SYNTHESIS, REDOX CHEMISTRY AND ANTIOXIDANT ACTIVITY OF SULFENIC ACIDS

by

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Abstract

Sulfenic acids figure prominently in biological and natural products chemistry as important intermediates. For example, cysteine derived sulfenic acids are key intermediates in cell signaling and play both catalytic and structural roles in enzymes. Due to the ubiquitous nature of protein sulfenic acids in cells, methods have been developed to detect and quantitate them. Although they can be detected, the mechanisms by which they form and react remain unclear.

In addition, sulfenic acids are important enzymatic intermediates in *Allium* chemistry. Garlic, a member of the *Allium* genus, is known to have powerful antioxidant activity and this has recently been attributed to allyl sulfenic acid. Allicin, the thisolufinate that gives garlic its characteristic odor and flavor, decomposes to yield allyl sulfenic acid, which is believed to trap chain-carrying peroxyl radicals by readily donating a hydrogen atom, thus inhibiting autoxidations of hydrocarbons.

Despite their important biological roles, little is known of the physicochemical properties of sulfenic acids. This is primarily due to their instability in air and high reactivity as both electrophiles and nucleophiles, giving them the tendency to self-condense and form thiosulfinates. Few persistent sulfenic acids, stabilized by alkyl steric protecting groups surrounding the sulfenic acid functional group, have been reported in the literature. Herein we report our synthetic efforts toward two such sulfenic acids, 9-triptycene sulfenic acid, and *trans*-9-decalinsulfenic acid, which were expected to be appropriate models for cysteine-derived and allyl sulfenic acids. Using 9-triptycene sulfenic acid, we were able to provide insight into the thermodynamics (O-H BDE) and kinetics (k_{inh}) of the reactions of sulfenic acids with peroxyl radicals, which provide a clear connection between the antioxidant activity in garlic and sulfenic acids. We also preliminarily characterized the electrochemical behaviour of this compound, as well as determined its pK_a.

Acknowledgements

Foremost, I would like to thank my supervisor, Dr. Derek Pratt, who truly is a knowledgeable, ambitious, and innovative scientist from whom I have learned a great deal. Derek has taught me to persevere through, and be patient with chemistry, which has led to the success of this project. I am very grateful to have had an enthusiastic supervisor like Derek, and would like to thank him for the countless hours he has spent assisting me with my work.

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Lastly, and most importantly I would like to thank my parents for their encouragement throughout my time at Queen's. Dad, I'm forever grateful for your love of road trips.

Statement of Originality

With the exception of the EPR equilibration studies and inhibited autoxidations of styrene, which were carried out by Dr. Luca Valgimigli, I hereby certify that all of the work described within this thesis is the original work of the author. Any published (or unpublished) ideas and/or techniques from the work of others are fully acknowledged in accordance with standard referencing practices.

Alaina McGrath

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Introduction

1.1 Introduction to Autoxidation

1.1.1 Historical Background and Significance

The rancidification of foods, caused largely by the chemical reaction between atmospheric oxygen and lipids, is commonly observed in the kitchen and results in undesirable odors and flavors. The recognition of lipid deterioration by oxygen is believed to date back to the 15th century when it was found to be useful for the preparation of oil paints and printing inks, and even earlier as a problem associated with storing oils.[1] The first scientific studies on lipid oxidation were published by Nicolas Théodore de Saussure in his book "Recherches Chimiques sur la Végétation" in 1804. There he reports that the amount of oxygen uptake by walnut oil is associated with increased viscosity and unpleasant smell. This process, by which oxygen reacts with organic material spontaneously under mild conditions, is known as autoxidation.

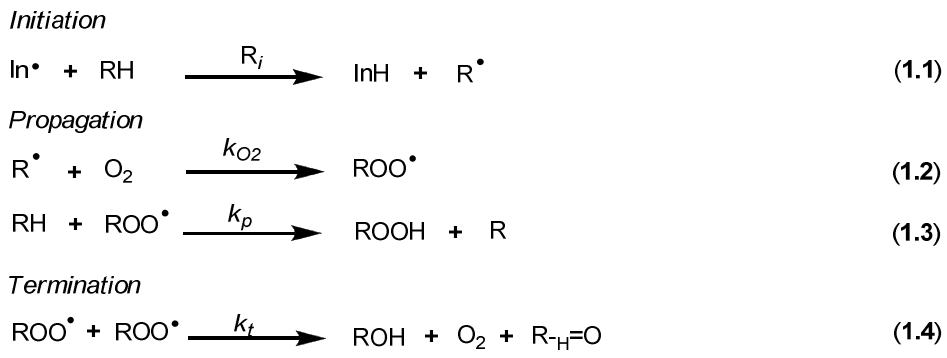
Autoxidation affects more than just food; it can also lead to the degradation of useful hydrocarbon-based materials such as rubber and petroleum products. Bateman and Bolland, of the British Rubber Producers Research Association, were the first to perform systematic studies on hydrocarbon autoxidation in an effort to understand the destruction of these naturally occurring compounds in the 1940's.[2,3] As a result, commercial interest in autoxidation and preventative measures increased and studies contributing to a better understanding of the mechanism by which autoxidation occurs were carried out.[4,5]

By virtue of their existence in an oxygenated atmosphere, living organisms are constantly exposed to oxidative stress. The process of autoxidation in a biological context is called lipid peroxidation, and has been implicated in the pathogenesis of various degenerative diseases, including cancer,[6] cardiovascular disease,[7] and Alzheimer's.[8] Lipid peroxidation can be initiated by reactive oxygen species (ROS), which are generated inadvertently by normal cellular metabolism; these include $O_2^{\bullet}$, $HOO^{\bullet}$, $HO^{\bullet}$, H_2O_2, and $^1O_2$.[9] Potential damage arises when

oxidants are produced at an elevated rate or there is an imbalance between oxidant production and antioxidants.[10] Halliwell and Gutteridge define an antioxidant as 'a substance that, when present at low concentrations compared with that of an oxidizable substrate, significantly delays or inhibits oxidation of that substrate'. In nature, antioxidants can be enzymatic or non-enzymatic; enzymatic antioxidants include superoxide dismutases, catalases, and glutathione peroxidases[10], while non-enzymatic antioxidants include phenolic compounds (e.g. α-tocopherol),[10] and ascorbic acid.[11] Non-enzymatic antioxidants will be discussed in more detail in Chapter 1.2.1.

1.1.2 Mechanism of Hydrocarbon Autoxidation

The mechanism of hydrocarbon autoxidation can be attributed to several scientists including Criegee and Farmer who established that hydroperoxides were the primary products.[12-15] In addition, Bolland, Bateman and coworkers were the first to establish that free radicals had a role in the process, which led to the generally accepted free radical chain mechanism represented in Scheme 1.1.

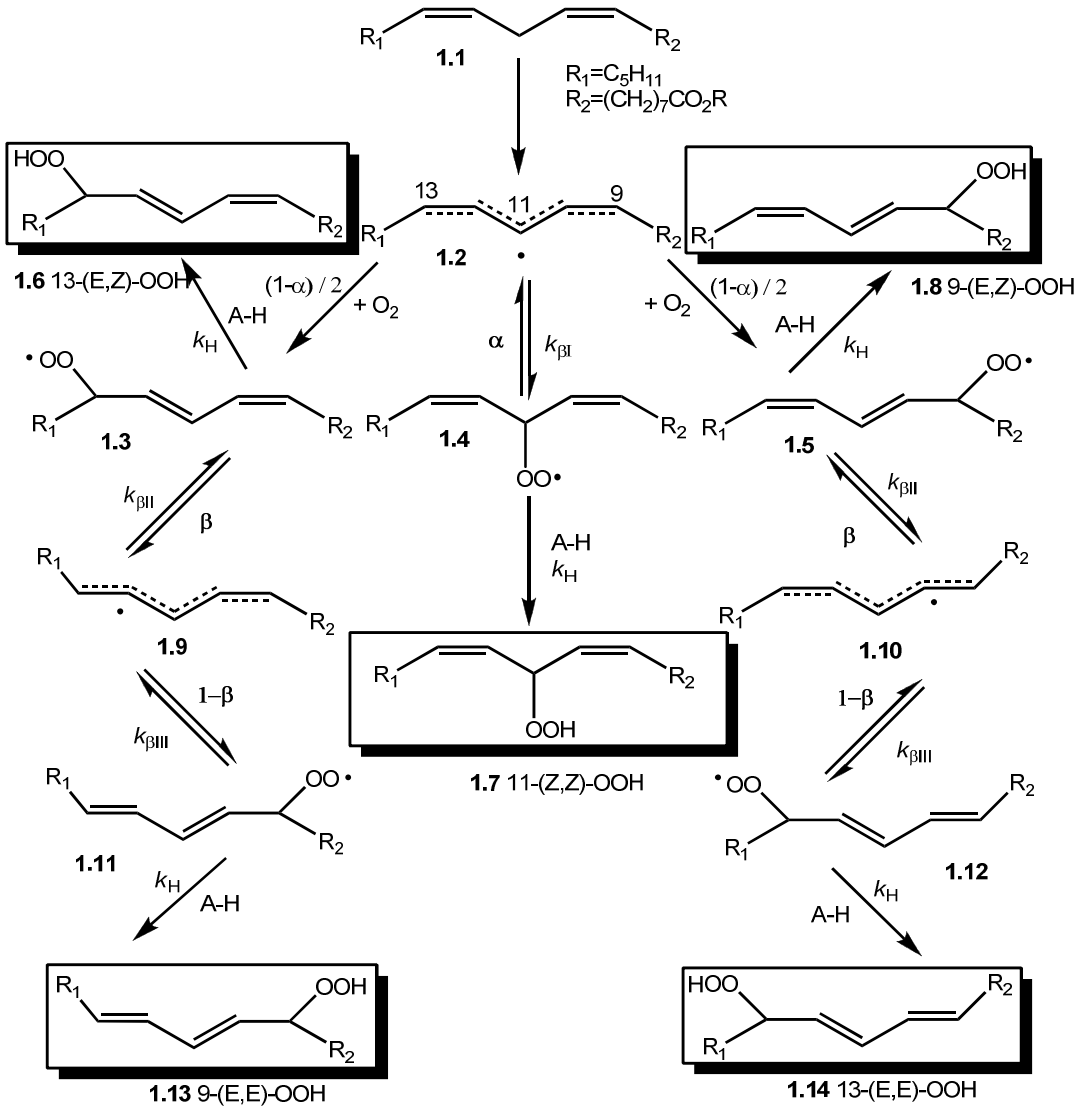


Scheme 1.1 General mechanism of hydrocarbon autoxidation.

The first step for each chain reaction involves the production of an initiator (In•) which subsequently abstracts a hydrogen atom (H-atom) from a hydrocarbon molecule to create a carbon-centered radical (R•, Equation 1.1). Initiator radicals can be any radical that can abstract a H-atom from a hydrocarbon; these are usually generated from peroxides and/or hydroperoxides whose O-O bonds are split homolytically under thermal or photochemical conditions, or via a one electron reduction. In the laboratory, azo initiators or peroxide precursors with even more labile O-O bonds such as peresters or diacylperoxides are generally used.[16] During propagation, the carbon-centered radical reacts in a diffusion controlled manner with oxygen to form a peroxyl radical (ROO•, Equation 1.2)[17] which subsequently, and more slowly,[4] abstracts a H-atom from another hydrocarbon molecule to form another carbon-centered radical and a hydroperoxide (Equation 1.3). The propagation steps are eventually terminated when two chain-carrying peroxyl radicals react to give non-radical products by means of the so-called Russell termination reaction (Equation 1.4).[18] Thus, for each initiation event that occurs, several hydrocarbon molecules may become oxidized to form hydroperoxides.

Autoxidation of biological lipids, coined lipid peroxidation, is well represented by the mechanism shown for methyl linoleate (**1.1**) in Scheme 1.2.[19] Oxidation is initiated by abstraction of the bis-allylic hydrogen atom, forming a pentadienyl radical (**1.2**). The pentadienyl radical can react with oxygen at three different positions: either terminus or the central (bis-allylic) position. In the presence of a hydrogen atom donor (A-H), the conjugated (**1.3**, **1.5**) and non-conjugated diene peroxyl radicals (**1.4)** are subsequently trapped via donation of an H-atom to the radical to form hydroperoxides (**1.6**-**1.8**). It should be noted that these kinetic products rearrange to the thermodynamic products, the *trans*, *trans* conjugated diene hydroperoxides (**1.13, 1.14**). In the presence of high concentrations (i.e. 0.1-1 M) of a good H-atom donor (e.g. a-tocopherol), the bis-allylic hydroperoxide (**1.7**) can be observed.[20]

Polyunsaturated lipids (e.g. linoleate and arachidonate) are particularly susceptible to autoxidation due to their weak C-H bonds (ca. 76 kcal/mol).[21] This is because upon H-atom abstraction from the bis-allylic position, a highly stabilized pentadienyl radical is formed.[22] Monounsaturated lipids (e.g. oleate and cholesterol) are less prone to autoxidation than polyunsaturated lipids, as their C-H bonds are stronger (ca. 84 kcal/mol),[21,23] and corresponding simple allylic radicals less stable. Saturated lipids (e.g. stearate, palmitate) are the least susceptible to autoxidation due to their strong C-H bonds (ca. 98 kcal/mol).[23]



Scheme 1.2. General mechanism of linoleate oxidation in the presence of and H-atom donor, A-H where k_H = rate of H-atom transfer, α = partition coefficient of O_2, $k_{\beta I}$ = 2.4 x 10^6 s^{-1},[20] $k_{\beta II}$ = 27 s^{-1}, $k_{\beta III}$ = 430 s^{-1}.

1.2 Antioxidants

1.2.1 Introduction to Antioxidants

Antioxidants protect hydrocarbons against oxidative degradation by decreasing the rate of autoxidation, and can be divided into two broad classes: preventive antioxidants and chain-breaking antioxidants. Preventive antioxidants reduce the rate of chain initiation by trapping chain initiators such as reactive oxygen species (ROS) in the body. One particular ROS, superoxide ($O_2^{\bullet}$) can be formed in the body as a byproduct of cellular respiration in mitochondria; in this process, electrons travel through a series of proteins via redox reactions, with the final destination for two electrons being an oxygen molecule. Usually oxygen is reduced to form water, but in a small number of cases it is incompletely reduced to give superoxide. On its own, superoxide is not particularly reactive, but can inactivate particular enzymes or initiate lipid peroxidation in its $HO_2^{\bullet}$ form. An example of a preventive antioxidant is superoxide dismutase, which catalyzes the conversion of superoxide to oxygen and hydrogen peroxide, thus preventing radical chain initiation.[24] While H_2O_2 is another ROS, as it reacts with low valent metals to form hydroxyl radicals, it is acted upon by catalase, another example of a preventive antioxidant, which converts H_2O_2 into oxygen and water.[25]

Chain-breaking antioxidants trap chain-carrying peroxyl radicals (ROO•) in the rate-limiting propagation step of lipid peroxidation to make hydroperoxides and radicals that are more stable and, in general, do not continue the radical chain. Radical-trapping chain-breaking antioxidants are extremely important for the maintenance of good health. The most important naturally-occurring antioxidants are lipid soluble; these include Vitamin E, ubiquinol,[26] and bilirubin[27] (Figure 1.1, **1.15-1.17**),[16] since it is the lipids that are most susceptible to autoxidation, and the proximity of lipids to each other in the bilayer of membranes or lipoproteins facilitates chain propagation.

