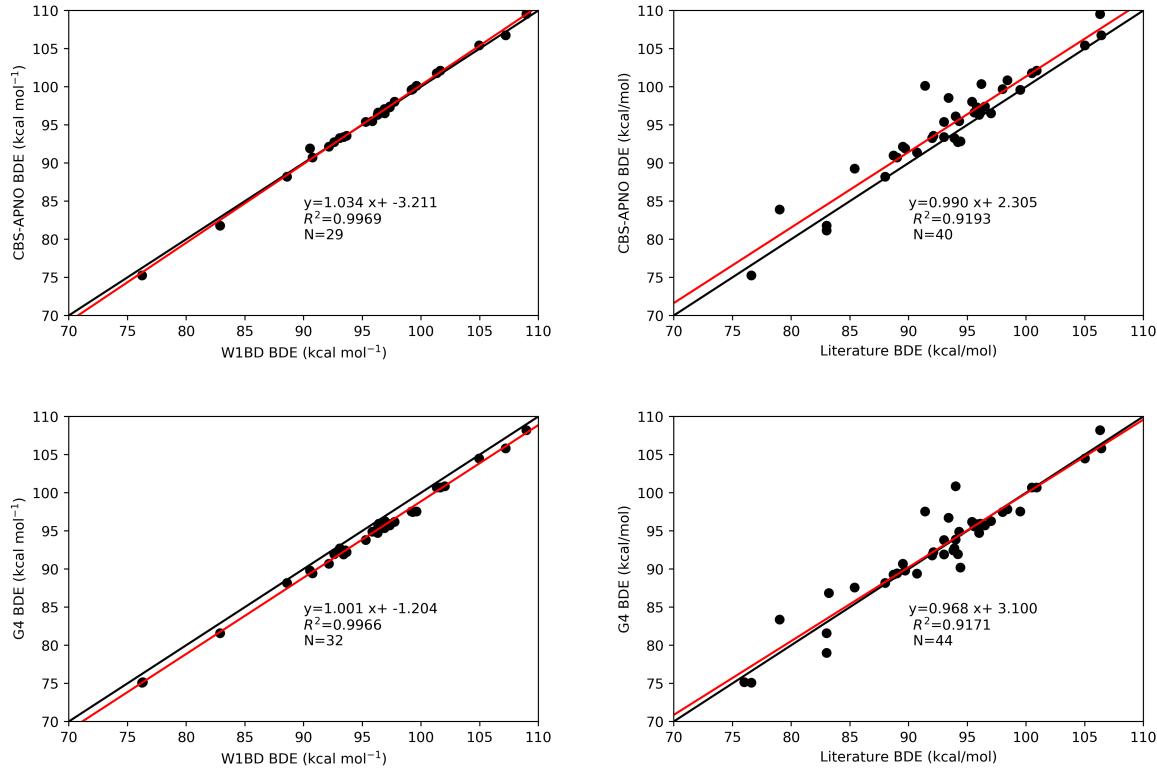


Figure B.1: Continued: One-to-one plots of composite methods compared to literature and W1BD.

Appendix B. Chapter 4 Additional Data

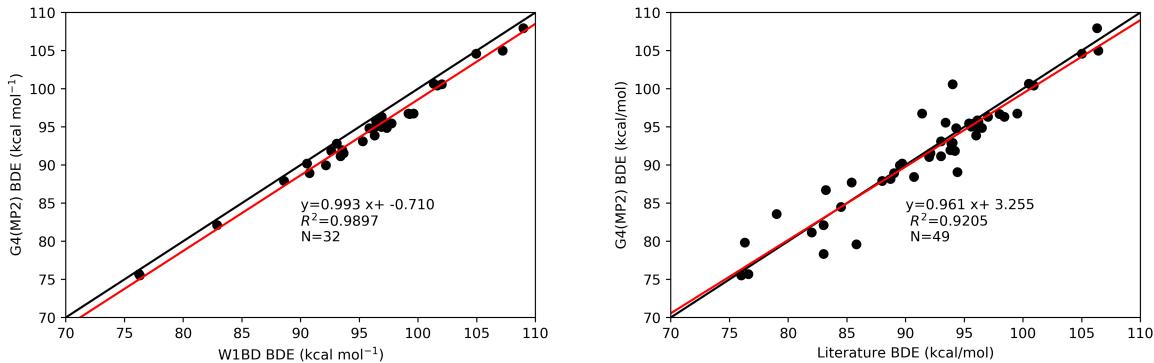


Figure B.1: Continued: One-to-one plots of composite methods compared to literature and W1BD.

Table B.1: Summary of experimental rate constants ($M^{-1}s^{-1}$) and literature¹⁷⁶ bond dissociation enthalpies (BDEs, kcal mol⁻¹).

