Introduction

Hydrogen atom transfer (HAT) reactions involve chemical species with an odd number of electrons, or free radicals. These fundamental chemical transformations have been studied extensively for over a century.[? ?] All HAT reactions involve the transfer of at least one hydrogen atom ($H^{\bullet}$), although there exist various mechanisms by which this can occur. Free radicals and HAT reactions play an important role in many chemical and biological processes.[?]

1 Processes involving hydrogen transfer reactions

1.1 Hydrogen atom transfer reactions in biological processes

In biology, oxygen centred radicals are referred to as reactive oxygen species (ROSs). Nearly all ROSs derive from the metabolic processes involving molecular oxygen, O_2.[?] At conditions relevant to biology, organic matter exists in the singlet ground state while O_2 exists in a triplet ground state: the quantum mechanical selection rule prohibits electronic interactions. As a result, evolution has driven organisms to develop techniques to overcome this. Most commonly, enzymes containing transition metals are used to activate O_2, producing reactive radical intermediates or products, i.e. ROSs. ROSs play an important role in normal biological functions, however an "imbalance" may lead to the oxidation of important biomaterials, or oxidative stress.[?] In humans, oxidative stress has been linked to many degenerative disease states such as Alzheimer's disease,[? ?] Parkinson's disease,[?] ageing, and cancer.[?]

It is widely accepted that the vast majority of ROSs originate from reactions of O_2 with the redox-active metals copper and iron.[?] A common example is the Haber-Weiss reaction, the second step in the Fenton cycle (Equations **??** – **??**):

$$Fe^{3+} + {}^{\bullet}O_2^{-} \longrightarrow Fe^{2+} + O_2 \tag{1}$$

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^{-} + {}^{\bullet}OH \tag{2}$$

$$\overline{\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad}$$

$${}^{\bullet}O_2^{-} + H_2O_2 \longrightarrow {}^{\bullet}OH + OH^{-} + O_2 \tag{3}$$

It is the production of the highly reactive hydroxyl radical ($^{\bullet}OH$) which is responsible for the initiation of the majority of oxidative stress through the abstraction of a hydrogen atom. Given its very short *in vivo* half-life of about 10^{-9} s, $^{\bullet}OH$ reacts with practically all biomaterials.[?]

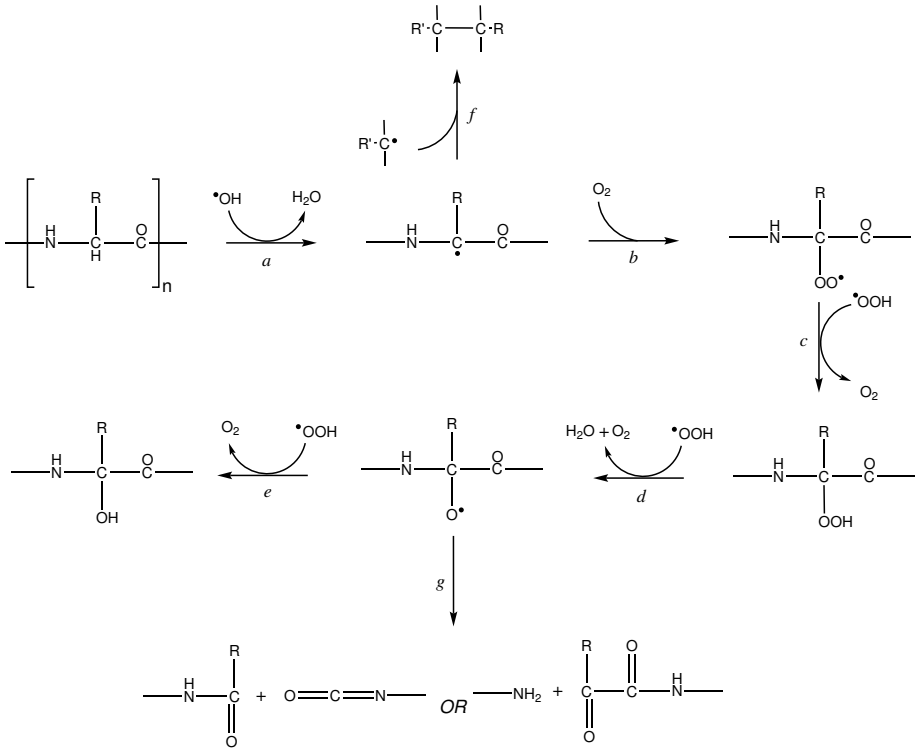
DNA and RNA are susceptible to radical damage,[? ?] and reactions of $^{\bullet}OH$ with DNA molecules have been studied in some detail. Damage can occur to both the pyrimidine and purine bases, as well as the deoxyribose backbone, with over 20 DNA lesions having been identified.[? ?] The most commonly studied

product is 8-hydroxyguanine (or the tautomer 8-oxo-2′-deoxyguanosine), which is the result of the oxidation of the guanine nitrogenous base. This particular oxidation can result in mismatched base pairing of guanosine with adenine (rather than cytosine), contrary to the Watson-Crick model, leading to possible substitutions in the genome.[?] It is important to realise that although there are enzymes which actively repair DNA and remove lesions,[?] oxidation represents the permanent modification of genetic material which is the first step in mutagenesis, carcinogenesis, and ageing.