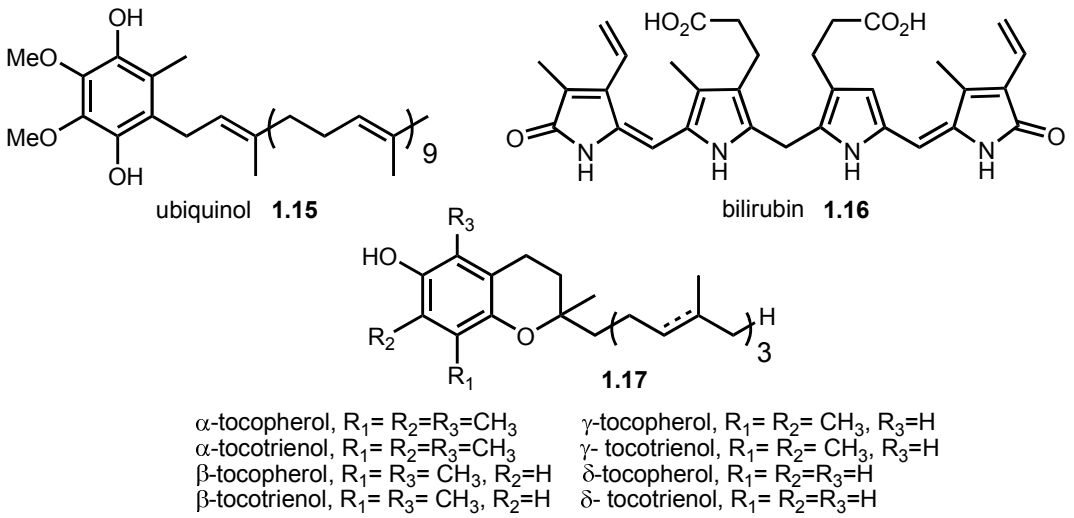


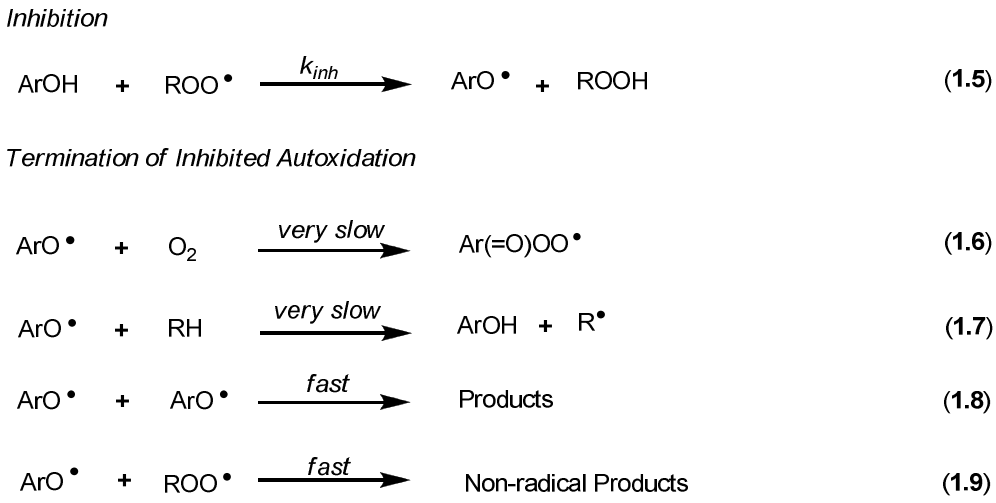
Figure 1.1 Various lipophilic antioxidants present in membrane lipids.

The term vitamin E refers to four congeners of both the tocopherols and tocotrienols. The tocotrienols differ from the tocopherols only in the presence of three double bonds in the phytyl tail. The congeners of the tocopherols and tocotrienols differ from one another in the number and position of the methyl groups on the phenolic ring.[16] Of the eight phenolic congeners, α-tocopherol is known to be the most abundant and reactive towards chain-carrying peroxyl radicals; it is also recognized as nature's best lipid-soluble chain-breaking antioxidant.[28]

1.2.2 Phenolic Antioxidants

Phenols can work efficiently to inhibit lipid peroxidation by scavenging chain-carrying peroxyl radicals (ROO•) as shown in Equation 1.5. The phenoxyl radicals that are produced are resonance stabilized and are eventually destroyed by reacting with a second phenoxyl radical or a peroxyl radical (Equations 1.8 and 1.9). The ability of a phenol to act as a chain-breaking antioxidant is dependent on several factors, one of which is the rate at which it can trap peroxyl radicals (Equation 1.5) relative to the rate of chain propagation (Equation 1.7). Specifically, for a chain-

breaking antioxidant to be effective, the inhibition rate must be much larger than the chain propagation rate (i.e. [ArOH]k_{inh} >> [RH]$k_{1.3}$). Thus, to compare the efficacy of different compounds as antioxidants, their k_{inh} values must be measured under comparable conditions. The inhibition rate constants of some synthetic and natural phenols are shown in Tables 1.1 and 1.2.[29]



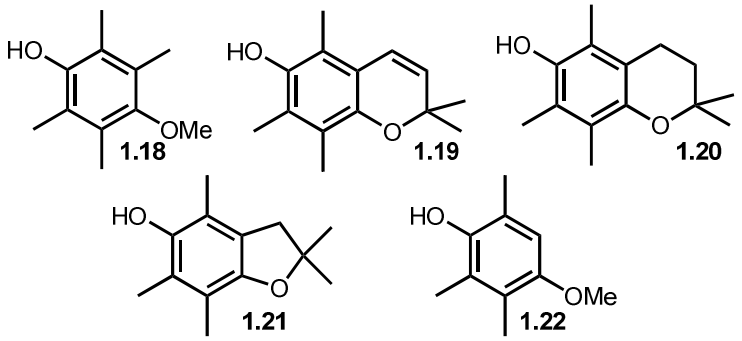
Scheme 1.3. Inhibition and termination of a phenolic-inhibited autoxidation.

Table 1.1. Values of k_{inh} at 30 °C for Tocopherols and Butylated Hydroxytoluene (BHT).

Phenol	k_{inh} (10^4 $M^{-1}s^{-1}$)
α-Tocopherol	320
β-Tocopherol	130
γ-Tocopherol	140
δ-Tocopherol	44
BHT	1.4

Table 1.2. Values of k_{inh} at 30 °C for selected artificial phenols.

Phenol	k_{inh} (10^4 $M^{-1}s^{-1}$)
1.18	39
1.19	250
1.20	380
1.21	570
1.22	130



From Table 1.1, it can be seen that the tocopherols follow the order of antioxidant activity α > β ≈ γ > δ. Furthermore, α-tocopherol and its structurally related model compound, **1.20**, are shown to have similar inhibition rate constants, indicating the importance of the electronic effects of the tocopherol "head" with antioxidant activity. The purpose of the phytyl "tail" of the tocopherols is thought to only serve the purpose of increasing the solubility of the "head" in regions of biological systems which require antioxidant protection.[28]

Tables 1.1 and 1.2 indicate that the antioxidant activity of α-tocopherol and its synthetic analogues **1.19**, **1.20**, and **1.21** is due to their superior ability to donate hydrogen atoms to peroxyl radicals, thus inhibiting autoxidations. This ability is reflected in the O-H bond dissociation enthalpy (BDE), which can be decreased due to electronic and steric effects.[28,30,31] For the former,

an increase of electron density in the aromatic ring by electron-donating groups should stabilize the electron deficient phenoxyl radical, and thus lower the O-H BDE. The latter refers to the fact that electron-donating groups (i.e. alkoxy group) at the *para* position of phenols must lie coplanar to the aryl ring so that it can conjugate with the aromatic π-system to stabilize the radical. In fact, substituent effects on the ArO-H BDE were studied thoroughly by Pedulli *et al.* and they found that electron-donating groups always lower the BDE of the ArO-H bond when compared to unsubstituted phenol. They also found that α-tocopherol and its artificial analogue (**1.20**) have the lowest BDEs of any of the substituted phenols studied (Table 1.3).[30]

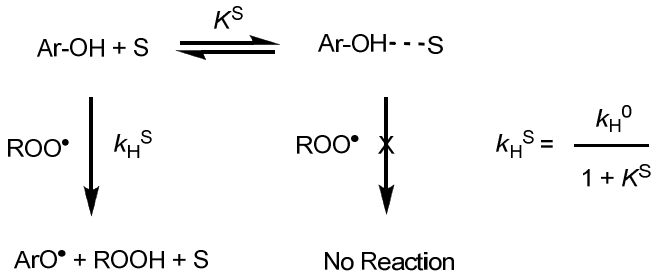
Table 1.3. Bond dissociation enthalpies for selected substituted phenolic antioxidants.

Phenol	BDE (kcal mol^{-1})
α-tocopherol	78.23 ± 0.25
1.18	81.88 ± 0.20
1.20	78.25 ± 0.18
1.22	79.20 ± 0.15

1.2.3 Mechanistic Studies of H-Atom Abstractions

As shown in Equation 1.5, the process by which an antioxidant traps a peroxyl radical occurs when a H-atom is formally transferred from the antioxidant to the peroxyl radical. The direct H-atom transfer for phenols has been confirmed by substantial deuterium kinetic isotope (DKIEs) effects observed in phenol-inhibited autoxidations in non-polar media. For example, deuteration of the phenolic hydrogen atom in α-tocopherol resulted in a reduction of antioxidant activity where $k_{inh}^{H}/k_{inh}^{D} = 5.4 \pm 0.4$,[29] indicating that H-atom abstraction is the rate limiting step. Compounds **1.18** and **1.20** were also found to have significant deuterium kinetic isotope effects of

10.6 ± 3.7 and 5.5 respectively.[32] Even compound **1.21,** which is more reactive than α-tocopherol (and its synthetic analogue) towards peroxyl radicals, has a deuterium isotope effect of k_{inh}^{H}/k_{inh}^{D} = 4.4 ± 0.4 confirming H-atom transfer and not electron transfer is rate controlling. In addition to determining how antioxidants inherently donate their H-atom to peroxyl radicals, the environment in which they do this is also an important mechanistic consideration. For example, a solvent can affect the rate of H-atom donation for a phenol by hydrogen bonding to the phenolic hydrogen (Scheme 1.4) and in general, those solvents that have strong hydrogen bond accepting groups, i.e. carbonyls or nitriles, tend to slow the rate of hydrogen atom donation substantially. This phenomenon supports a hydrogen atom transfer mechanism since electron transfer would be facilitated under these conditions. For comparison, α-tocopherol donates a H-atom at a rate of k_H = 2.0 x 10^7 $M^{-1}s^{-1}$ in hexanes and k_H = 2.3 x 10^5 $M^{-1}s^{-1}$ in ethyl acetate demonstrating a 100-fold decrease in rate when changing to a strong hydrogen bond acceptor solvent;[33] clearly antioxidant activity is highly dependent on solvent conditions.



Scheme 1.4. Kinetic solvent effect on the reaction of phenols with peroxyl radical.

In general, there are two types of mechanisms by which a proton and an electron are transferred in a single step: hydrogen-atom transfer (HAT) and proton-coupled electron transfer (PCET). In HAT, the proton and electron are transferred together as a hydrogen atom, while

PCET is usually considered a process where the proton and electron are transferred between different sets of orbitals.[34] The later process is more complex than HAT and is also less widely understood; complicated by the fact that it is essentially impossible to distinguish between the two when the orbitals between which the electron and proton are being transferred are located on the same atoms between which the H-atom is being transferred by experimental means. However, the results of theoretical calculations suggest that formal H-atom transfer reactions between phenolic antioxidants and peroxyl radicals go by the PCET mechanism.

The PCET mechanism that Mayer and Borden initially predicted for the identity reaction between a phenoxyl radical and a phenol is shown in Figure 1.2. In this reaction mechanism, the reactants can form a hydrogen-bonded complex (Figure 1.3A) that is computed to be lower in energy than the separated reactants by 9.9 kcal mol^{-1}. The transition state structure was predicted to be 1.3 kcal mol^{-1} lower in energy than the separated reactants and is shown in Figure 1.3B. For this self-exchange reaction, the hydrogen-transfer is thought to be part of a four-electron, three-centered hydrogen bond involving the lone pair on the oxygen atom of the phenoxyl radical and the O-H bond of the phenol, thus, a proton is being transferred. In the same direction, an electron is transferred from the doubly occupied 2p-π orbital on the phenol to the singly occupied 2p-π orbital of the phenoxyl.[34]

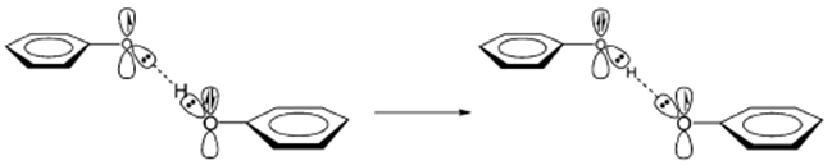


Figure 1.2. PCET mechanism between phenol and phenoxyl radical.

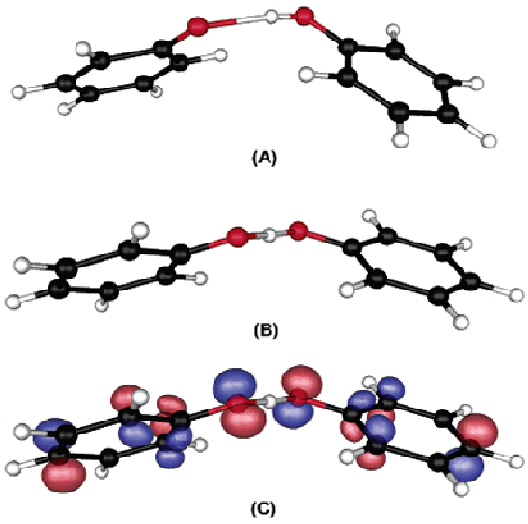


Figure 1.3. Phenoxyl/phenol reaction: (A) geometry of the hydrogen-bonded complex, (B) the TS geometry and (C) the SOMO at the PCET transition structure.

Self-exchange between iminoxyl radicals and oximes have also been suggested to undergo PCET mechanisms and presumably go through H-bonded pre-reaction complexes similar to phenoxyl/phenol systems. However, they differ as iminoxyl/oxime reactions are predicted to go via a five-center, cyclic transition state (Figure 1.4). Thereby, the proton is transferred across the hydrogen bond from the oxime oxygen to the iminoxyl radical, and the electron is transferred in the same direction from the nitrogen atom on the iminoxyl to the nitrogen atom on the oxime.[35]

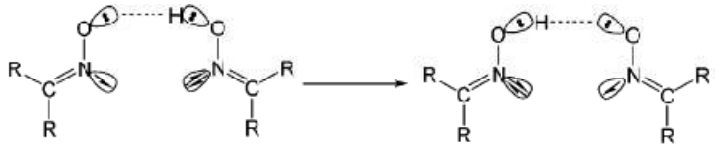


Figure 1.4. PCET mechanism between oxime and iminoxyl radical.

More recently, it has been published by DiLabio and Johnson that reactions between peroxyl radicals and phenolic antioxidants probably occur by concerted PCETs. In their computational studies on the reaction between a *tert*-butylperoxyl radical and phenol, they find that two important effects come from lone pair-π overlap in the syn *tert*-butylperoxyl/phenol transition state: First, the bonding interaction causes the cisoid transition state to be lower in energy than the transoid transition state. Second, the orbital overlap provides a channel for an electron transfer (Figure 1.5). In the cisoid transition state, a proton is transferred from the lone pair on the phenol to the lone pair on the peroxyl radical. Simultaneously and electron is being transferred via a different set of combined orbitals: the partially bonding π-orbital involving the central oxygen atoms and the oxygen lone pair-ring π overlap.[36] These theoretical results may explain the large rate constant for the reaction between a *tert*-butylperoxyl radical and phenol which is experimentally determined to be $k = 2.5 \times 10^3$ M^{-1} s^{-1}.[36,37]

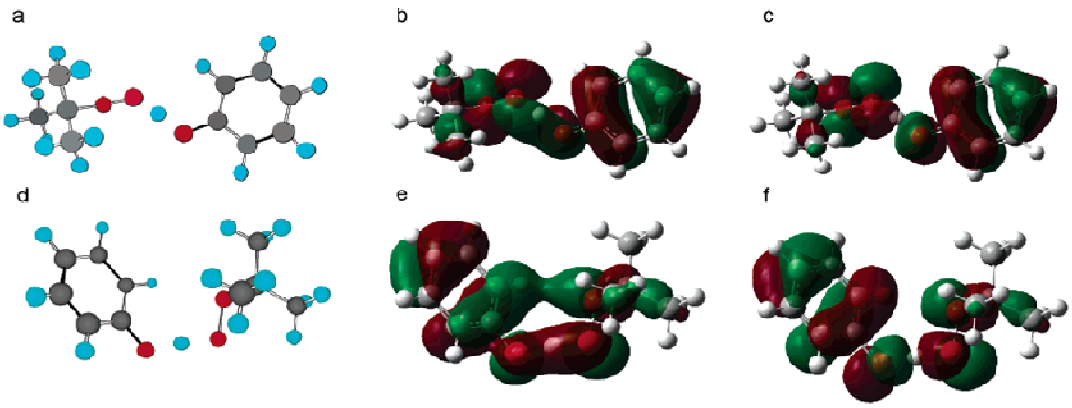
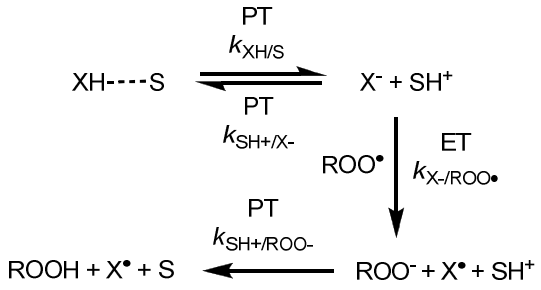


Figure 1.5. Transoid (a) and Cisoid (d) transition states of the *tert*-butoxyl/phenol couple with the associated HOMOs (b and e) and SOMOs (c and f).