Molecule	k_H	Normalized k_H	BDE
1,4-cyclohexadiene	6.60×10^7	1.65×10^7	76
1,4-diazabicyclo[2.2.2]octane	9.60×10^6	8.00×10^5	93.4
2,2-dimethylbutane	9.50×10^4	4.75×10^4	98
2,3-dimethylbutane	5.60×10^5	2.80×10^5	95.4
9,10-dihydroanthracene	5.04×10^7	1.26×10^7	76.3
Acetone	$< 1 \times 10^4$	2×10^3	96
Acetonitrile	$< 1 \times 10^4$	3×10^3	97
Adamantane (2°)	6.90×10^6	5.75×10^5	98.4
Adamantane (3°)	6.90×10^6	1.73×10^6	96.2
Benzaldehyde	1.20×10^7	1.20×10^7	88.7
Benzyl alcohol	2.97×10^6	1.49×10^6	79
Cumene	5.60×10^5	5.60×10^5	83.2
Cycloheptane	2.20×10^6	1.57×10^5	94
Cyclohexane	1.10×10^6	9.17×10^4	99.5
Cyclooctane	2.98×10^6	1.86×10^5	94.4

Appendix B. Chapter 4 Additional Data

Cyclopentane	9.54×10^6	9.54×10^5	95.6
Dibenzyl ether	5.60×10^6	1.40×10^6	85.8
Diethyl ether	2.60×10^6	6.50×10^5	93
Dimethyl sulfoxide	1.80×10^4	6.00×10^3	94
Dioxane	8.20×10^5	1.03×10^5	96.5
Diphenylmethane	8.71×10^5	4.36×10^5	84.5
Ethylbenzene	7.90×10^5	3.95×10^5	85.4
Hexamethylphosphoramide	1.87×10^7	1.04×10^6	
Morpholine	5.00×10^7	1.25×10^7	92
Piperazine	2.30×10^8	2.90×10^7	93
Piperidine	1.10×10^8	2.80×10^7	89.5
Pyrrolidine	1.20×10^8	3.10×10^7	89
Tetrahydrofuran	5.80×10^6	1.45×10^6	92.1
Toluene	1.85×10^5	6.17×10^4	89.7
Triethylamine	2.10×10^8	3.5×10^7	90.7
Triphenylmethane	3.04×10^5	3.04×10^5	81

Appendix C

Chapter 5 Additional Data

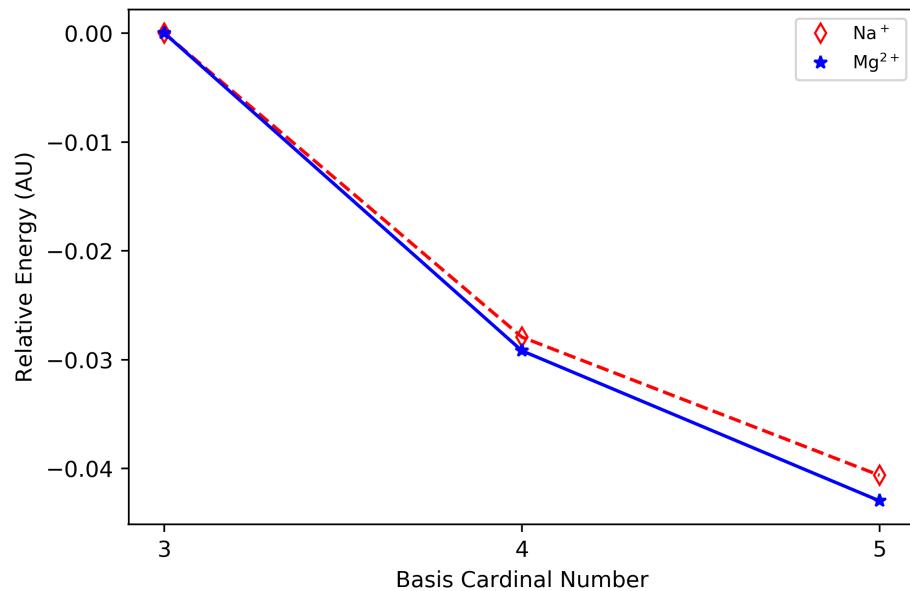
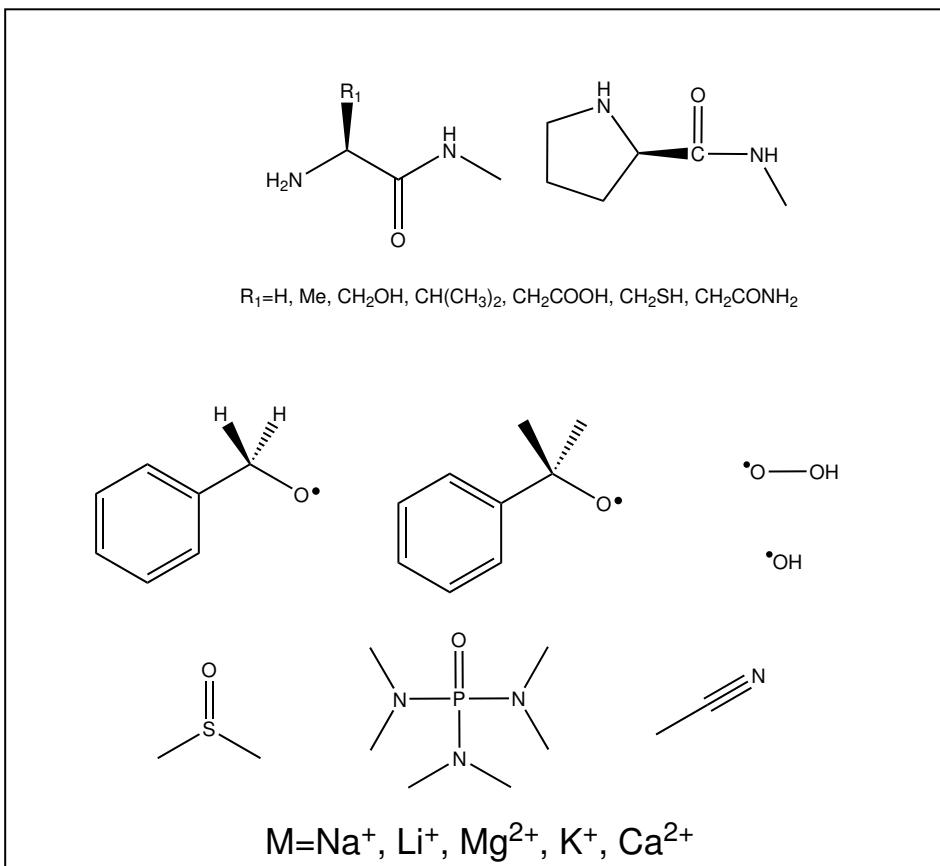