Polyunsaturated fatty acids are extremely sensitive to oxidation. Specifically, the autoxidation of polyunsaturated fatty acids and esters occurs rapidly, and has been intensely investigated.[? ? ? ? ?] This radical chain reaction is initiated by reactions of lipids with $^{\bullet}$OH forming a pentadienyl radical. Oxygen adds rapidly (although reversibly) to the intermediate carbon radical,[?] giving a lipid peroxyl radical (LOO$^{\bullet}$). Once formed, LOO$^{\bullet}$ can propagate to form further carbon centred radicals, terminate through the reaction with another LOO$^{\bullet}$, or can rearrange through a cyclisation reaction to form an endoperoxide. The endoperoxide product reacts further to produce mainly aldehydes, and most predominantly malondialdehyde (MDA).[?] MDA is highly reactive and has been shown to be either mutagenic or carcinogenic in mammalian and bacterial models.[?]

Our work is primarily concerned with models for proteins. The oxidation of protein by ROSs occurs through a radical chain mechanism which has been studied in detail.[?] Through experiments in which proteins were exposed to ionising radiation, it was demonstrated that protein oxidation is initiated through hydrogen atom transfer (HAT) reactions with $^{\bullet}$OH. The propagation often occurs through radical-mediated oxidation, as illustrated in **??**.

[h!]



[Common reactions involved in radical-mediated oxidation of proteins]Common reaction involved in radical-meditated oxidation of proteins. The reactions are as follows: *a* initiation or radical chain through abstraction by the hydroxyl radical, *b* radical addition of molecular oxygen, *c* HAT with an incipient peroxyl radical, *d* additional reaction with an incipient peroxyl radical producing water and oxygen, *e* termination by HAT with an incipient peroxyl radical, *f* possible cross-linking mechanism of two carbon centred radicals *g* possible fragmentation pathways of an oxygen centred radical intermediate. Figure adapted from Reference **?** .

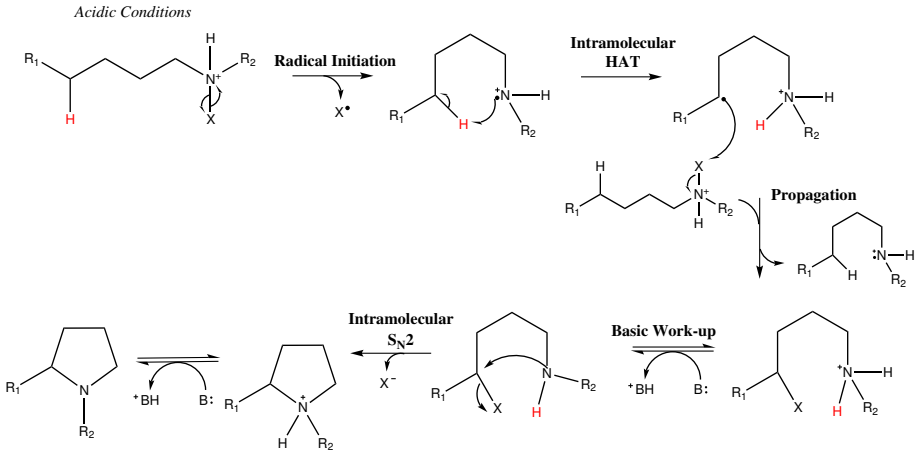
Initial abstraction occurs primarily at the α-carbon position (Reaction *a*), although the side-chains are also susceptible to oxidation. Those side-chains containing sulfur,[?] as well as tyrosine (which has a fairly weak phenolic O-H bond of about 89 kcal mol^{-1}),[?] are particularly susceptible to oxidation. The course of propagation through radical mediated protein oxidation is determined by the availability of either singlet oxygen ($^1O_2$), or superoxide ($O_2^{\bullet -}$) (or the protonated form, hydroxyl radical ($^{\bullet}OOH$)). Reactions that proceed with singlet oxygen are shown in *b*-*e*. The radical chain reaction can be terminated through two mechanisms, protein-protein cross-linking (Reaction *f*) or protein fragmentation (Reaction *g*). These processes lead to the accumulation of oxidised proteins which is associated with many degenerative diseases.[?]

1.2 Hydrogen atom transfer reaction in chemical processes

Given the importance of HAT reaction in biological systems, it seems obvious for chemists to develop means in which this tool can be used as well. Given the highly reactive nature of free radicals, this has certainly been a challenge. However, there exists multiple examples of utilising HAT reactions in important energy conversion processes,[?] as well as in chemical synthesis.[? ?]