Another H-atom transfer mechanism that prevails in highly ionizing solvents, such as alcohols and water, is a sequential proton loss electron transfer (SPLET) which should not be

ruled out for the reaction between antioxidants and peroxyl radicals. In this mechanism, the proton migrates from the antioxidant (XH) to the solvent (S) first, followed by an electron transfer from the anion (X^-) to the peroxyl radical ($ROO^\bullet$). Sequentially the proton transfers from the solvent to the newly formed anion (Scheme 1.5).



Scheme 1.5. SPLET mechanism.

1.3 Sulfenic Acids: Occurrence and Relevant Chemistry

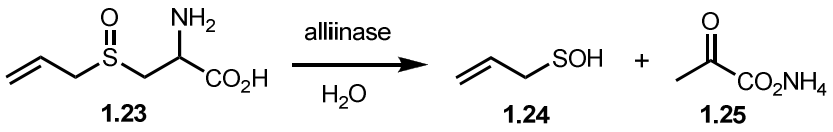
1.3.1 Historical Perspective on the use of Garlic

Garlic, a member of the *Allium* species, has long been believed to be of great medicinal benefit and has been used historically worldwide in folk medicines to treat various disorders. The earliest accounts of using garlic as a medicinal agent were from the working class Egyptians, who ingested garlic to increase their strength when participating in heavy labour, including building the pyramids. There is also evidence that during the first Olympic competitions, the ancient Greeks fed garlic to their athletes as one of the first performance enhancing substances. In ancient Chinese medicine, garlic was used to aid respiration and digestion as well as in the treatment of diarrhea and worm infestation.[38] In more recent reports, garlic has been known for prevention of stroke, coronary thrombosis, and atherosclerosis, as well as for the treatment of various diseases including infections and vascular disorders.[39]

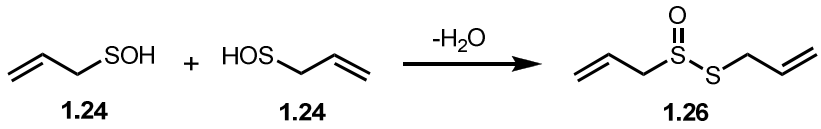
Many of the positive health benefits of garlic have been ascribed to its antioxidant activity; however, the mechanism by which garlic acts as an antioxidant remains unclear. As mentioned above, lipid peroxidation has been implicated in various pathologies, such as the development of atherosclerosis. It is generally accepted that the key initial event that occurs is the oxidative modification of low density lipoproteins which eventually leads to coronary heart disease. Studies have shown that the presence of an antioxidant, such as α-tocopherol, atherosclerosis is suppressed, and the risk of heart disease decreases.[40] Thus, if garlic contains a compound that traps peroxyl radicals similarly or better than α-tocopherol, it could act as an equal or superior antioxidant and could suppress pathologies such as atherosclerosis.

1.3.2 Garlic's Allicin: Potent Antioxidant?

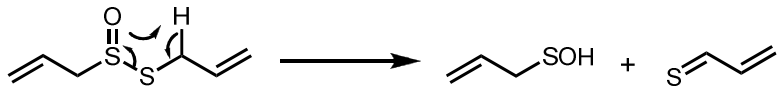
About 5% of the dry weight of garlic is made up of non-protein sulfur-containing amino acid secondary metabolites such as (+)-*S*-allyl-L-cysteine *S*-oxide (alliin, **1.23**).[41] Upon cutting or crushing garlic, alliin is cleaved by the C-S lyase enzyme alliinase to yield ammonium pyruvate (**1.25**) and allyl sulfenic acid (**1.24**, Equation 1.10). Allyl sulfenic acid, a highly reactive organosulfur intermediate, is believed to subsequently dimerize to form the diallyl thiosulfinate, allicin (**1.26**, Equation 1.11).[42] Allicin offers garlic its distinct odor, flavor and healthful properties[39] which have been attributed to its antioxidant activity.[43]



1.23 **1.24** **1.25** (**1.10**)



1.24 **1.24** **1.26** (**1.11**)

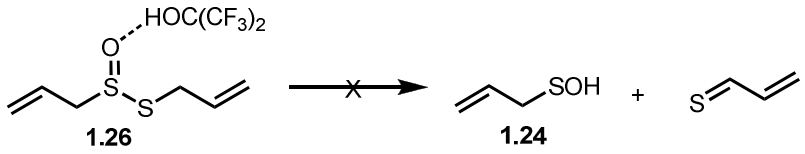


1.26 **1.24** (**1.12**)

In attempt to elucidate the mechanism for allicin's antioxidant activity, Okada *et al.* have performed inhibited autoxidations of methyl linoleate that revealed a k_{inh} of 1.6 x 10^5 $M^{-1}s^{-1}$ for the reaction between allicin and methyl linoleate-derived peroxyl radicals.[43] Previous work had indicated that the $S(O)SCH_2CH=CH_2$ moiety was essential for the antioxidant activity of allicin[44] thus, they suggested a mechanism involving abstraction of the allylic H-atom adjacent to the divalent sulfur atom. This mechanism for scavenging peroxyl radicals by thiosulfinates is unlikely for two reasons: first, rate constants for H-atom transfer from hydrocarbons to peroxyl radicals are much lower than that reported for the allicin-inhibited autoxidation reactions (e.g. the rate constant for H-atom abstraction from methyl linoleate from a peroxyl radical to form a highly delocalized pentadienyl radical is 60 $M^{-1}s^{-1}$), and second, carbon-centered radicals generally undergo diffusion controlled reactions with oxygen to yield peroxyl radicals, which continue to propagate the autoxidation chain reaction.

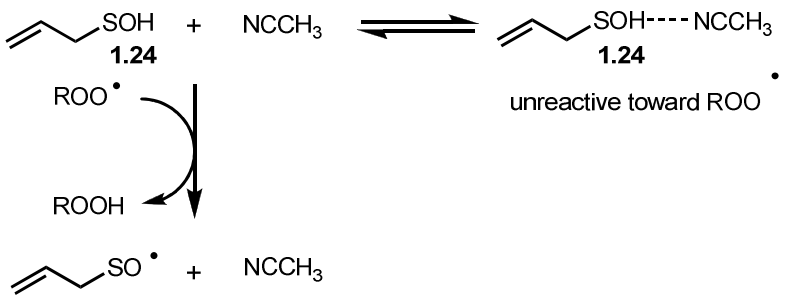
Taking into consideration these discrepancies, previous work in our group suggested that it is actually the decomposition product and biological precursor, allyl sulfenic acid, that gives garlic its antioxidant activity (Equations 1.12 and 1.11 respectively). Experimentally, we demonstrated indirectly that allyl sulfenic acid is the active antioxidant in garlic by performing

autoxidations under conditions by which the decomposition of allicin is inhibited (i.e. by a hydrogen-bond donor solvent). In the presence of hexafluoroisopropanol (HFIP), very little allicin decomposed after one hour (Equation 1.13); the normal half life of allicin is approximately one hour. When HFIP was added to the autoxidation mixture, the induction period disappeared, indicating that the oxidation of methyl linoleate was not inhibited and that allicin is not likely the active antioxidant in garlic.



1.26 **1.24** (**1.13**)

In the presence of a hydrogen bond acceptor, acetonitrile, the rate of allicin decomposition was affected by insignificant amounts. However, the presence of acetonitrile significantly reduced the ability of allicin to inhibit the autoxidation of methyl linoleate. This experiment confirmed the idea that allicin itself is not the active antioxidant but instead its decomposition product is being 'tied up' by the hydrogen bond acceptor solvent. Allyl sulfenic acid is expected to be a strong hydrogen bond donor and would therefore form a strong hydrogen bond with acetonitrile, thus decreasing its ability to trap peroxyl radicals and inhibit autoxidations (Scheme 1.6).[45] These experiments give a good indication that allyl sulfenic acid is the species in garlic that is responsible for trapping peroxyl radicals in the autoxidations of lipids.



Scheme 1.6. Mechanistic scheme explaining the decreased ability of allicin to inhibit autoxidations of methyl linoleate.

The key thermodynamic parameter associated with the rate of this reaction is the O-H BDE of the H-atom donor. Therefore, the O-H BDEs of sulfenic acids were determined theoretically and compared to the analogous hydroperoxides (Table 1.4). Table 1.4 reveals two interesting features of the O-H BDEs of sulfenic acids. First, they are much lower than the analogous hydroperoxides and second, they are practically independent of the alkyl chain size. An explanation for the impressively low BDEs could be due to the ability of the sulfur atom in a sulfenic acid to delocalize the radical to a greater extent than the internal oxygen atom in a hydroperoxide (i.e. the spin is delocalized 50:50 between the sulfur and oxygen atom in the sulfenic acid and 70:30 between the terminal and non-terminal oxygen atoms in the hydroperoxide). It is also important to note that the O-H BDEs computed for sulfenic acids are among the lowest known and comparable to hydroxylamines such as TEMPO-H (69.6 kcal mol^{-1}; TEMPO=2,2,6,6-tetramethylpiperidin-1-oxyl).[46]

Table 1.4. O-H BDEs (in kcal mol^{-1}) for selected sulfenic acids and hydroperoxides.

Sulfenic Acid	O-H BDE	Hydroperoxide	O-H BDE
MeSO-H	68.4	MeOO-H	86.2
$C_2H_3CH_2SO$-H	68.6	$C_2H_3CH_2OO$-H	86.2
*t*BuSO-H	68.6	*t*BuOO-H	84.8
$C_6H_5CH_2SO$-H	68.6	$C_6H_5CH_2OO$-H	86.1

To provide insight into the reactions between sulfenic acids and peroxyl radicals, the transition structures of the reaction between a variety of sulfenic acids and peroxyl radicals as well as associated activation energies were predicted computationally. It was found that the syn transition state structures were lower in energy than the transoid transition states by 6-7 kcal mol^{-1} (Figure 1.6, Table 1.5). In Figure 1.6, HOMO-1 shows significant overlap between the sulfenic acid sulfur atom and the internal peroxyl oxygen atom; this overlap is similar to that seen in other PCET mechanisms for H-atom transfer discussed above whereby the proton is being transferred via a different set of orbitals than the electron transfer. This indicates the possibility that an electron is being transferred from the sulfenic acid sulfur atom to the internal oxygen of the peroxyl radical, while the proton is being transferred from the oxygen on the sulfenic acid to the external oxygen on the peroxyl radical.[45]

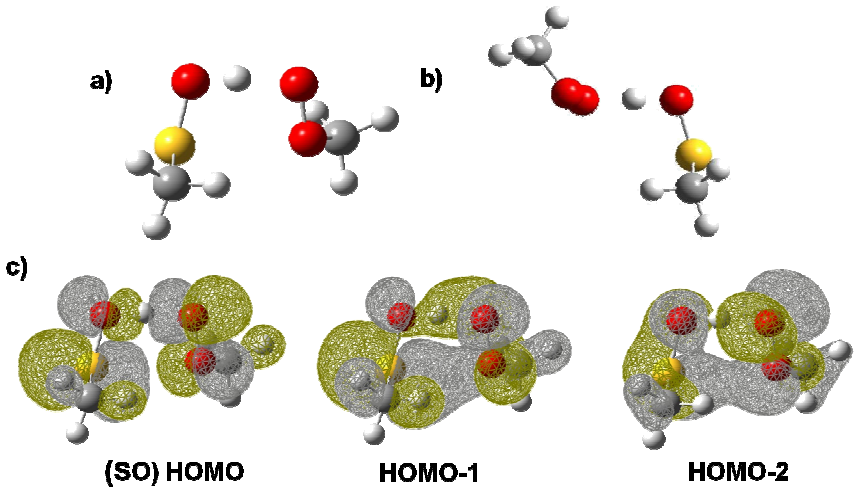


Figure 1.6. a) Cisoid and b) transoid TS structures for the MeSOH/•OOMe reaction. c) Three of the highest occupied MOs of the structure (a) showing overlap between the sulfenic acid S atom and the internal peroxyl O atom.[45]

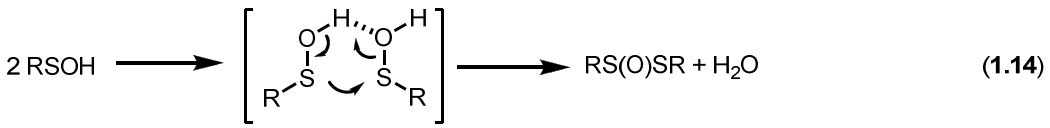
Table 1.5. Activation energies (in kcal mol^{-1}) for H-atom transfer between sulfenic acids and peroxyl radicals.

Sulfenic Acid	E_a (cisoid TS)	E_a (transoid TS)
MeSO-H/•OOMe	4.6	11.0
CH_2=$CHCH_2$SO-H/•OOMe	4.3	10.9
*t*BuSO-H/•OOMe	4.2	9.8

PCET reactions between sulfenic acids and peroxyl radicals are predicted to occur very quickly. As mentioned previously, PCETs are expected to first proceed through a pre-transition state hydrogen-bonded complex. For the alkyl sulfenic acids investigated, the associated hydrogen bonded complexes (RSOH$^{\cdots}$•OOR) were computed to be 4.5-5 kcal mol^{-1} lower in

energy than the separated reactants. This implies that the corresponding TS structures are equal or slightly lower in energy than the separated reactants and that reactions between peroxyl radicals and sulfenic acids are diffusion controlled.[45] Therefore, sulfenic acids are potentially the most potent of all chain-trapping antioxidants, even better than nature's best: α-tocopherol. For comparison, the self-exchange reaction between a hydroperoxide and peroxyl radical (i.e. MeOOH/•OOMe) has a much higher activation energy (9.0 kcal mol^{-1}) and a much slower rate of reaction (on the order of 10^2-10^3 $M^{-1}s^{-1}$).[47]

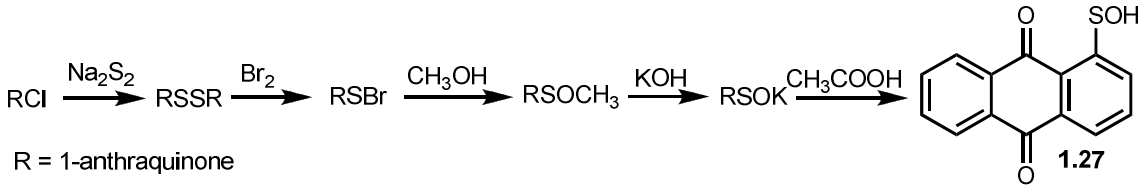
From this initial work, several significant insights were made: first, the antioxidant ability of garlic is most likely due to allicin's decomposition product, allyl sulfenic acid, and not allicin itself. Second, allyl sulfenic acid and other alkyl sulfenic acids are predicted to have some of the lowest BDEs known, meaning they can readily donate a hydrogen atom to peroxyl radicals. Finally, sulfenic acids are predicted to react at a near diffusion rate with peroxyl radicals via PCETs. The problem with these findings is that they are either indirect or computational evidence for the sulfenic acids remarkable antioxidant activity. Experimentally, sulfenic acids are difficult to work with, as they are highly transient species and very reactive as both electrophiles and nucleophiles; this leads to self-condensation via a five-membered hydrogen-bonded transition state (Equation 1.16).[48] Ideally, the sulfenic acid functional group could be rendered less reactive by hindering self-condensation, such that direct studies could be carried out. Section 1.3.3 covers the literature on the synthesis of kinetically stable (persistent) sulfenic acids.



(**1.14**)

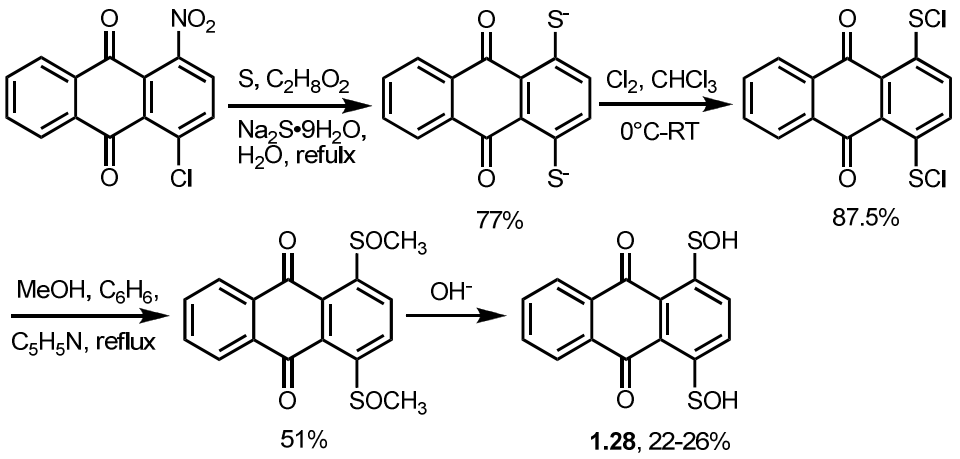
1.3.3 Stable (Persistent) Sulfenic Acids

The first isolated kinetically stable (i.e. persistent) sulfenic acid reported was 1-anthraquinone sulfenic acid, which was published by Fries *et al.* in 1913 (Scheme 1.7).[49] The stability of this compound can be attributed to hydrogen bonding between the sulfenic acid group and the adjacent carbonyl group on the quinone which inhibits the formation of the five-membered transition state between the two sulfenic acid moieties; this would prevent self-condensation and the formation of thiosulfinates. The final product (**1.27**) was accomplished by hydrolyzing the corresponding methyl sulfenate with strong potassium hydroxide solution and subsequently liberating the sulfenic acid by treatment of acetic acid to from stable red crystals.