Figure C.1: Basis set convergence of CCSD(T,Full)/cc-pVCXZ ($X=3,4,5$) for sodium and magnesium ions. The relative energy of each basis set relative to the cc-pVCDZ for each metal. The cardinal number of the basis sets is X .



Scheme C.1: Initial proposed benchmark set of substrates/radicals and metal cations. Note this set consists of all combinations of substrates and metal cation, thus there are 75 complexes in the set. Conformational analysis using the Hyperchem package²⁶¹ to identify the lowest energy conformers of all the substrates was completed using the AM1 semi-empirical approach. Geometry optimizations were then performed without metal cations at the LC- ω PBE-D3(BJ)/6-31+G(2d,2p) level of theory. Several binding sites were investigated and optimized at the same level of theory. Benchmark quality structures have been optimized at the LC- ω PBE-D3(BJ)/6-311+G(3df,3pd) level of theory. I am awaiting computational resources to perform CCSD(T)-F12*/Def2-QZVPPD calculations.

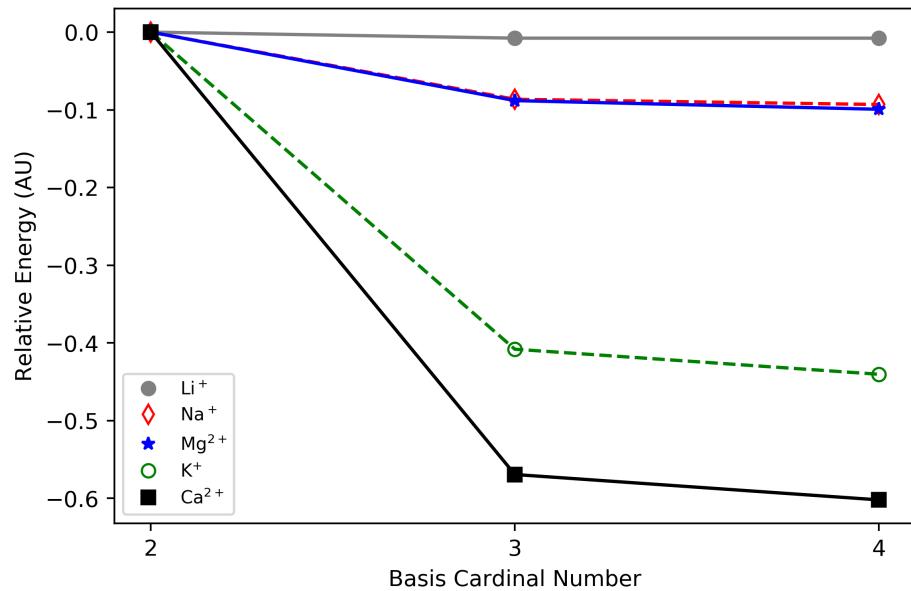


Figure C.2: Explicitly correlated CCSD(T,Full)-F12*/Def2- X ($X=\text{SVP}, \text{TZVPPD}, \text{QZVPPD}$) basis set convergence for alkali and alkaline earth-metal cations. The relative energy of each basis set relative to the cc-pVCDZ for each metal. The cardinal number of the basis sets is X .