In organic synthesis, the replacement of specific C-H bonds (C-H bond functionalisation) has long been of interest. One such way to achieve this is through radical reactions.[?] Intramolecular radical reactions were first utilised in the late 1800s when Hofmann showed that homolysis of bromamines and chloramines lead to functionalisation of δ-methylene or methyl groups.(citation needed, see ?) Now called the Hofmann-Löfler-Freytag reaction, this reaction is used to form cyclic amines, and proceeds through an intramolecular HAT, as shown in **??**. The reaction is initiated by the cleavage of a nitrogen-halogen bond, either by radiation or a radical initiator. Next is a key intramolecular HAT reaction that proceeds through a six-membered cyclic transition state which can adopt an unstrained chair conformation. Another related reaction is the Barton reaction[?] which involves photo-initiated homolytic cleavage of a nitrite (RO-NO) bond, followed by δ-hydrogen abstraction, and radical coupling to form a δ-nitroso alcohol. The Hofmann-Löfler-Freytag reaction served as a proof of concept that HAT could be useful in synthetic chemistry.

[htb]



[Reaction mechanism of the Hofmann-Löfler-Freytag reaction] Reaction mechanism of the Hofmann-Löfler-Freytag reaction. The reaction proceeds under acidic conditions so that the amine is protonated. Step one is radical initiation, typically through radiation or a radical initiator, step two is the intramolecular HAT reaction, step three is the propagation of the radical activating addition amines and abstracting a halide, step four begins the basic work up with deprotonation of the amine, followed by S_N2 attack of the δ position with a halide, and finally the second deprotonation of the amine

centre.

Since the early days of Hofmann, a great deal of work has been done, and new methods for C-H functionalisation have been achieved. The most commonly used technique is the hydroxylation of C-H bonds, which then serve as a synthetic handle. Transition metal chemistry is now typically employed to achieve C-H bond functionalisation. This often involves highly reactive metal-oxo intermediates responsible for triggering C-H bond cleavage, with an inorganic HAT reaction being an essential part of the mechanism.[?] Reactions of this nature are subject to low selectivity and complex product mixtures due to the similarly thermodynamics and kinetics of hydroxylation and dehydrogenation pathways.[?] A similar mechanism is found in metalloenzymes, which prompted important work investigating the selectivity and tunability of these reactions, with considerable success. This work along several works of others,[?] are exemplary cases where a detailed understanding of the HAT reaction mechanism can lead to significant contributions to chemistry.

2 Physico-chemical determinants of formal hydrogen transfer reactions

Given the importance of HAT reactions in biology and chemistry, a thorough understanding of these reactions is clearly important. In order to fully understand HAT reactions, we much understand the factors which influence these reactions.

2.1 Understanding chemical reactions

The potential energy surface (PES) for any chemical reaction is a complex hypersurface that depends on many variables. Typically this problem can be simplified by examining only the relevant geometry changes. Often the two most important coordinates can be isolated, giving a 3-dimensional potential energy surface. Furthermore, in chemistry we simplify this problem to 2-dimensions, such that the so-called intrinsic reaction coordinate, or the lowest energy cross section of a higher dimension PES. This yields a reaction coordinate diagram, as is illustrated below in **??**.

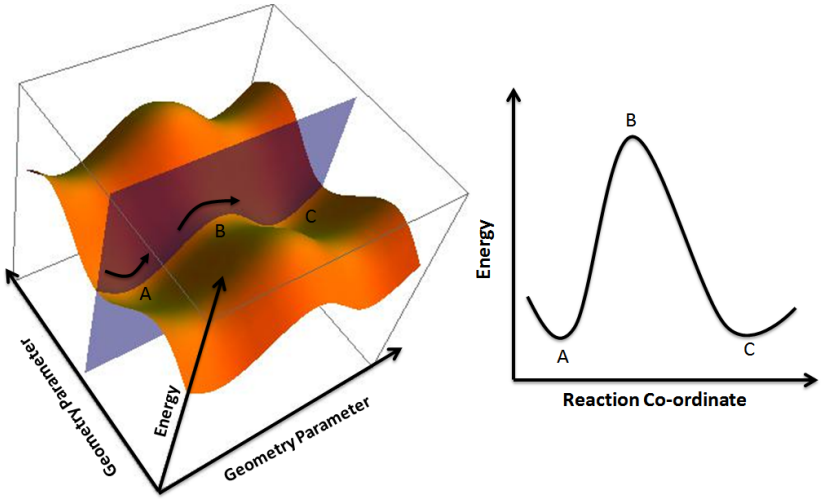


Figure 1: Placeholder PES from Wikipedia

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

In quantum chemistry, we are generally not concerned with the dynamics of a chemical reaction, but rather the thermodynamic and kinetic properties of a

reaction. This is achieved through the investigation of stationary states (reactants, pre-reaction complex, TS complex, post-reaction complex, and products) along the reaction coordinate. Thermodynamic analysis of a reaction requires the understanding of the stability of the products relative to the reactants, measured by change in Gibbs free energy ΔG, while kinetic analysis requires the understanding of the stability of the TS complex relative to the reactants measured by the Gibbs free energy barrier $\Delta G^{\ddagger}$.(Need to modify figure to include energy)

To fully understand HAT reactions, one must analyse the factors which influence the thermodynamics and kinetics of these reactions. Thermodynamically this is relatively simple; the most important factor to consider is relative bond strengths. Typically, a reaction will be exergonic if the bond being formed is stronger than the bond being broken. Entropic changes (ΔS) in HAT reactions are in all but the most unusual cases, negligible ($\Delta S \approx 0$).[?] Kinetic analysis can be considerably more complicated, as there are numerous factors which can stabilise or destabilise the reactants or TS complex. The important factors include solvent interactions, non-covalent interactions, bond strengths, and stereo-electronic interactions, each of which is described below.