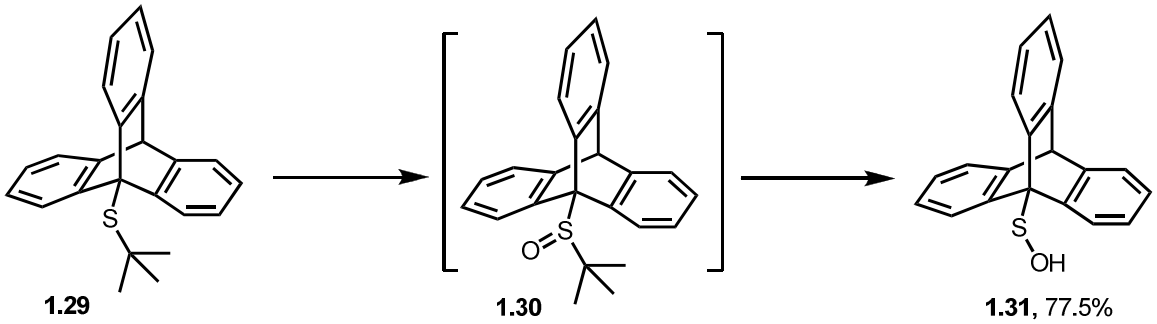
Scheme 1.7. Synthesis of the first isolated stable sulfenic acid: 1-Anthraquinone sulfenic acid

Several years later, the first disulfenic acid and second sulfenic acid was synthesized by Bruice *et al.* in 1957. This compound, anthraquinone-1,4-disulfenic acid (**1.28**), is stable for similar reasons as the mono-sulfenic acid prepared by Fries. The methods used to prepare this compound were also inspired by Fries (Scheme 1.8), however, an analytically pure sample was never achieved; recrystalization from acetone gave the purest product which still contained minute amounts of impurities. As purple crystals, the disulfenic acid was stable for multiple weeks in the absence of air.[50]



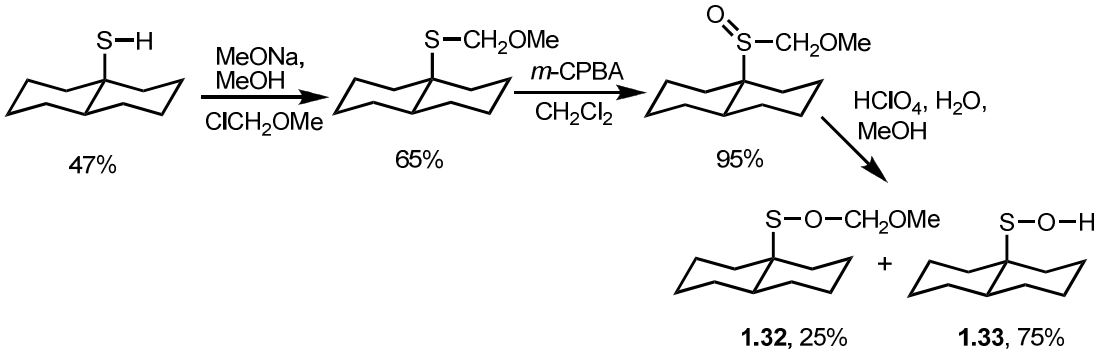
Scheme 1.8. Synthesis of a disulfenic acid, anthraquinone-1,4-disulfenic acid.

Isolation of a sulfenic acid stabilized purely by steric effects was first accomplished in 1983 by Nakamura (Scheme 1.9). In this communication, a propeller-like triptycene backbone is used to sterically protect the sulfenic acid group from self-condensation. 9-Triptycenesulfenic acid (**1.31)** was prepared by *meta*-chlorobenzoic acid oxidation of 9-(*tert*-butylthio)triptycene (**1.29**). Mechanistically the sufenic acid is predicted to first go through the *tert*-butyl sulfoxide (**1.30**) intermediate, which undergoes elimination to form the final product. There is no formal evidence for the formation of the sulfoxide, and 9-triptycenesulfenic acid is reported as the only new product formed from the reaction. The sulfenic acid **1.31** was separated from unreacted starting material using preparative thin layer chromatography and was reported to be stable at room temperature in air for more than several weeks.[51]



Scheme 1.9. Synthesis of 9-triptycene sulfenic acid from the corresponding *tert*-butyl thioether.

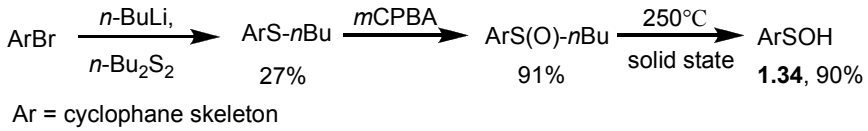
In 1992, a communication was published reporting the first synthesis of a stable sulfenic acid without an unsaturated double bond or heteroatom (Scheme 1.10) by Yoshimura *et al.* This aliphatic sulfenic acid is stabilized by the four axial protons on the *trans*-decalyl group, protecting it from self-condensation. *Trans*-decalin-9-sulfenic acid (**1.33**) was prepared by direct acid hydrolysis of the sulfoxide precursor in 75% yield along with the rearranged sulfenate (**1.32**) in 25% yield. The final product was isolated by column chromatography as a crystalline solid with a melting point of 52-54°C.[52]



Scheme 1.10. Synthesis of *trans*-decalin-9-sulfenic acid.

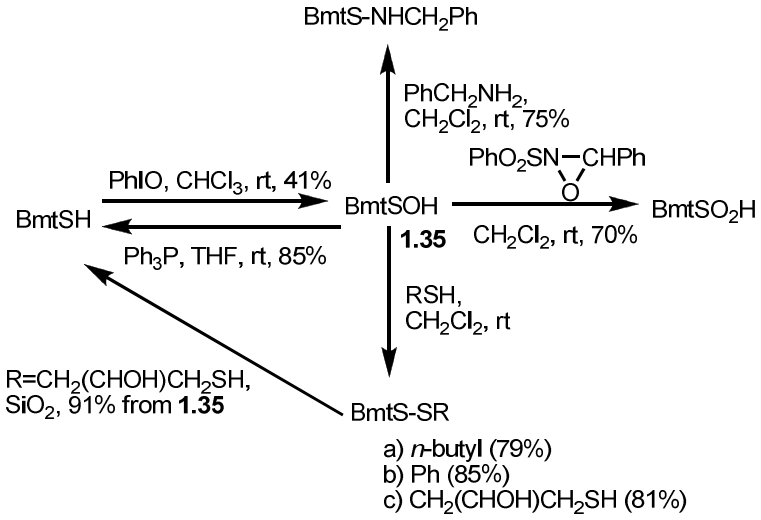
Throughout the 1990's and into the 2000's, Okazaki and Goto were able to stabilize sulfenic acids using three types of protective molecular cavities: bimacrocyclic cyclophanes,[53] bridged calix[6]arenes[54] and molecular bowls with an all-carbon and acyclic framework.[55,56] Although these large molecular cavities are synthetically challenging, the stability they provide for the sulfenic acid group is quite remarkable; as well, the bulky protecting groups allow for investigation of different functional group manipulations which result in the formation of sulfenic acids. There are four particularly interesting conversions that were reported: solid state pyrolysis of an alkyl sulfoxide precursor, direct oxidation of a thiol, and hydrolysis of a thionitrate or sulfenylbromide. What is also significant about these bowl-type protecting groups is their ability to stabilize the analogous selenium compounds, selenenic acids. In fact, the first isolable selenenic acid bears the bulky calix[6]arene group.[57]

In 1995, Goto and coworkers published a communication reporting the synthesis of a persistent arenesulfenic acid bearing a macrobicyclic cyclophane skeleton which was synthesized via solid state pyrolysis of the *n*-butylsulfoxide; the corresponding sulfenic acid, **1.34**, was isolated as a crystalline solid in 90% yield based on conversion of the sulfoxide. The sulfenic acid was isolated by preparative TLC and its melting point was 174ºC. **1.34** is stable at room temperature in air for several weeks and upon heating to 80 ºC for 12 hours, only slight decomposition occurred, demonstrating its incredible stability.[53]



Scheme 1.11. Synthesis of a stable sulfenic acid bearing a bimacrocyclic cyclophane protecting group (Ar).

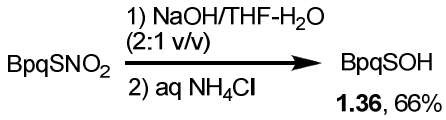
Using the Bmt protecting group, the first direct oxidation of a thiol to prepare a sulfenic acid was achieved. Treatment of Bmt-SH with a mild oxidant, PhIO, gave Bmt-SOH (**1.35**) in 41% yield after silica gel chromatography (Scheme 1.12). This sulfenic acid is stable in air at room temperature for several weeks. The intrinsic reactivity of the Bmt-SOH was explored as revealed in Scheme 1.12, demonstrating some of the chemistry sulfenic acids located in the active sites of enzymes may be undergoing (the biological relevance of sulfenic acids will be discussed in Chapter 1.3.4). [55]



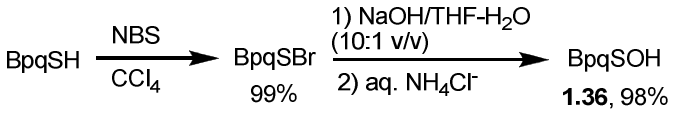
Scheme 1.12. Preparation and reactivity of Bmt-sulfenic acid.

Bpq sulfenic acid (**1.36**) was the first sulfenic acid prepared by alkaline hydrolysis of a thionitrate precursor, and was done so in 66% yield as a crystalline solid after column chromatography (Scheme 1.13). Likewise, **1.36** could be achieved by alkaline hydrolysis of the corresponding sulfenylbromide using a slightly different solvent ratio in 98% yield (Scheme 1.14).[56] This work is relevant because in biological systems, hydrolysis of thionitrates is assumed

to generate sulfenic acids and nitrite (NO_2^-) by nucleophilic substitution at the sulfur atom.[58] Previous to the Bpq steric protection study, no direct evidence was available for this reaction due to the inherent instability of both R-SNO_2 and R-SOH.

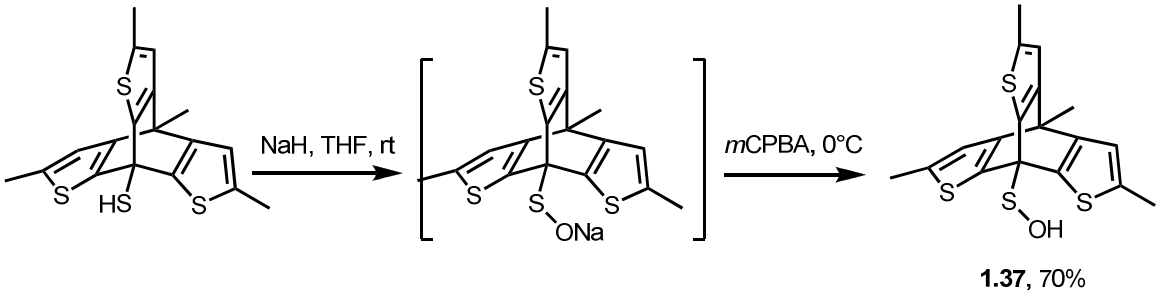


Scheme 1.13. Synthesis of Bpq sulfenic acid by alkaline hydrolysis of Bpq thionitrate.



Scheme 1.14. Synthesis of Bpq sulfenic acid by alkaline hydrolysis of Bpq sulfenyl bromide.

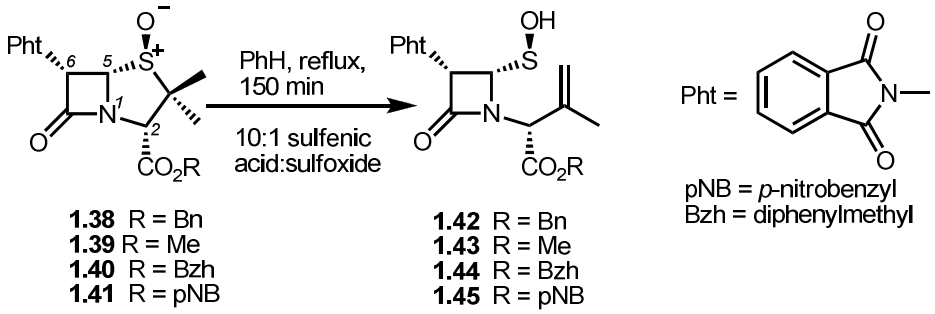
During the time in which the molecular bowl sulfenic acids were being investigated, a stable sulfenic acid called thiophenetriptycene-8-sulfenic acid (**1.37**) was synthesized by Ishii *et al*. in 1997. This was the first sulfenic acid bound to a sp^3 carbon that was prepared by peroxyacid oxidation of the corresponding sodium thiolate (Scheme 1.15). The thiophene sulfenic acid was prepared by first forming the thiolate anion, followed by *m*CPBA oxidation, and isolated as pale yellow crystals. The product was stable in the absence of light for a long time.[59]



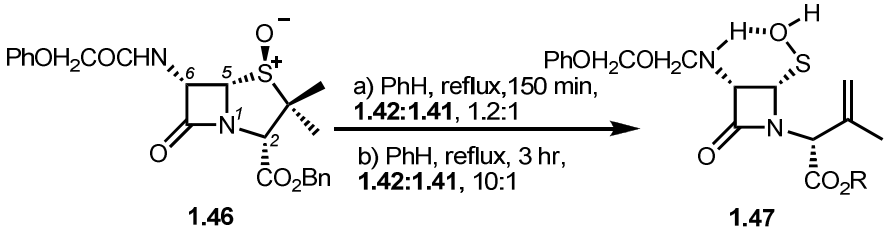
1.37, 70%

Scheme 1.15. Synthesis of thophenetriptycene-8-sulfenic acid by peroxyacid oxidation of a thiol.

Unusually stable azetidinone sulfenic acids were prepared unexpectedly when sulfoxides of (2S,5S,6S)-penams rearranged upon heating in benzene for 150 minutes (Scheme 1.16); this work was done by Fekner and coworkers. The yield of this new sulfenic acid, **1.42**, was 90% by ^{1}H NMR, with the other 10% being unreacted sulfoxide. Attempts to drive the reaction to completion were unsuccessful after prolonged heating (40 hours) of **1.38**, demonstrating a thermal equilibrium between the sulfoxide and sulfenic acid. Compounds **1.43-1.45** show increased stability due to the steric bulk of the modified azetidinone group, preventing formation of the prerequisite complexes for thiosulfinates, and to the relative instability of the starting sulfoxide, disfavoring re-cyclization. Unfortunately attempts to purify these sulfenic acids from the parent sulfoxides were ineffective. An analogue of sulfoxide **1.38** containing an amido substituent on C*6* (**1.46**) was also found to form a stable sulfenic acid (**1.47**). The stability of this compound may be improved by the intramolecular hydrogen bonding shown in Scheme 1.17.[60]



Scheme 1.16. Preparation of azetidinone sulfenic acids.



Scheme 1.17. Preparation of C-*6* amido substituted azetidinone sulfenic acid.

It is interesting to note the few stable selenenic acids that have been prepared in addition to those sulfenic acids mentioned. Selenenic acids are significant from both a synthetic and biological point of view as discussed in Appendix A. However, selenenic acids are highly reactive and undergo disproportionation rapidly to form the corresponding diselenide and seleninic acid, which is why stabilizing these compounds is also a non-trivial endeavor.

