

Introduction

Radicals are chemical species which 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 metabolism but biological molecules, 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.^{1–5}

In biological systems, radicals are derived from both endogenous sources, such as transition metal-ion redox processes and other *in vivo* processes, as well as exogenous sources, for instance, solar radiation and air pollutants. Oxygen centred radicals, known as reactive oxygen species (ROSs) in biology, are particularly important due to the nature of the aerobic respiration. The radicals of primary concern are the highly reactive hydroxyl radical (HO^\bullet), alkoxyl radicals (RO^\bullet), superoxide ($\text{HOO}^\bullet/\text{O}_2^{\bullet-}$), and peroxy radicals (ROO^\bullet).⁵ Damage occurs when an ROS initiates a radical chain reaction through hydrogen atom transfer (HAT), electron transfer, or addition reactions, leading to rapid propagation. HAT is the most relevant reaction and is the focus of my work.

Hydrogen atom transfer (HAT) reactions are a fundamental radical chemical transformation which has been studied for over a century.^{6,7} At the macroscopic level, HAT reactions which involve oxygen centred radicals and non-radical organic substrates are reasonably well characterised: the effects of bulk solvent are well understood.⁸ However, the roles of substrate-radical and substrate-radical-medium interactions at the microscopic (molecular) level continue to be relatively poorly understood.

Recent work from our group, in collaboration with colleagues at University of Rome Tor Vergata, has focused on the importance of substrate-radical interactions. Specifically, it has been shown that the three-dimensional structures of oxygen centred radicals, as well as the organic substrates, impacts the nature of the interactions involved in HAT reaction pathways. In our work, we utilise primarily the BnO^\bullet and CumO^\bullet radicals, which serve as a convenient proxy to biological oxygen centred radicals. Reaction involving BnO^\bullet and CumO^\bullet can be easily monitored using highly resolved laser flash photolysis (LFP) techniques. A combination of theoretical and experimental techniques, have been used to examine reactions involving BnO^\bullet and CumO^\bullet with a variety of organic substrates. A detailed discussion of these results shall be reserved for following chapters, however, a great deal of insight has been gained into the role of the structural of the radicals and substrates, and resulting intermolecular interactions.

Recent experimental result 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 and 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.^{9–11} This effect has been attributed partially to the effects of hyperconjugative overlap. Take for example tetrahydrofuran (THF), shown in 1. 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 \cdot 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 $\text{Mg}(\text{ClO}_4)_2$.⁹

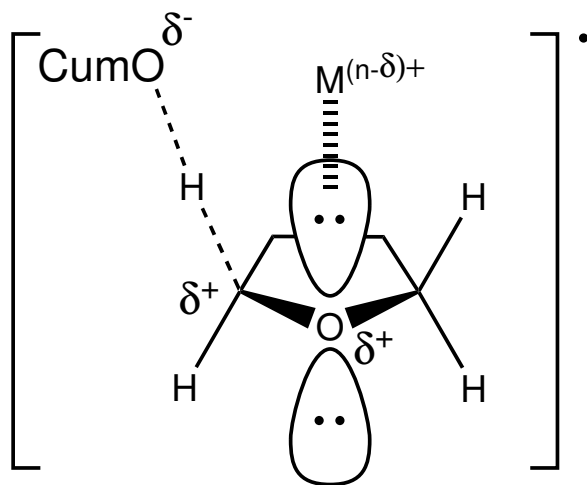


Figure 1: Hyperconjugative overlap in tetrahydrofuran and the effect of non-redox active metal cations. The metal cation acts accepts electron density from the heteroatom lone pair, reducing overlap with the C-H σ^* anti-bonding orbital and increasing the C-H bond strength.

The nature of the interactions between non-redox active metal cations and organic substrates is poorly understood. The primary goal of this thesis is to understand the fundamental physico-chemical properties which lead to the experimentally observed trends in reactivity. This problem is explored in Chapter 5 update. The observed effects have led us to hypothesise that the presence of non-redox active metal cations have a chemoprotective effect against the radical induced oxidation of biomaterials such as proteins.

References

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