2.2 Factors influencing the kinetics of HAT reactions

2.2.1 Solvent interactions

Kinetic solvent effects (KSEs) describe the effect on a reaction from solvent interactions. Solvent has the ability to stabilise or destabilise the TS complex of a HAT reaction. Since the earliest studies describing KSEs in 1964,[?] a great deal of literature exists describing KSEs, especially for HAT reactions involving phenols.[?] Hydrogen bond (HB) formation between phenols and HB accepting solvents is attributed to the observation that increasing solvent polarity decreases the rate constants for HAT reactions (k_H). Unlike phenols, our amide models possess an HB accepting moiety, and thus interact strongly with HB donating solvents. Experimental work from our colleagues in Rome has demonstrated that for C-H bond HAT from substrates with HB accepting capabilities, k_H decreases with solvent HB donating ability. Evidence for this is summarized in **??**: for HAT reactions of CumO$^{\bullet}$with N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and triethylamine (TEA), as the polarity and HB donating ability of the solvent increases, the rate constant k_H, decreases.

The KSEs observed in **??** can been explained on the basis of hyperconjugation, the donation of electron density from neighbouring orbitals into C-H σ^* antibonding orbitals. Hyperconjugation has a net stabilising effect, however it decreases the strength of C-H bonds by accepting electron density into a C-H σ^* orbital. For the species listed in **??**, abstraction occurs primarily from C-H bonds adjacent to a heteroatom or π system. Hyperconjugative overlap between the heteroatom and C-H σ^* antibonding orbitals in these species is decreased by the formation of a hydrogen bond with solvent, effectively increasing the strength of the C-H bond and thus destabilising the TS complex and increasing

Solvent	N,N-dimethylformamide[a]	Tetrahydrofuran[b]	Triethylamine[c]
isooctane	$(7.7 \pm 0.1) \times 10^6$	$(1.21 \pm 0.02) \times 10^7$	$(2.9 \pm 0.1) \times 10^8$
benzene	$(3.1 \pm 0.1) \times 10^6$	$(7.2 \pm 0.7) \times 10^6$	$(2.8 \pm 0.1) \times 10^8$
MeCN	$(1.24 \pm 0.02) \times 10^6$	$(5.8 \pm 0.2) \times 10^6$	$(2.0 \pm 0.1) \times 10^8$
t-BuOH	$(1.38 \pm 0.03) \times 10^6$	$(5.8 \pm 0.2) \times 10^6$	$(1.61 \pm 0.03) \times 10^8$
MeOH	$(9.8 \pm 0.2) \times 10^5$	$(4.9 \pm 0.2) \times 10^6$	$(3.8 \pm 0.1) \times 10^6$
TFE	$< 1 \times 10^4$	$(2.7 \pm 0.1) \times 10^6$	

Table 1: Second-order rate constants (k_H, $M^{-1}s^{-1}$) for HAT from C-H bonds of hydrogen bond accepting substrates to the cumyloxyl radical measured in different solvents at 25 °C. [a]Reference **?** . [b]Reference **?** and **?** . [c]Reference **?** .

2

$\Delta G^{\ddagger}$. This is the key kinetic effect of solvation in the our model systems.

2.2.2 Non-covalent interactions

Non-covalent interactions (NCIs; eg. van der Waals interactions, hydrogen bonding, etc.) play a central role in all chemistry. It has already been demonstrated that HB formation between substrates and solvents plays an important role, however oxygen centres can also hydrogen bond with substrates as both acceptors and donors.[?] 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. No literature currently exists which discusses how the strengths of these interactions impacts the kinetics of a reaction, however these effects cannot be ignored. Chapter **??** of this thesis shall deal with this specifically.

Non-covalent interactions are known to be important in the stabilisation of TS complexes in HAT reactions.[? ?] Although the effects of NCI stabilisation are difficult to quantify, the concept of TS complex stabilisation is being recognised in applications such as enzyme catalysis[?] and synthetic catalysis.[?]

It has been demonstrated that the formation of pre-reaction complexes can in fact be the rate-limiting step of a reaction.[? ? ?] Combined experimental and computational examinations of HAT reactions between the cumyloxyl ($CumO^{\bullet}$) or benzyloxyl ($BnO^{\bullet}$) radicals with tertiary alkylamines and alkylamides demonstrated that the relatively acidic α-C-H of $BnO^{\bullet}$is capable of forming hydrogen bonds with enthalpies (ΔH) of 4.0 kcal mol^{-1} for alkylamines to 8.5 kcal mol^{-1} in alkylamides. The comparison of k_H for these HAT reactions between $CumO^{\bullet}$and $BnO^{\bullet}$(k_H^{BnO}/k_H^{CumO}) demonstrates large rate enhancements, ranging from 2.8 for the very sterically hindered triisobutylamine, to 1094 for 1,4-diazabicyclo[2.2.2]octane. In this case, NCIs control the kinetics of the reaction not through stabilisation, but rather through changing the rate-determining step.