The calix[6]arene protecting group was used to synthesize the first isolable selenenic acid which was reported by Saiki and coworkers in 1997.[57] The selenenic acid was prepared by *m*CPBA oxidation of the *n*-butylselenide, followed by thermolysis to form the calix[6]arene protected product as colorless crystals with a melting point of 168°C.[57] From the same group, Goto *et al.*have demonstrated that the Bmt group was useful for demonstrating the first direct oxidation of a selenol to a selenenic acid in 2001. This transformation is important as it is

believed to be part of the catalytic cycle of glutathione peroxidase. The Bmt selenenic acid was prepared by hydrogen peroxide oxidation of the precursor selenol and isolated by column chromatography in 77% yield as stable pale yellow crystals.[61]

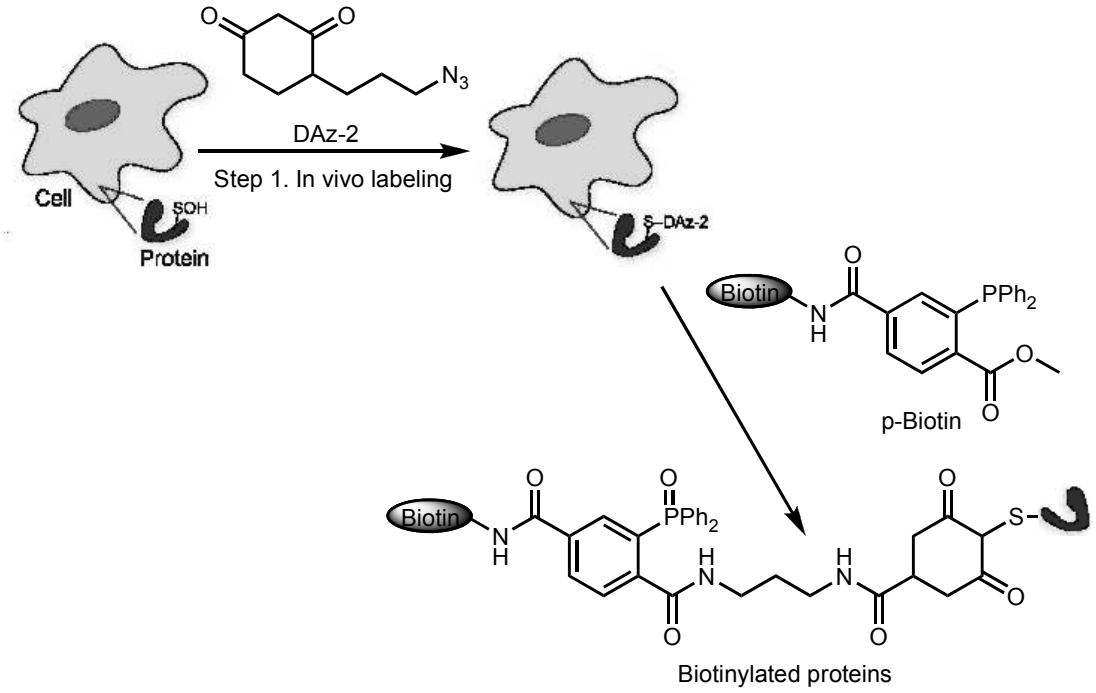
The synthesis of both thiophenetriptycene- (Thtrip-) and triptycene- (Trip-) selenenic acids were attempted in 1999 by Ishii *et al.* The preparation of Thtrip-SeOH proved unsuccessful, but TripSeOH was reported as the first stable alkyl selenenic acid and was isolated in 79% yield from the selenoxide. When Thtrip-*n*-butylselenide was oxidized, the corresponding selenoxide was formed; the selenoxide decomposed gradually in solution at room temperature to form the undesired self-condensation product in 70%, which was actually the first isolated selenoseleninate reported. Crystal structures of both these compounds were obtained and the difference in stability of the two selenenic acids is attributed to steric effects.[62]

1.3.4 The Biological Relevance of Sulfenic Acids

Until recently, sulfenic acids have been of interest typically because of their synthetically challenging nature and possible intermediacy in several transformations.[41,45,63,64] More recently, the biological role of sulfenic acids has come to the fore. In their biological context, they are known to be important intermediates in cellular signal transduction,[65,66] play both structural and catalytic roles in enzymes, and participate in non-enzymatic protein folding.[67] The best examples of their enzymatic roles include peroxiredoxins,[68] hydrogenases,[69] NHDH peroxidises[70] and nitrile and thiocyanate hydrolases.[71]

The ubiquitous nature of cysteine sulfenic acids, especially in cell signalling processes, has prompted the development of methods to detect and quantitate them.[72,73] The presence of sulfenic acids can be identified in cells via trapping experiments and rationalization of end products. However, this process is complicated by the fact that the trapping agent must be cell-permeable, in addition being chemoselective to sulfenic acids. One such trapping agent, DAz-2,

selectively tags sulfenic acid modified proteins in living cells via the process shown in Scheme 1.18. Using this reagent, global proteomic studies have been performed, and sulfenic acids have been identified and found to be distributed in various locations throughout the cell. This corresponds to the idea that sulfenic acids function in a diverse array of biological processes and highlights the need for future research in this field.[72]



Scheme 1.18. Two-step strategy for detecting cellular sulfenic acid modifications using Azido-probe DAz-2.

Redox signalling is a well-accepted stress response to high oxidant exposure and low antioxidant defence in cells that leads to a variety of effects including the increased expression of protective and repair enzymes. This imbalance of oxidants and antioxidants, called oxidative stress, can modulate various signaling pathways including the activation and inactivation of

transcription factors, membrane channels, and metabolic enzymes, and regulation of calcium-dependent and phosphorylation signalling pathways. These processes consist of the major regulatory networks of cells, giving redox signals the ability to stimulate and tune most aspects of cell physiology.[74]

1.4 Research Objectives

Sulfenic acids have been of interest to scientists for many years. The literature surrounding this – at first glance esoteric - functional group includes synthetic methods for kinetic stabilization, intermediacy in the chemistry of *Allium* species, which includes its possible role as an antioxidant, and role in cellular redox processes. As discussed, several groups have prepared persistent sulfenic acids, and often the goal in mind was simply to see if it could be done.[49-52] Other groups wanted to simulate the environment of clefts in enzymes by hindering the sulfenic acid by large molecular bowls.[55,56] Sometimes, sulfenic acids were discovered accidently when other compounds were targeted.[60] The first goal of this thesis is to prepare a persistent sulfenic acid suitable for experiments aimed at understanding its redox activity, and to optimize its synthesis to provide reasonable amounts of material for biomimetic studies. A good experimental model sulfenic acid would be absent of any unusual electronic effects or internal hydrogen bonding effects and be rendered persistent primarily due to steric bulk. 9-Triptycenesulfenic acid (**1.31**) is the most desirable sulfenic acid for the purposes of this project as it fits the criteria mentioned and is reported to be synthesized and purified with relative ease and has good stability in air.

Recent indirect evidence that allyl sulfenic acid may be the active antioxidant in garlic has been reported[45] however, no direct verification for this has been shown. In the presence of a stable sulfenic acid, **1.31** (as a model for allyl sulfenic acid), autoxidations could be performed as

experimental evidence for the sulfenic acid's role as an antioxidant and a rate constant for the reaction between sulfenic acids and peroxyl radical could be obtained. The BDE of an antioxidant is the main thermodynamic parameter associated with trapping peroxyl radicals, however, BDEs of sulfenic acids have only been predicted computationally.[45] The ability of a sulfenic acid to donate a hydrogen atom can be determined experimentally by using the model sulfenic acid with electron paramagnetic resonance (EPR) equilibration technique. Both experimental determination of the rate constant of the reaction between a sulfenic acid and peroxyl radical, and the BDE of a sulfenic acid are two additional research objectives for this thesis.

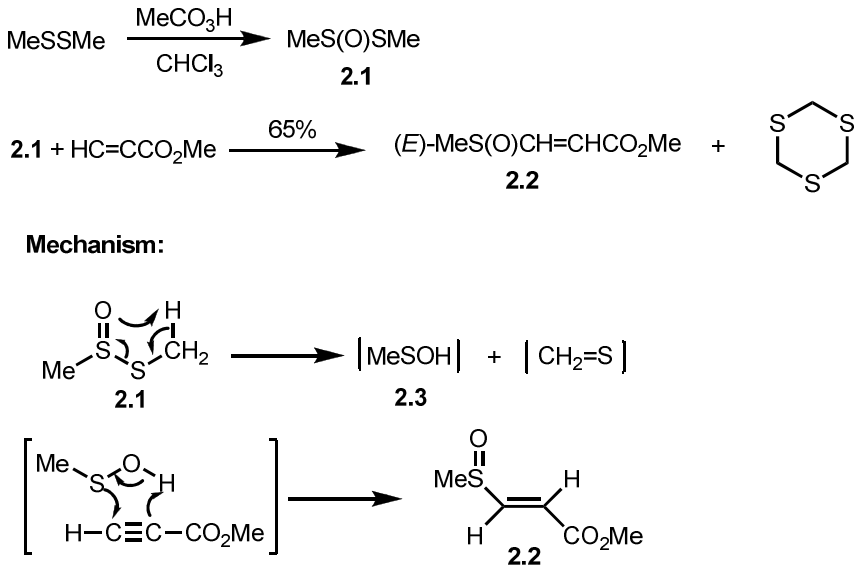
Furthermore, other physicochemical data that is missing for the sulfenic acid include pK_a determination and electrochemical properties. The pK_a has been reported for few sulfenic acids and unfortunately the values for these compounds are perturbed by intramolecular hydrogen bonding and/or electronic effects.[75,76] Thus another research goal is to determine the pK_a of 9-triptycenesulfenic acid which is lacking these undesirable effects. In this area, there is one report of a pK_a of a sulfenic acid absent of electronic effects, the non-persistent 2-methyl-2-propanesulfencic acid, but this is only an estimate, since this compound cannot be isolated.[77] In addition, the electrochemical properties of a sulfenic acid have never been reported; the electrochemistry of phenols has been studies in detail,[78,79] which gives us some ideas about how the sulfenic acid may behave electrochemically.

Chapter 2

Synthetic Efforts Toward Sulfenic Acids

2.1 Introduction

The preparation, isolation and purification of sulfenic acids have posed challenges for chemists for a long time. This is generally due to their high reactivity as both electrophiles and nucleophiles which leads to their self-condensation to form thiosulfinates.[80,81] Facile thiosulfinate formation is attributed to the 5-membered hydrogen bonded transition state formed between two sulfenic acid molecules as shown in Equation 1.14.[48] Despite the transient nature of sulfenic acids, their chemistry has often been studied indirectly via flash vacuum pyrolysis of thiosulfinates and rationalization of end products. For example, the intermediacy of sulfenic acids in the elimination of thiosulfinates was initially determined by introducing unsaturated trapping reagents into the reaction. As shown in Scheme 2.1, pyrolysis of methane methylthiosulfinate (**2.1**) in the presence of methyl propiolate, affords methyl (*E*)-β-(methylsulfiny)acrylate (**2.2**) via the trapping of methanesulfenic acid (**2.3**).[82] In fact, a variety of non-persistent alkylsulfenic acids have been identified in this manner.[64]



Scheme 2.1. Decomposition of methyl methanethiosulfinate in the presence of methyl propiolate to form an α,β-unsaturated sulfoxide, (*E*)-β-(methylsulfiny)acrylate and the associated mechanism.

Although several sulfenic acids have been detected indirectly via the products of trapping experiments or self-condensation, [48,64,80-84] to facilitate understanding of their chemical and physical properties, many groups have isolated them and have rendered them kinetically stable (or persistent) via the nature of the chemical scaffold to which they are attached (See Chapter 1.3.3).[49-56,59] Despite these efforts to prepare sulfenic acids, very little remains known of their antioxidant activity and physicochemical properties.

2.1.1 Selection of an Appropriate Model

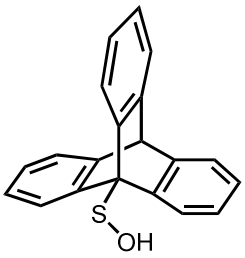
Since our project was inspired by the antioxidant activity of garlic, to learn directly about this relationship, pertinent experiments would be performed on allylsulfenic acid (**1.24**). However, **1.24** is not an isolable compound and thus we sought to synthesize an appropriate

model. Using the model, information about H-atom transfer between a sulfenic acid and peroxyl radical (i.e. measurement of k_{inh} and O-H BDE) could be obtained and used to confirm or disprove our predictions about allyl sulfenic acid giving garlic its extraordinary antioxidant activity.

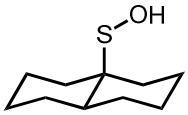
When selecting an appropriate sulfenic acid to serve as our model compound, there are several factors that must be taken into consideration. First, the model sulfenic acid should be attached to a sp^3 carbon, similar to that of **1.24**; this is so that when the sulfenic acid donates a hydrogen atom, the sulfinyl radical is not additionally stabilized by resonance. It should be noted that increasing the s-character leads to higher electronegativity and reactivity of the sulfenic acid by stabilizing the sulfinyl radical as well, but it would be to a much lesser extent. The model sulfenic acid should also be absent of any inter- or intramolecular hydrogen bonding and heteroatoms. Hydrogen bonding to the sulfenic acid can effectively 'tie up' the SO-H hydrogen, preventing H-atom abstraction by a peroxyl radical, hence affecting its BDE and inhibition rate. This is due to the fact that the SO-H hydrogen can no longer form the hydrogen bonded pre-TS complex with a peroxyl radical which is required for a PCET to occur (see Chapter 1.2.3). Heteroatoms may participate in hydrogen bonding with the sulfenic acid or may influence the electronic properties of the sulfenic acid. The heteroatom may donate or withdraw electron density from the sulfenic acid depending on its nature which would in turn affect the sulfenic acid's ability to donate a hydrogen atom by stabilizing the sulfinyl radical to a greater or lesser extent.

Other favorable properties for the model sulfenic acid to have that are perhaps intuitive, but worth mentioning are: straight forward and efficient synthetic route, effective method for purification, sufficient air and solution stability, crystalline or solid at room temperature, and good solubility in a variety of solvents. We chose two sulfenic acids mentioned in Chapter 1.3.3

that we thought were most appropriate for our study: 9-triptycene sulfenic acid (**1.31**)[51] and *trans*-decalin-9-sulfenic acid (**1.33**).[52]



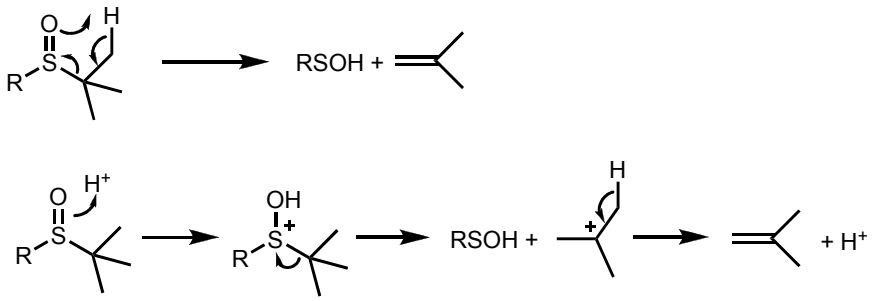
1.31



1.33

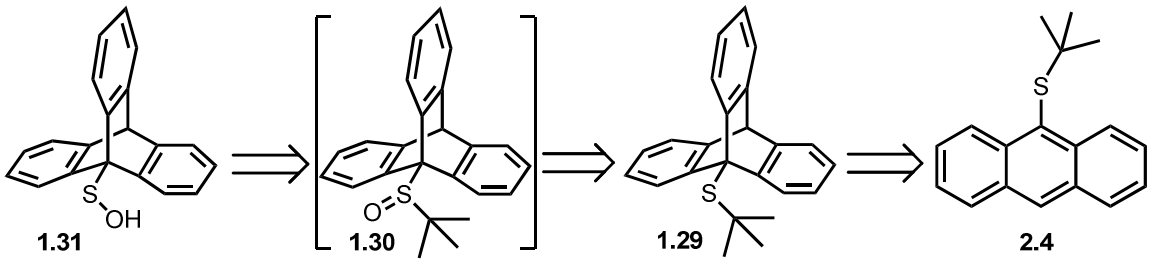
2.1.2 Synthetic Approach Towards (9-Triptycene)sulfenic Acid

Frequently, sulfenic acids are formed by *meta*-chloroperbenzoic acid (*m*CPBA) oxidation of a corresponding alkylthioether containing a β-hydrogen (see Chapter 1.3.3 for examples); in Nakamura's preparation of our desired model, 9-triptycenesulfenic acid, this is also the route taken. His hypothesis for how this reaction works is that the thioether first becomes oxidized to form the corresponding sulfoxide which subsequently undergoes Cope elimination at room temperature to form the sulfenic acid.[51] Although there is no direct evidence for formation of the sulfoxide intermediate, this seems like a highly probably sequence of events. However, the mechanism by which the sulfoxide eliminates in the presence of *m*CPBA is unclear. The role of *m*CPBA is clearly to oxidize the substrate, but it may also act as an acid to catalyze the elimination in a step-wise fashion, as opposed to the concerted pericyclic Cope elimination. Scheme 2.2 shows two proposed mechanisms for the elimination of a *tert*-butyl sulfoxide.



Scheme 2.2. Proposed mechanisms for elimination of *tert*-butylsulfoxides.

Since the oxidation/elimination strategy for preparing sulfenic acids is at the centre of most approaches, the second synthetic consideration is how to assemble the precursor, a 9-(alkylthio)triptycene. It can be envisioned that the 9-(alkylthio)triptycene could be assembled two ways: functionalization of an appropriately-substituted triptycene or formation of the triptycene with an S-containing functionality intact. Nakamura uses the latter approach,[51,85] and the overall synthetic route is shown in Scheme 2.3.

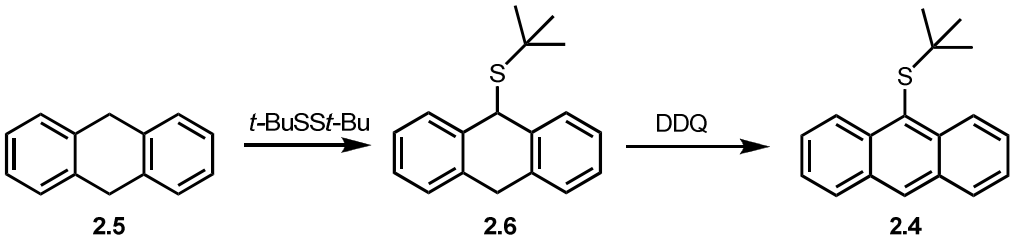


Scheme 2.3. Published approach to 9-triptycene sulfenic acid.

The eliminable group used by Nakamura is *tert*-butyl, but in theory, any alkyl sulfoxides containing a β-proton would suffice to undergo Cope elimination to form the sulfenic acid. The

major difference in using different alkyl groups would be the ease with which elimination would occur, and this is dependent on the C-H bond strength or steric effects. For example, allicin contains a labile hydrogen atom and can readily undergoe Cope elimination due to formation of thioacrolein, a resonance stabilized byproduct. Thus, the *tert*-butyl and the 2-phenethylthioether are compounds we thought might be useful sulfenic acid precursors as β-elimination should occur quite readily. The decision to use either of these compounds as a precursor would depend on whether the reaction for thioether formation was compatible with coupling bulky substrates.

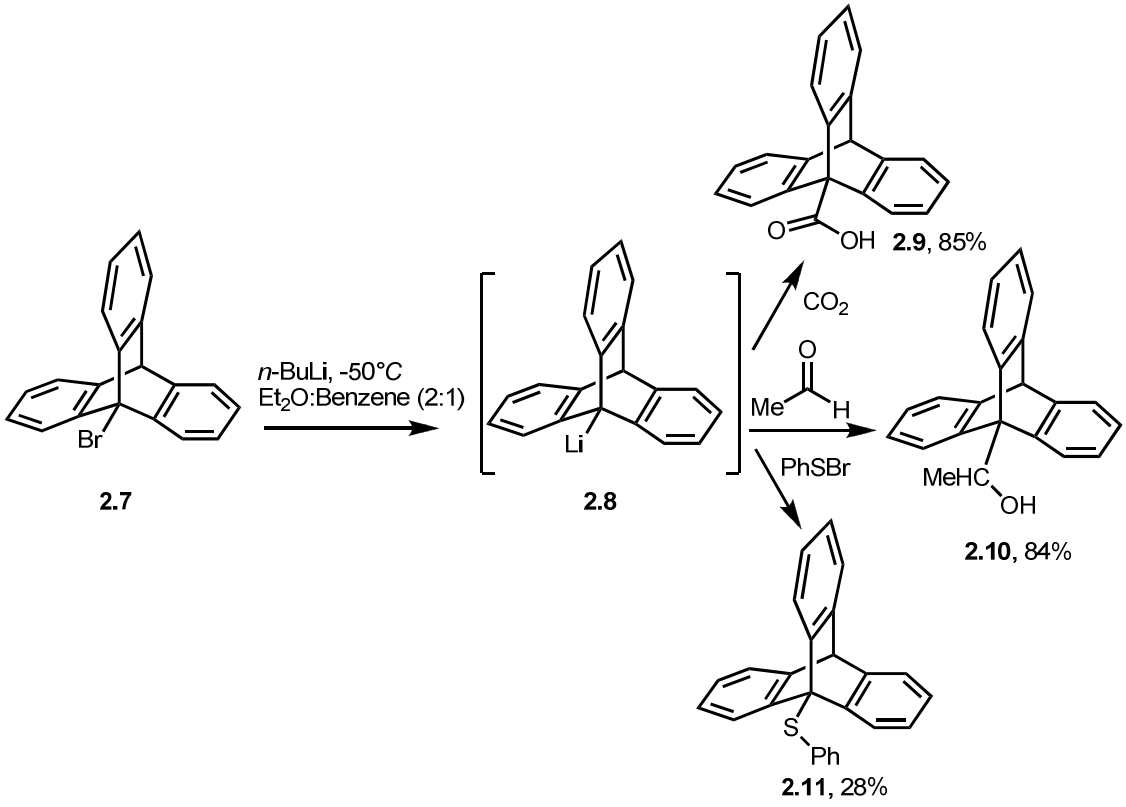
The synthesis of 9-triptycenesulfenic acid is outlined in two published articles.[85,51] However, to our knowledge, a third paper which was made reference to as submitted and which purportedly contained the experimental details for incorporation of the sulfide moiety to the 9-position of anthracene, did not appear. Instead, all that was reported was that sulfenylation reactions were performed on 9,10-dihydroanthracene (**2.5**) with the appropriate disulfide to form **2.6**, followed by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, Scheme 2.4). It can be predicted that the sulfenylation reaction was accomplished by a radical process; however, the radical addition of a disulfide to 9,10-dihydroanthracene would presumably be highly unselective and inefficient, therefore, this reaction was not attempted. The absence of experimental details from the original papers by Nakamura prompted us to explore the literature for preparing 9-triptycenesulfenic acid by other methods.



Scheme 2.4. Two step formation of 9-(*tert*-butylthio)anthracene from 9,10-dihydroanthracene.

2.1.3 Approach to 9-Triptycenesulfenic Acid by Functionalization of an Appropriately-Substituted Triptycene

The simplest method that we envisioned for preparing 9-triptycenesulfenic acid was to form the triptycene backbone first, followed by installation of the *tert*-butylthioether at the 9-carbon. One way to go about doing this is to do a cycloaddition on 9-bromoanthracene (**2.7**, see Chapter 2.1.5), followed by lithium-halogen exchange, and quenching with the appropriate dialkyl disulfide. This approach, if successful, will only be three synthetic steps. It turns out that other groups have performed lithium-halogen exchange on 9-bromotriptycene, but they quench with other electrophiles, such as carbon dioxide, aldehydes, or ketones.[86] To our knowledge no one has attempted to quench with a disulfide before, although, 9-(phenylsulfanyl)triptycene has been prepared in 28% yield using a sufenylbromide as the electrophile.[87]

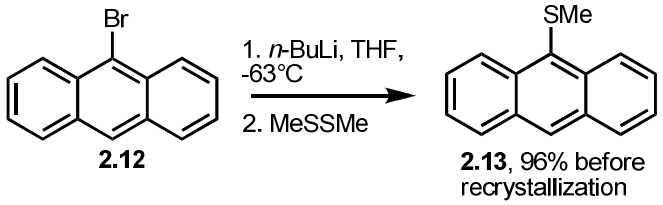


Scheme 2.5. Formation of functionalized triptycene compounds at the 9-position by lithium-halogen exchange on 9-bromotriptycene followed by quenching with an appropriate electrophile.

2.1.4 Formation of 9-Alkylthioanthracenes

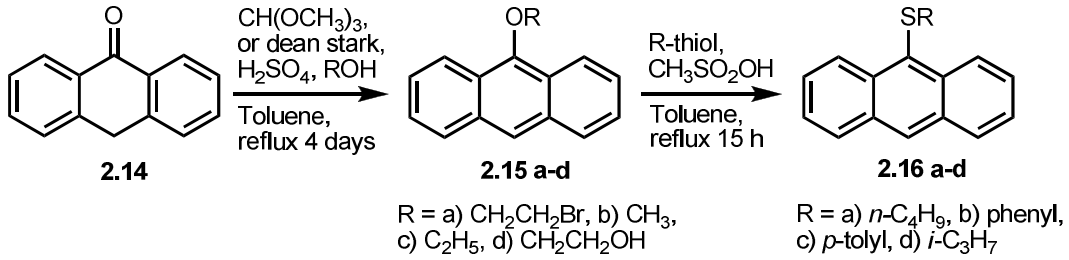
Alternatively, methods for formation of triptycene with an S-containing functionality intact could be explored. There are a number of ways, besides the approach shown in Scheme 2.4, to attach *tert*-butylthioethers to anthracenes. One option is to start with 9-bromoanthracene (**2.12**), carry out a lithium-bromine exchange, and then quench the 9-anthryllithium with the appropriate di-*tert*-butyl disulfide. To our knowledge, this reaction has only been reported using dimethyl disulfide (Scheme 2.6)[88] but quenching with other dialkyl disulfides would presumably result in formation of the corresponding products. Although there is vast literature for this type of reaction

starting from bromobenzene, there are not many examples using 9-bromoanthracene as the starting material.



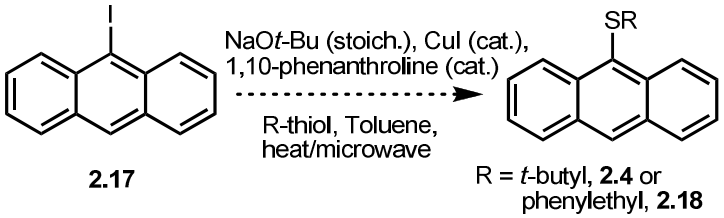
Scheme 2.6. One step formation of 9-methylthioanthracene (2.8) by lithium/halogen exchange

Another approach to 9-(*tert*-butylthio)anthracene is to do two subsequent substitution reactions starting from anthrone (**2.14**). The yields for sulfide formation range from 23%, for the more hindered *iso*-propyl sulfide (**2.16d**), to 85%, for the less hindered *n*-butyl sulfide (**2.16a**). Ether formation from anthrone ranges from 70-90% yield. Clearly, the overall yield for this pathway is low, especially for hindered systems; the author simply states that the examples they offer are simple, convenient, procedures amenable to large scale.[89]



Scheme 2.7. Two step formation of 9-alkylthioanthracenes from anthrone.

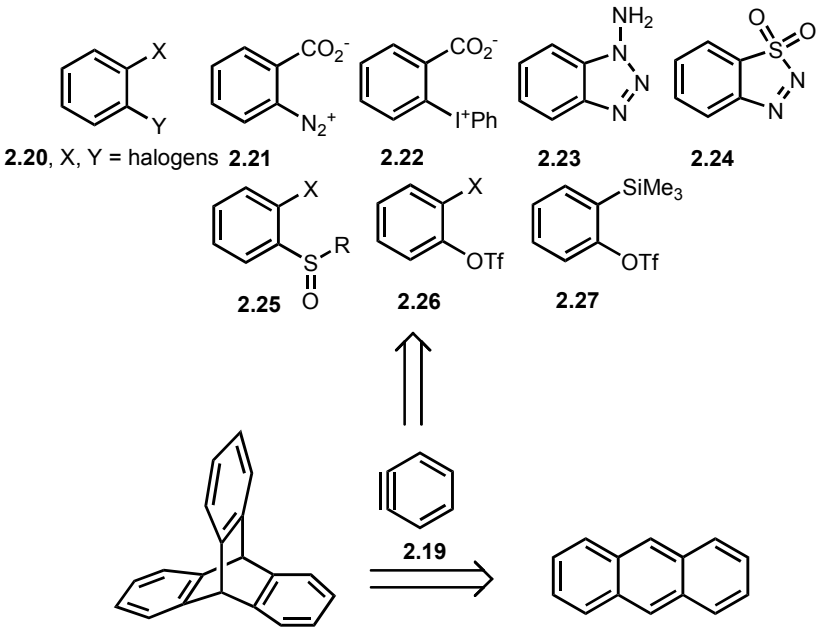
We also envisioned a third approach – an Ullmann-type coupling of a mercaptan and 9-iodoanthracene (**2.17**). To our knowledge, no one has performed Ullmann couplings with 9-iodoanthracene and alkylthiols. There is literature precedent for coupling alkyl thiols with other aryl iodides (e.g. phenyl iodides) in very good yields,[90] however there were no attempts to couple bulky thiols, like *tert*-butylthiol. With this in mind it was anticipated that we may have to use the less hindered 2-phenylethylthiol as a coupling partner or use excessive heating or even microwave radiation to couple the robust iodoanthracene with *tert*-butylthiol.



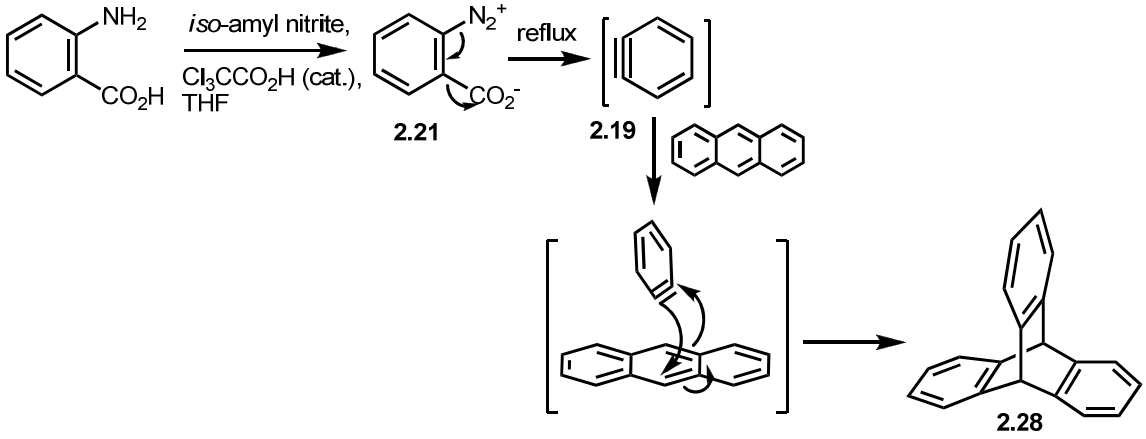
Scheme 2.8. Two step formation of 9-(*tert*-butylthio) or 9-phenethylanthracene from bromoanthracene.

2.1.5 Formation of the Triptycene Backbone via [4+2] Cycloadditon

Triptycene compounds are typically prepared by [4+2] cycloadditions of benzyne (**2.19**) with anthracene derivatives. Many groups have studied benzyne precursors; a representative list is shown in Scheme 2.9. Compound **2.21**[91] initially drew our attention for two reasons: first it is prepared from readily available and cheap starting materials (anthranilic acid and an alkyl nitrite) and second, this is the method reported by Nakamura for his synthesis of 9-triptycenesulfenic acid.[91] **2.21** can be formed in 1-1.5 hours at room temperature and once isolated can be combined with the benzyne acceptor and heated for the cycloaddition to occur (Scheme 2.10).



Scheme 2.9. Various benzyne precursors.

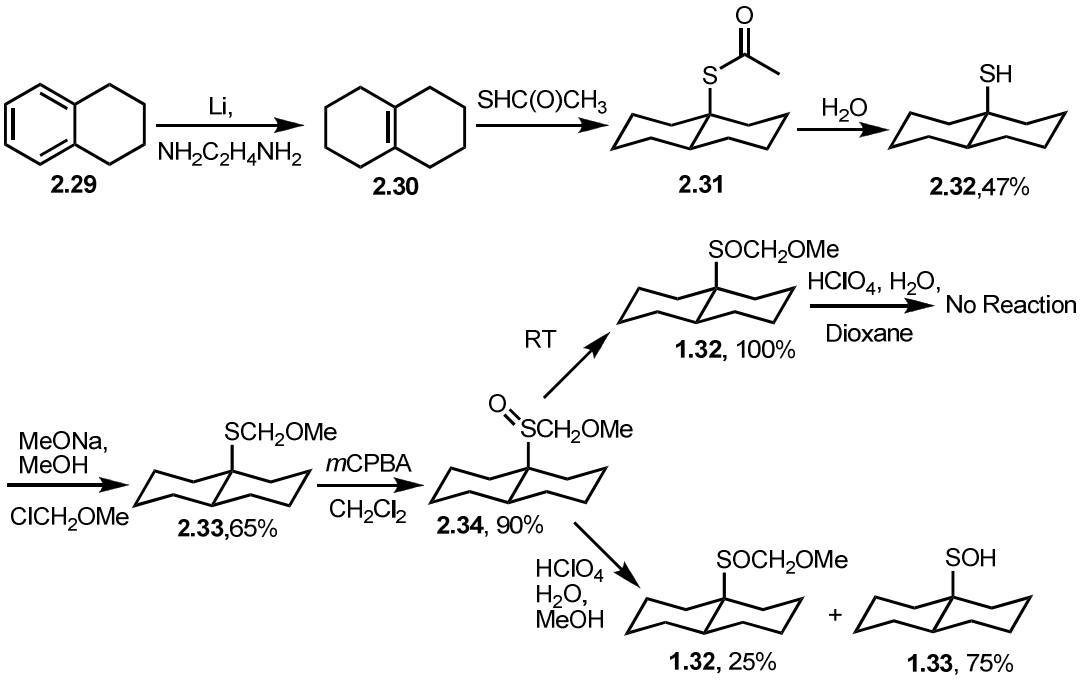


Scheme 2.10. Reaction of benzyne with anthracene to form triptycene (**2.24**).