2.2.3 Bond strengths and the Bell-Evans-Polanyi Principle

It has long been the interest of chemists to understand chemical reactions from both a thermodynamic and kinetic standpoint. The measurement and comparison of bond strengths, that is bond dissociation enthalpies (BDEs), is central to the understanding of reactivity with respect to thermodynamics. There exists a tremendous amount of literature in which BDEs are linked to chemical reactivity, especially for HAT reactions.[? ? ? ? ?]

Often, BDEs are used in linear free energy relationships (LFERs) to relate chemical reactivity to bond strength. One such example[?] is the application of BDEs to the Hammett equation,[?] which can be used to study substituent effects from thermodynamic (Equation **??**) or kinetic analysis (Equation **??**).

$$\log \frac{K_X}{K_H} = \rho\sigma_X \tag{4}$$

$$\log \frac{k_X}{k_H} = \rho\sigma_X \tag{5}$$

In the above equations, K is an equilibrium constant and k is a rate constant for either a reference reaction with a hydrogen substituent H or a given substituent X. The substituent parameters σ_X, have been measured for various different reference reactions, although the original parameters were measured for the acidity of benzoic acid.[?] Plots of $\log(K_X/K_H)$ or $\log(k_X/k_H)$ against σ_x have been used to determine ρ, the sensitivity constant. Originally ρ was used to determine whether a reaction was more sensitive ($\rho > 1$), less sensitive ($\rho < 1$), or equally sensitive to substituents than benzoic acid, with negative charges being produced. If ρ is negative then positive charge is said to be formed as a result of substituents.

In the context of BDEs, **?** examined a series of substituents (Y) on toluenes, anilines, and phenols (4-YC_6H_4−ZX), and showed that the Z-X BDEs can be correlated to the electrophilic substituent constants, σ_p^+(Y). This was surprising because it demonstrated that homolytic properties correlated with properties derived from the heterolytic S_N1 solvolyses of para-substituted cumyl chlorides.[?] Specifically, this showed that since σ_p^+(Y) describes the relative ability of Y to stabilise a positive charge, the ability to stabilise strong electron withdrawing (EW) moieties can be well described in general by these parameters. This means that BDEs for toluenes and anilines are well correlated to σ_p^+(Y), since $O^\bullet$ and $NH^\bullet$ can be described like positive charges (strong EW groups). Toluenes, which have resulting radicals ($CH_2^\bullet$) which are neither electron withdrawing nor donating, are poorly correlated with σ_p^+(Y).

Another interesting LFER, which is utilised in Chapter **??**, is the Bell-Evans-Polanyi (BEP) Principle,[? ?] which states that the difference in activation energy (E_a) for two related reactions (within the same family), is proportional to the differences in reaction enthalpy (ΔH):

$$E_a = E_0 + \alpha\Delta H \tag{6}$$

This relationship has been more generally used to compare larger families of reactions. The remaining terms in Equation **??** are E_0, the activation energy of a reference reaction, and α is a constant which characterises the position of the TS along the reaction coordinate. This can be rationalised by considering a series of reactions with similar energy profiles: if the reaction becomes more exothermic, the barrier height will decrease (the opposite is also true for endothermic reactions), as illustrated in **??**.

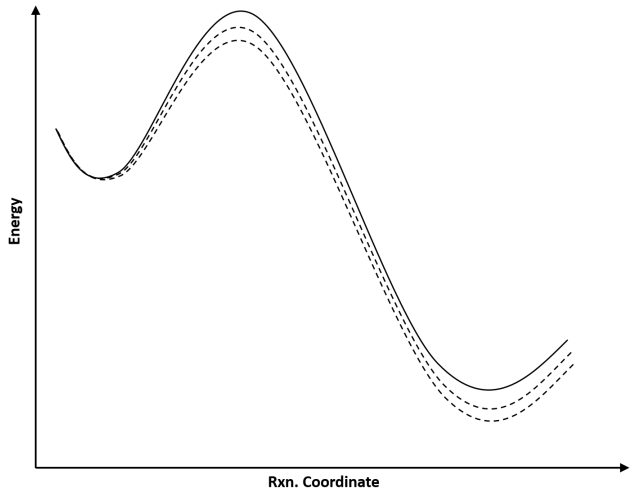


Figure 2: Energy profiles for a series of related exothermic reactions illustrating the Bell-Evans-Polanyi Principle.

If the BEP relationship holds for a series of related HAT reactions, then BDEs should correlate with the activation energy, where increased bond strengths would represent a destabilisation in the TS complex. In practice, plots of BDEs against the logarithm of rate constant are used. An interesting example of this is the work of **?**, in which the free radical oxidation of unsaturated lipids is examined. They achieve this through the correlation of theoretically determined C-H and C$-$OO$^\bullet$ bond strengths with experimentally measured HAT rate constants and O_2 addition rate constants, respectively. BEP plots (BDE vs. $\log k$) for a large range of polyunsaturated fatty acid models show good correlation for both the C-H bonds and C$-$OO$^\bullet$ bonds examined. This demonstrates that BDEs have a direct impact on the reaction barrier height, giving validation to the BEP Principle.