The other precursor that stood out was **2.27**[92]; this is due to the fact that it can produce benzyne under mild conditions (room temperature) and in relatively short reaction time. However, the *o*-trimethylsilylphenyl triflate is fairly expensive in comparison to anthranilic acid. When **2.27** was treated with a fluoride source such as tetramethylammonium fluoride, benzyne could be trapped almost quantitatively when the benzyne acceptor was used in large excess.[93]

2.1.6 Synthetic Approach Towards *trans*-Decalin-9-Sulfenic Acid

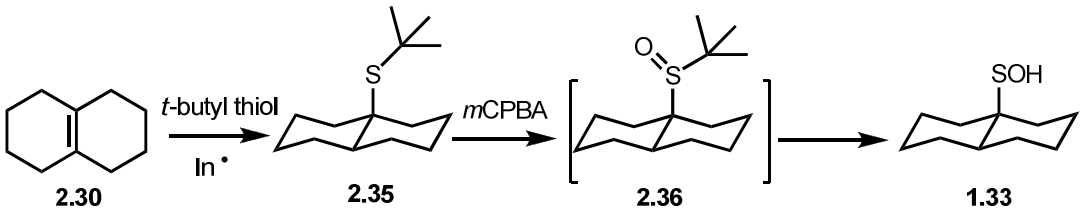
Like 9-triptycenesulfenic acid, *trans*-decalin-9-sulfenic acid could be assembled various ways. The first consideration on how to prepare this compound was via the literature (Scheme 2.11),[52] which like 9-triptycenesulfenic acid was lacking in experimental details. In fact, Yoshimura does not report any supporting information or an experimental section in this communication. However, the overall route is six steps, and uses fairly simple chemistry. It was reported that the sulfenic acid precursor, sulfoxide **2.34**, was unstable at room temperature and rearranged quantitatively to form sulfenate **1.32** after eight hours. However, direct acid-hydrolysis of the sulfoxide with 7% perchloric acid in 2:1 MeOH-H_2O at room temperature for ten minutes afforded the sulfenic acid **1.33** in 75% yield. Although this route seems straight forward, there are some steps that can be improved upon; hence, we put together some alternative synthetic pathways.



Scheme 2.11. Literature preparation of *trans*-decalin-9-sulfenic acid.

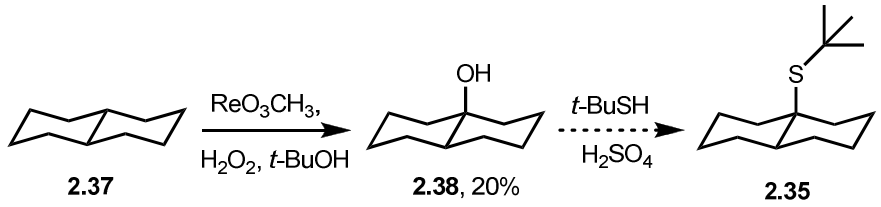
2.1.7 Formation of *Trans*-decalin-9-alkythioethers

There are a couple ways to possibly improve the literature route to **1.33**. One is to install a *tert*-butylthioether at the 9-position of decalin and obtain the sulfenic acid via Cope elimination similar to Nakamura's method. This could significantly shorten the route from 7 steps to 3, and avoid formation of the rearranged byproduct. The thioether could be installed by a radical addition of *tert*-butylthiol to the double bond in octalin (**2.30**), and then upon *m*CPBA oxidation the sulfenic acid could be produced (Scheme 2.12).



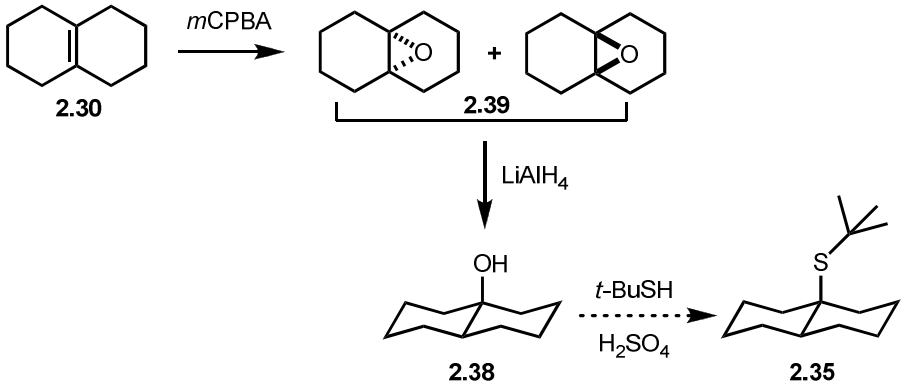
Scheme 2.12. Formation of *trans*-decalin-9-sulfenic acid via radical addition of an alkylthiol to octalin.

Another option is to start from *trans*-decalin and oxidize one of the tertiary C-H bonds to form the alcohol followed by S_N1 substitution of the alcohol by *tert*-butylthiol (Scheme 2.13). There is literature for *trans*-decalin C-H insertions at the 9-position by hydrogen peroxide using methyltrioxorhenium (MTO) as the catalyst.[94] In this paper, *trans*-decalin (**2.37**) is oxidized to the alcohol (**2.38**) in only 20% yield, but the overall route to the sulfenic acid is only three steps, which is still much better than the literature preparation.



Scheme 2.13. Installation of a *tert*-butylthioether onto *trans*-decalin by MTO oxidation followed by thiol substitution.

An alternative oxidative route is *m*CPBA oxidation of octalin to form the epoxide, followed by lithium aluminum hydride reduction to form the alcohol (Scheme 2.14). The *m*CPBA oxidation is much higher yielding (97% for a similar substrate) than the MTO oxidation and the reduction is also high yielding (90%).[95]

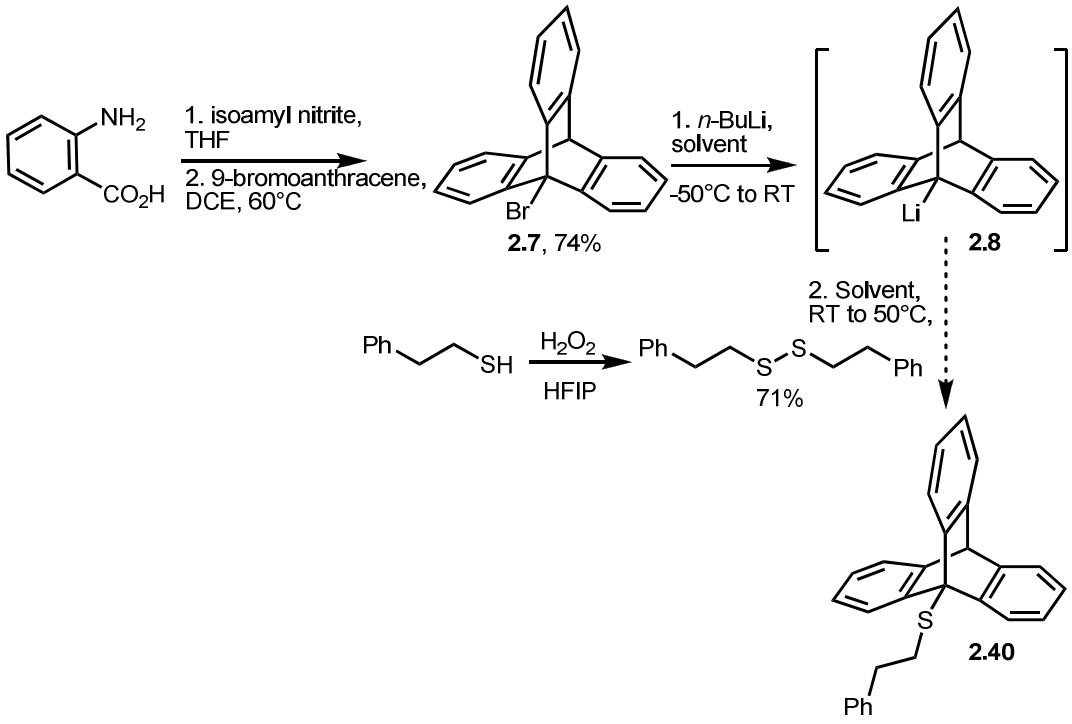


Scheme 2.14. Installation of an alkylthioether onto octalin by epoxidation formation followed by reduction and thiol substitution.

2.2 Results and Discussion

2.2.1 Approach toward 9-(*tert*-butylthio)triptycene by lithiation of 9-bromotriptycene

The first approach we took towards making the sulfenic acid precursor, 9-(*tert*-butylthio)triptycene (and 9-(phenethylthio)triptycene), involved performing a cycloaddition on 9-bromoanthracene followed by lithium-halogen exchange and quenching with the appropriate disulfide (Scheme 2.15). The first step in this synthesis was the cycloaddition with 9-bromoanthracene (see Table 2.4 for optimization of conditions). Accordingly, the benzenediazonium-2-carboxylate salt (**2.21**) was prepared, isolated and added to 9-bromoanthracene followed by heating overnight to form 9-bromotriptycene in 74% yield after column chromatography.



Scheme 2. 15 Summary of synthetic work attempted to make 9-triptycene sulfenic acid via lithium-halogen exchange on 9-bromotriptycene followed by disulfide quenching.

Secondly, lithium-halogen exchange was to be performed, followed by disulfide quenching. Here it seemed reasonable to attempt quenching with di(phenethyl)disulfide, the less hindered of the two disulfides of interest. Table 2.1 shows the two ways that were attempted to make di(phenethyl)disulfide. It turned out that hydrogen peroxide[96] worked better than air[97] as an oxidant for this particular reaction, which was probably due to the fact that the oxygen concentration was not high enough in the latter reaction. For the reaction with hydrogen peroxide, the thiol clearly was consumed by TLC analysis and 71% yield of the pure disulfide was obtained. When 2-phenethyl thiol was exposed to air in the presence of triethylamine in DMF, the thiol never fully disappeared by TLC and so a balloon of oxygen gas was bubbled through the

reaction, in attempt to push it forward. However starting material was still present, and since the thiol would be very difficult to separate from the disulfide, this method was discarded.

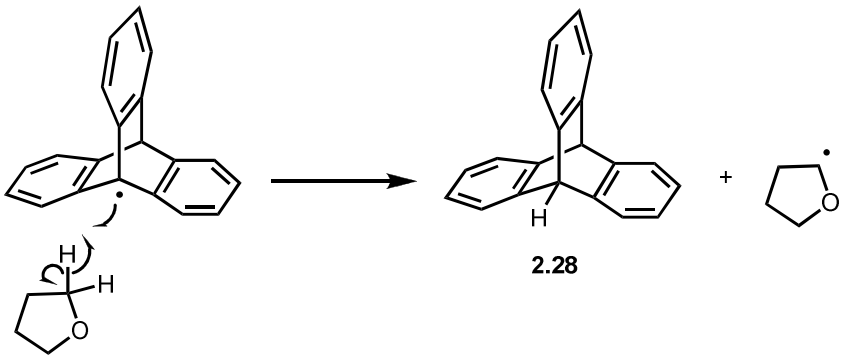
Table 2.1. Conditions attempted for preparation of diphenethyldisulfide

Trial	Oxidizing Reagent	Solvent	Conditions	Yield
1	1 eq. H_2O_2	HFIP	Stir at RT overnight	71%
2	Air	DMF	Sonicate with NEt_3	N/A

The first preparation of 1-triptyllithium was attempted according to the literature,[86] where *n*-butyllithium was added to a solution of 9-bromotriptycene in 1:1 (v:v) THF:benzene. Care was taken to distill both the THF and benzene from benzophenone ketyl immediately before use. By TLC, consumption of the bromide indicated that lithiation had occurred after about fifteen minutes. At this point the disulfide was added as a solution in benzene, and the reaction was monitored after 45 minutes and two days. By TLC, the reaction looked like a mixture of triptycene and disulfide at both time periods and the ^{1}H-NMR spectrum reflected the same mixture. The aromatic phenyl and triptycene signals overlap significantly and are not very distinguishable; however, the bridgehead proton of the triptycene and ethyl protons of the disulfide are distinguishable, making it clear that the reaction mixture only consists of the disulfide and triptycene.

If the reaction between 1-triptycyllithium and a disulfide occurs by a radical process (similar to that between 1-triptycyllithium and carbon dioxide), the poor electrophilicity of the disulfide would be less significant and proper solvent conditions that are compatible with the reaction would be important.[86] For example, if the solvent contained a hydrogen atom that was

easily abstracted, the triptycyl radical species could become quenched with the hydrogen atom to make triptycene as a byproduct (Scheme 2.16).[86] With this in mind, it was decided to remove the solvent after 1-triptycyllithium formation and re-solvated using benzene only.[87] Even after using a solvent without a readily abstractable hydrogen atom, it appeared by TLC that the reaction was only a mixture of triptycene and disulfide and not surprisingly, the ^{1}H-NMR confirmed this. To round out our solvent conditions we also attempted the reaction using α,α,α-trifluorotoluene which does not contain any abstractable hydrogen atoms either, but perhaps would help with solvation of the reactants. In this attempt lithiation appeared to go as expected, however, again no desired product was formed and 79% mass recovery of the disulfide was obtained along with trace amounts of the bromide.

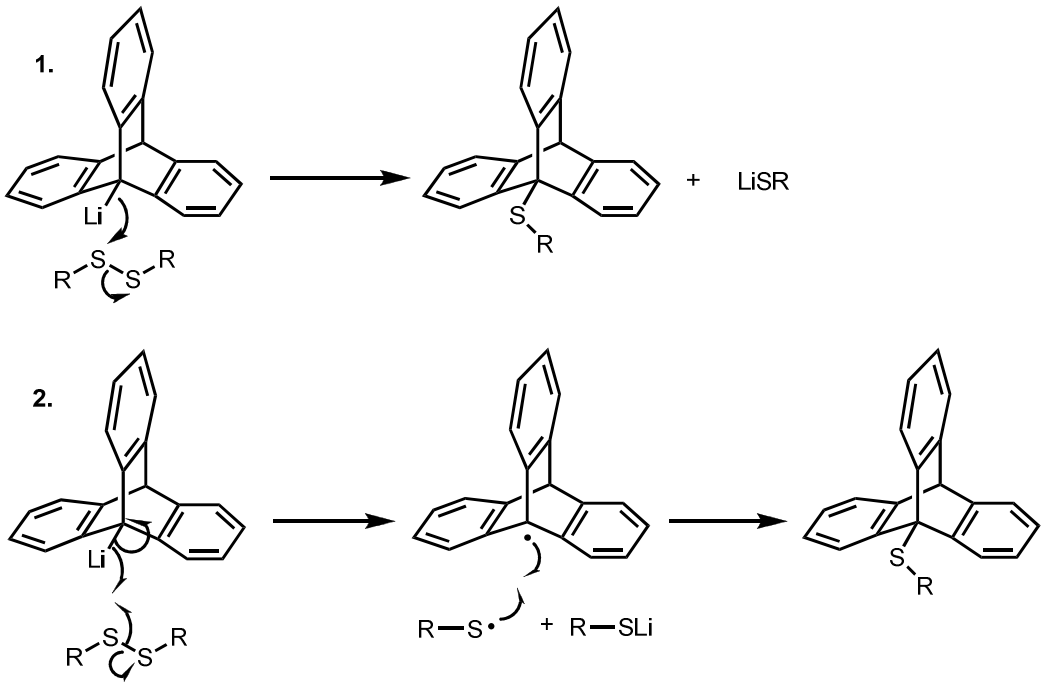


Scheme 2.16. Abstraction of a hydrogen atom from a solvent molecule (THF) by triptycylradical.