Although chemists often consider the importance of BDE in thermodynamic analysis, bond strengths are an important consideration in kinetic analysis as well. As such, the altering of bond strengths can be an important factor in related HAT reactions. The generallity of application of the BEP Principle is discussed in Chapter **??**.

2.2.4 Stereo-Electronic interactions

The effects of sterics and electronics have been shown to play an important role in HAT reactions. Generally, these effects are described as two seperate phenomena: polar effects and steric effects.

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 **??**, there are four obvious resonance forms. For a series of related reactions, E_a would be expected to decrease as the contribution of dipolar ion resonance forms increases.[?] Oxygen centred radicals are electrophilic in nature, thus the importance of the third resonance structure becomes important. HAT is favoured from C-H bonds which are electron rich, or nucleophilic.[?]

[htb] $\left[\mathrm{X}^{-}\mathrm{H}^{-}\mathrm{Y}\right]^{\ddagger}$

$[\mathrm{X}^{\bullet}\mathrm{H}{-}\mathrm{Y}]^{\ddagger} \longleftrightarrow [\mathrm{X}{-}\mathrm{H}\mathrm{Y}^{\bullet}]^{\ddagger} \longleftrightarrow [\mathrm{X}{:}^{-}\mathrm{H}^{\bullet}\mathrm{Y}^{+}]^{\ddagger} \longleftrightarrow [\mathrm{X}^{+}\mathrm{H}^{\bullet}\mathrm{Y}{:}^{-}]^{\ddagger}$ A generic HAT transition state structures and possible resonance forms.

An example of this effect is from the work of our colleagues in Rome,[? ?] in which rate constants (k_H, normalised for the number of abstractable hydrogens) for cyclohexane and acetone to the cumyloxyl radical (CumO$^{\bullet}$) were measured and compared to theoretically determined C-H BDEs. Cyclohexane has a C-H BDE = 99.5 kcal mol^{-1} and $k_H = 9.2 \times 10^4$ M^{-1}s^{-1} , while acetone has C-H BDE of 96.0 kcal mol^{-1} and $k_H = < 2 \times 10^3$ M^{-1}s^{-1} . As a result of polar effects, although cyclohexane has a greater bond strength, it is at least an order of magnitude more reactive in HAT than acetone.

The effects of steric bulk also play an important role in HAT, and have been studied extensively by our colleagues in Rome, as well as by others.[? ? ? ? ? ? ? ? ?] Although a C-H bond may be weaker 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 destabilisation of the TS complex. For example, in reactions of tertiary acetamides with CumO$^{\bullet}$,[?] where abstraction occurs mainly from C-H bonds α to the nitrogen atom, a two fold decrease in normalised rate constant is observed in going from N,N-dimethylacetamide to N,N-diisobutylacetamide (k_H $= 2.0 \times 10^5$ and 7.8×10^4 M^{-1}s^{-1} , respectively).

2.3 Mechanistic details of hydrogen transfer reactions

For a simple HAT reaction, as shown in **??**, 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.[? ? ? ? ? ? ? ? ? ? ? ?] Primarily, the distinction between the two processes is unclear because the two processes cannot be entirely separated physically.[?]

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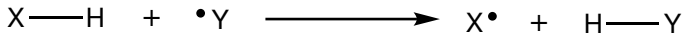

A generic formal hydrogen transfer reaction.

The quintessential example when comparing direct HAT to PCET is the self-exchange reactions of benzyl/toluene and phenoxyl/phenol shown in **??**, as described by **?**.

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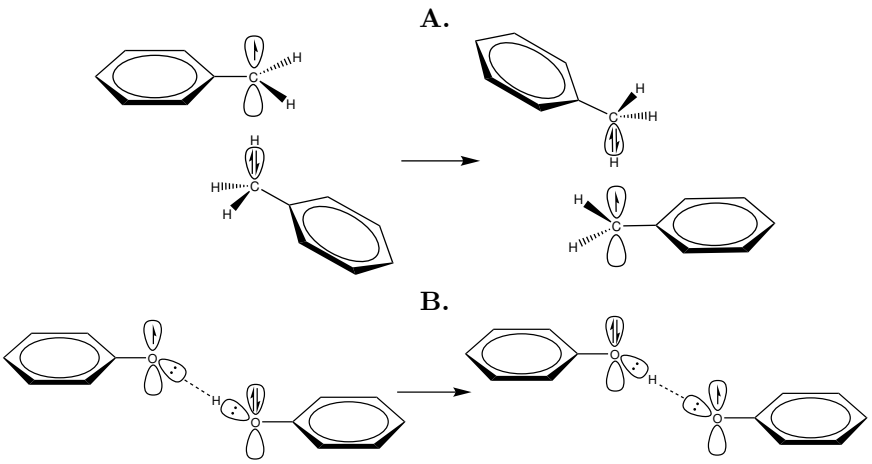

Self-exchange reactions of the **A.** benzyl/toluene couple through direct HAT **B.** phenoxyl/phenol couple through PCET.

In this work, the transition state structures, obtained through theoretical studies, were reported. The proposed structures have C_{2h} and C_2 symmetry for **??** A and B, respectively, 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 and little delocalisation of the radical into the π-system. Additionally, the singly occupied molecular orbital (SOMO) is of σ symmetry. The calculated enthalpic barrier ($\Delta H^{\ddagger}$) is 17.7 kcal mol^{-1} . For the phenoxyl/phenol pair, a fairly strongly hydrogen bonded pre-reaction complex is first formed (-8.1 kcal mol^{-1} , relative to reactants). The TS structure is such that the phenoxyl radical occupies a $2p$ orbital, and is allowed to overlap with the $2p$ lone pair of the phenol moiety and the aromatic π systems. This demonstrates that the SOMO is of π symmetry and highly delocalised, and that HAT occurs through a PCET mechanism. The reaction has a barrier height $\Delta H^{\ddagger} = 5.0$ 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 **?** 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.[? ?] In particular, **?** demonstrated that this neglected the important contributions of $\pi - \pi$ interactions and lone pair-π interactions. Additional calculations revealed there exists a TS structure for the benzyl/toluene couple which is 3.7 kcal mol^{-1} lower in energy than previously reported. This structure has C_2 symmetry with the aromatic rings oriented 34° relative to one another, allowing for optimal π-stacking, and thus $\pi - \pi$ overlap opens up an electronic channel for PCET to occur. They also suggest that the phenol/phenoxyl couple likely prefers a π-stacked TS structure, and compare this to a structural analogue, a naturally occuring tyrosyl/tyrosine couple. Additional work by **?** confirmed the existance of a π-stacked TS structure for the phenol/phenoxyl couple. They used an approach which utilises natural population analysis along the intrinsic reaction coordinate, and demonstrated that both the benzyl/toluene couple and phenoxyl/phenol couple favour a π-stacked TS structure and undergo HAT through a PCET mechanism. Interestingly, they also showed that reaction barrier heights for the PCET mechanism are systematically lower than those for direct HAT.

As there is not an obvious way to explore the differences in mechanism experimentally, computational examination of formal HAT reactions enables analysis of the mechanism of these reactions. Using a variety of tools, a general distinction between a HAT mechanism and PCET mechanism can be achieved, however, as stated previously, these mechanisms are not mutually exclusive. Regardless, important insight can be gained from understanding the electronic behaviour of these reactions.

2.4 The effects of metal cations on HAT reactions

Solvent interactions in HAT reactions can be described as Lewis acid/base interactions. In biological systems, the most common solvent is water, which can act as both a Lewis acid and base, due to its self-ionising equilibrium. Other important Lewis acids in biology are the non-redox active alkali and alkaline earth metal cations that are present ubiquitously throughout biological systems. Metal ions such as sodium, magnesium, potassium, and calcium are essential to biological function.[?] (Include something about number of ions per protein and/or biological concentrations)

Given the Lewis acid/base nature of these non-redox active metals, we were driven to explore the effects upon HAT reactions. Experimental investigation of these effects has been underway by the Bietti group in Rome. The effects of non-redox active metal cations on HAT from C-H bonds of cyclohexadiene (CHD), tetrahydrofuran (THF), and tertiary alkylamines to CumO$^{\bullet}$were examined.[?] This work is summarized in **??**. Additional experiments examining the same reactions of *N*, *N*-dimethylacetamide (DMA) and *N*, *N*-dimethylformamide (DMF),[?] as well as for various other acetylamides[?] have been performed, and provides

the experimental background for this thesis.

Substrate	Conditions	$k_H(M^{-1}s^{-1})$
CHD		$(6.65 \pm 0.02) \times 10^7$
	$LiClO_4$ 1.0 M	$(7.49 \pm 0.04) \times 10^7$
	$Mg(ClO_4)_2$ 1.0 M	$(7.0 \pm 0.1) \times 10^7$
THF		$(5.7 \pm 0.1) \times 10^6$
	$LiClO_4$ 1.0 M	$(2.87 \pm 0.04) \times 10^6$
	LiOTf 1.0 M	$(2.8 \pm 0.2) \times 10^6$
	$Mg(ClO_4)_2$ 1.0 M	$(1.8 \pm 0.1) \times 10^6$
TEA		$(2.0 \pm 0.1) \times 10^8$
	$LiClO_4$ 1.0 M	$(9.37 \pm 0.01) \times 10^7$
	$Mg(ClO_4)_2$ 0.005 M	$< 1 \times 10^{6*}$
PMP		$(1.70 \pm 0.02) \times 10^8$
	$LiClO_4$ 1.0 M	$(9.0 \pm 0.3) \times 10^7$
	$Mg(ClO_4)_2$ 0.005 M	$< 1 \times 10^{6*}$

Table 2: Summary of experimental rate constants of HAT with CumO$^\bullet$ for cyclohexadiene (CHD), tetrahyrofuran (THF), triethylamine (TEA), and 1,2,2,6,6-pentamethylpiperidine (PMP), including the effect of non-redox active metal cations. Rate constants were determined by LFP in 25 °C MeCN. *Rate constants are approximate as the effects of even small additions of metal cations cause rate outside the range of laser flash photolysis experiments.

In general, metal cation interactions lead to deactivation of C-H bonds and experimental rate constants decrease as a result. An explaination for this is the same as for KSEs, where Lewis acid binding causes a decrease in α-C-H bond σ^* population, thus increasing the effective C-H bond strength and decreasing k_H. For cyclohexadiene, a marginal increase in k_H was observed with additions of 1.0 M $LiClO_4$ and $Mg(ClO_4)_2$, which was explained on the basis of interactions of the metals with CumO$^\bullet$. This demonstrates that metal cations have a limited ability to influence HAT reactions of CumO$^\bullet$ with alkene based substrates. For THF, k_H is 2.0 and 3.2 times lower with the addition of 1.0 M $LiClO_4$ and $Mg(ClO_4)_2$, respectively. $LiClO_4$ has a roughly 2-fold decreasing effect on k_H for alkylamines, whereas $Mg(ClO_4)_2$ has a significantly greater effect, decreasing k_H by more than two orders of magnitude, an effect that has been attributed to the compact charge density of Mg^{2+}. As a whole, these results suggest that metal ions interact more strongly with substrates than CumO$^\bullet$, thus C-H bond deactivation is observed due to Lewis acid/base effect. The Lewis acidity of the metal appears to have an important role, since $Mg(ClO_4)_2 > LiClO_4$ in regards to Lewis acidity and effect on k_H. The Lewis basicity of the substrate is also clearly important. Alkylamines undergo a larger decrease in k_H, relative to THF, as they are stronger Lewis bases. Computational studies have validated these results, demonstrating that binding of $Mg(ClO_4)_2$ leads to a 5.1 kcal mol^{-1} decrease in the α-C-H BDE in TEA and that k_H decreases by > 4 orders of magnitude.[?]

Simple amides such as DMF and DMA are often used as simple peptide models.[?] As such the deactivation of C-H bonds in amides, as indicated by the observed decreases in k_H, leads to the central hypothesis of this thesis: *non-redox*

active metals cations can serve as chemoprotective agents for biomolecules. Experimental evidence for this is demonstrated in **??**. For $LiClO_4$ added to DMF and DMA, total inhibition of HAT occurs up to 2 and 1 molar equivalents, respectively. Inhibition of HAT occurs for 2 and 4 molar equivalents, respectively, followed by total non-inhibition. A much weaker effect is observed with $NaClO_4$, while a similar strong deactivating effect is observed for $Ca(ClO_4)_2$. The addition of $Mg(ClO_4)_2$ gives weak deactivation for the first two molar equivalents of both DMF and DMA, with strong activation for an additional two equivalents. This unusual behaviour is as of yet, unexplained. Additional discussion of experimental results shall be reserved for Chapter **??**.

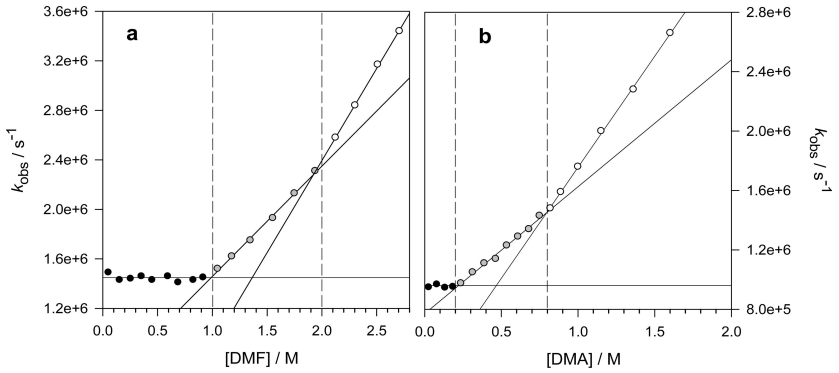

Figure 3: Plots of observed rate constants against concentation of substrate for HAT reactions with cumyloxyl radical: **a** Substrate = DMF, measured by LFP at 25°C in solutions of MeCN containing 1.0 M dicumyl peroxide and 0.5 M $LiClO_4$. Complete inhibition of HAT is observed at 0–1.0 M, while linear regression for the 1.0–2.0 M regions gives k_{H1} = 8.91 $\times 10^5$ $M^{-1}s^{-1}$, and k_{H2} = 1.49 ^{6} $M^{-1}s^{-1}$ in the 2.0–2.7 M region. **b** Substrate = DMA, measured by LFP at 25 °C in solutions of MeCN containing 1.0 M dicumyl peroxide and 0.2 M $LiClO_4$. Complete inhibition of HAT is observed at 0–0.2 M, while linear regression in the 0.2–0.8 M region gives k_{H1}=8.54 $\times 10^5$ $M^{-1}s^{-1}$ and k_{H2} = 1.49 $\times 10^6$ $M^{-1}s^{-1}$ in the 0.8–1.6 M region. Figure taken from Reference **?** .