Although attempts were made to address the possibility that 1-triptyllithium may react with electrophiles via one electron processes by using chemically inert solvents, no sulfide group was successfully attached. When the same reaction was attempted with diphenyldiselenide, we were able to prepare the desired selenotriptycene product, albeit in low yield (See Appendix A).

This suggests that since the S-S bond is shorter than the Se-Se bond, it may be more difficult for approach by the triptycyllithium species to undergo nucleophilic attack.

However, the possibility that the reaction goes by nucleophilic attack is not a definitive mechanism for this reaction. Another argument is that the reaction is a one-electron process given that we consistently obtained triptycene and disulfide as reaction products. Scheme 2.17 shows the nucleophilic substitution versus radical mechanism for the reaction. In the radical mechanism, it is proposed that there is a dissociate electron transfer from the organolithium species to the disulfide to yield a 1-triptycyl and thiyl radical pair and lithium thiolate ion pair. Subsequently, the triptycyl and thiyl radicals can combine to form the desired product or, the two thiyl radicals can combine to reform the disulfide and the triptycyl radical abstracts a hydrogen atom from a solvent molecule to produce triptycene. The radical pathway does verify our experimental observations, except for the fact that only freshly distilled solvents with non-abstractable hydrogen atoms were used; thus, our thoughts about the mechanism for this reaction are not yet conclusive.

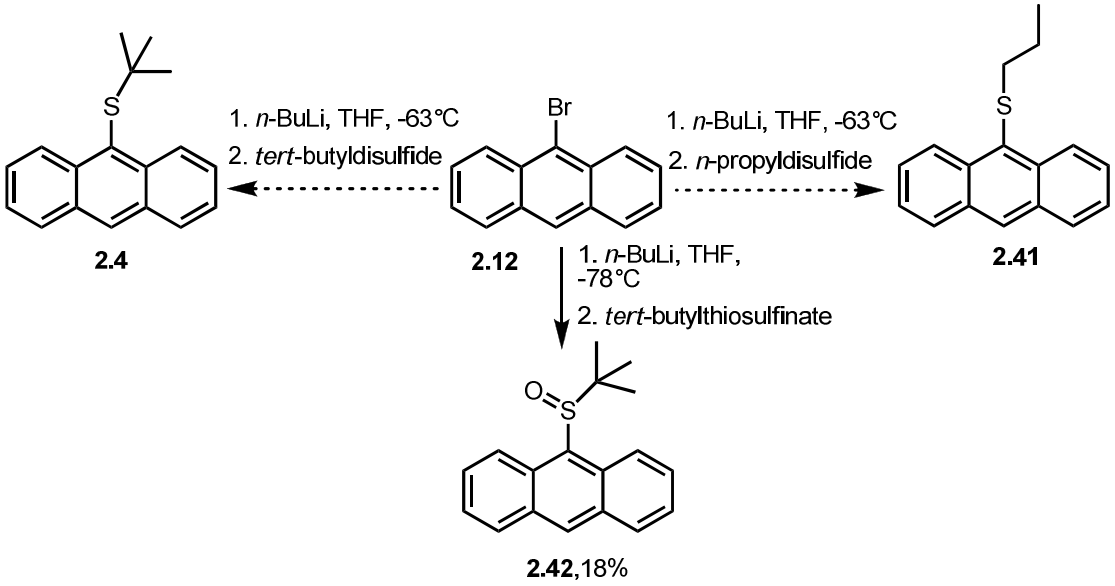


Scheme 2.17. Possible mechanisms for the reaction between 1-triptycyllithium and an alkyldisulfide to form a 9-(alkylthio)triptycene. 1. Nucleophilic substitution. 2. A dissociate electron transfer from 1-triptycyllithium followed by coupling of the triptycyl radical with a thiyl radical.

2.2.2 Formation of 9-(Alkylthio)anthracenes

Initial attempts to prepare 9-(*tert*-butylthio)anthracene involved lithium-halogen exchange followed by addition of di-*tert*-butyl disulfide (Scheme 2.18). Lithium-halogen exchange appeared to go to completion as observed by thin layer chromatography (TLC), but after addition of di-*tert*-butyl disulfide, there did not appear to be any change after stirring at room temperature overnight. An additional half of an equivalent of disulfide was added to try to push the reaction forward, but no significant product formation appeared by TLC. Following work-up the ^{1}H NMR spectrum was consistent with a mixture of anthracene and disulfide, confirming that no reaction had occurred. We next attempted a less hindered disulfide, di-*n*-propyl disulfide (Scheme 2.18) to

see if sterics were indeed prohibitive. Similar to the previous reaction, there appeared to be no reaction between the lithiated anthracene and di-*n*-propyl disulfide, but after adding an additional one and a half equivalents of disulfide three new spots appeared by TLC analysis. Upon work up and isolation, the crude mixture was mainly anthracene and disulfide, similar to the results above, with trace product, if any.

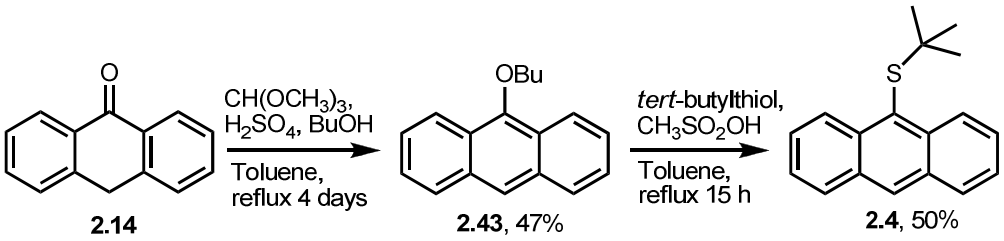


Scheme 2.18. Attempts at lithium-halogen exchange followed by disulfide or thiosulfinate quenching.

Due to the lack of success quenching 9-anthryllithium with the two disulfides, we decided to try a better electrophile; the corresponding thiosulfinate (Scheme 2.18). Di-*tert*-butyl thiosulfinate is not commercially available, but can be easily prepared by *m*CPBA oxidation of the disulfide precursor and isolated by column chromatography,[98] which was done in 98% yield. Quenching 9-anthryllithium with di-*tert*-butyl thiosulfinate gave 18% desired product and an unknown impurity after column chromatography. Due to this unexpectedly poor reaction, a control experiment was performed with phenyllithium and di-*tert*-butyl thiosulfinate – which

resulted in a 50% yield (the literature yield for this reaction was 92%[99]) suggesting that steric hindrance between the peri-hydrogens of 9-anthryllithium and the *tert*-butyl groups of the thiosulfinate slows the reaction dramatically. In hindsight, it may have been useful to heat the reactions of the tripticyllithium and disulfide following addition of the disulfide.

At this point we decided to try another route towards 9-*tert*-butylthioanthracene (Scheme 2.19). In the first step, anthrone was treated with butanol and trimethylorthoformate in the presence of catalytic sulfuric acid in toluene. The reaction conditions were slightly modified from Pirkle's procedure[89] as toluene was use instead of benzene and butanol was used as the nucleophile. The reaction was refluxed for four days as suggested, but the best yield was only 47%. The reported yields using other alcohols range from 70-90%.[89] The 9-butoxyanthracene was isolated easily by column chromatography using a hexanes:ethyl acetate gradient.

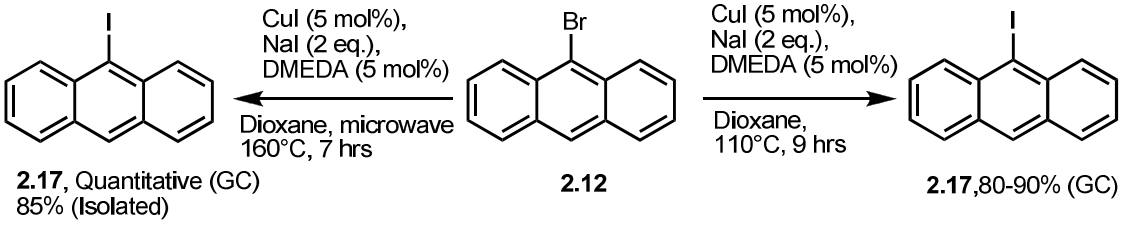


Scheme 2.19. Two-step formation of 9-*tert*-butylanthracene from anthrone.

For the second step, 9-butoxyanthracene was treated with *tert*-butyl thiol and catalytic methanesulfonic acid in toluene and refluxed overnight. The product was purified by column chromatography using hexanes as the eluting solvent to afford 9-(*tert*-butylthio)anthracene in 50% yield. Pirkle reports yields ranging from 23-85% for this reaction using various thiols. In

fact, the somewhat hindered *iso*-propyl thiol gave the lowest yield (23%), suggesting our yield is quite satisfactory.[89]

In an attempt to improve things further, we explored the third approach introduced above – an Ullman-type coupling of *tert*-butyl thiol and 9-iodoanthracene. To do so, we first prepared 9-iodoanthracene by a Cu-catalyzed Finkelstein-type reaction[100] on 9-bromoanthracene as shown in Scheme 2.20. This reaction worked quite well, giving a yield between 80 and 90% by GC-MS as long as the dioxane was freshly distilled before use, with the mass balance made up by the starting bromide. Unfortunately, following work-up, the product could not be separated from the starting material. In an effort to push the reaction to completion, it was carried out in a glass tube and placed in a microwave reactor at 160°C for seven hours. Under these conditions the starting material was completely consumed to give a single product signal with the correct mass by GC-MS. Table 2.2 shows the various reaction conditions attempted before optimization.



Scheme 2.20. Cu-catalyzed Finkelstein-type reaction on 9-bromoanthracene.

Table 2.2. Optimization of Finkelstein reaction on 9-bromoanthracene.

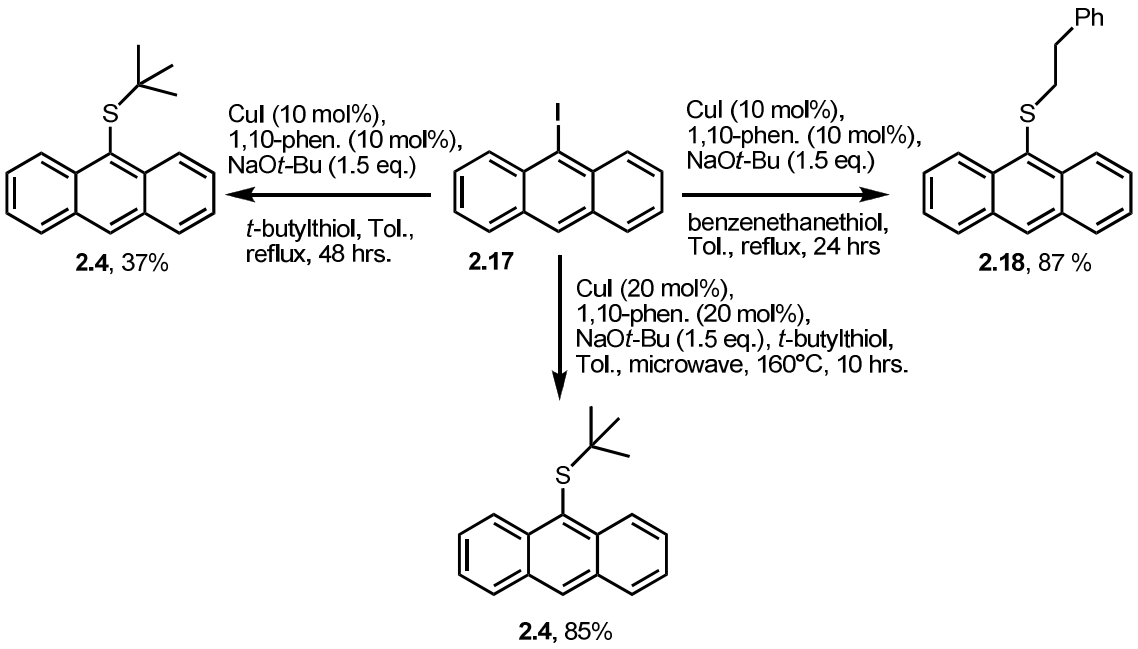
Trial	Heating Method	Temperature (°C)	Time (hours)	GC Yield
1	Oil Bath	110	9	80-90% (70%*)
2	Microwave	110	1	0%

3	Microwave	150	3	70%
4	Microwave	160	2	60%
5	Microwave	160	7	100% (86%*)

*Isolated yield

The Ullmann-type coupling of a thiol with 9-iodoanthracene was originally carried out using the reflux conditions shown in Scheme 2.21[90] and 2-phenethyl thiol as a coupling partner. 2-Phenethyl thiol should be an easier coupling partner as it is much less sterically hindered than *tert*-butyl thiol. After treatment of 9-iodoanthracene with 10 mol% copper iodide, 1,10-phenanthroline as a ligand, sodium *tert*-butoxide as base, and 2-phenethyl thiol, under reflux conditions for 24 hours, the desired product was obtained in 87% yield after purification by column chromatography.

This reaction was then attempted using *tert*-butyl thiol as a coupling partner and the same reaction conditions. However, after two days at reflux, the reaction stalled at 50% conversion by GC-MS and only a 37% isolated yield was obtained. Clearly, the bulkiness of the *tert*-butyl group had slowed the substitution. Due to our success using the microwave reactor for the Cu-catalyzed Finkelstein reaction, we made use of it for the current reaction and ended up with optimum conditions giving a quantitative GC yield and 85% isolated yield (see Table 2.3). It is important to note that the 9-*tert*-butylanthracene and the 9-iodo and 9-bromoanthracenes were not separable by TLC, making it absolutely necessary to push both the halogen exchange and coupling reactions to completion.



Scheme 2.21. Ullmann couplings on 9-iodoanthracene.

Table 2.3. Optimization of Ullmann couplings between 9-iodoanthracene and alkyl thiols

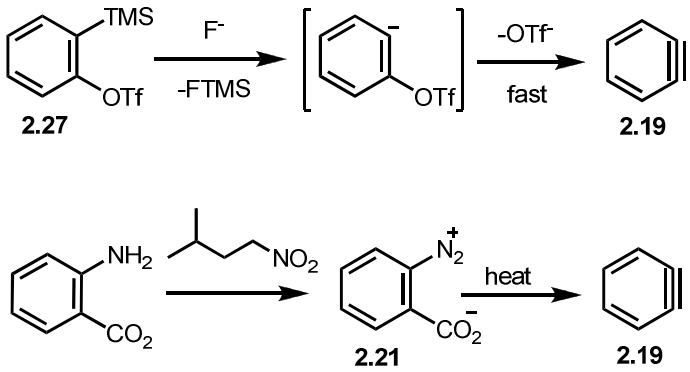
Trial	Coupling Partner	CuI (mol%)	Heating Method	Temperature (°C)	Time (hours)	GC Yield
1	Ethanebenzenethiol	10	Oil bath	110	24	87%*
2	*tert*-Butylthiol	10	Oil bath	110	72	50% (37%*)
3	*tert*-Butylthiol	10	Microwave	120	1	10%
4	*tert*-Butylthiol	10	Microwave	150	10	90%
5	*tert*-Butylthiol	20	Microwave	160	10	100% (85%*)

* Isolated Yield

2.2.3 Cycloadditions: Forming 9-(*tert*-butylthio)triptycene

Once the installation of the *tert*-butylthioether moiety at the 9-position of anthracene had been achieved, the next endeavor was formation of the triptycene backbone. We chose to explore two

benzyne precursor systems: treatment of *o*-trimethylsilylphenyl triflate with fluoride, and decarboxylation of *o*-diazoniumphenylcarboxylate (Scheme 2.22). Before we attempted the cycloaddition on our material, we wanted to survey conditions using the readily available unsubstitued benzyne acceptor, anthracene. Table 2.4 summarizes the results obtained for cycloaddition reactions with anthracene. In general, anthracene was not very soluble in the most common solvents used for cycloaddition chemistry, which resulted in poor yields. Optimization indicated that DCM and DCE were the most promising solvents for the corresponding reaction to make 9-(*tert*-butylthio)triptycene.



Scheme 2.22. Methods used to generate benzyne.

Table 2.4. Survey of conditions for the [4+2] cycloaddition of anthracene with benzyne.

Trial	Benzyne Precursor	Solvent	Yield	Eq. SM : Eq. Benzyne Precursor	Comments
1	Anthranilic acid	DCM/THF	9%	1:1	Product recrystalized from hexanes
2	Anthranilic acid	DCM/THF	26%	1:1	Product recrystalized from cyclohexane
3	2-(TMS)phenyl	CH_3CN	0%	4:1	SM not soluble

	triflate				
4	2-(TMS)phenyl triflate	Toluene	0%	4:1	SM slightly soluble
5	2-(TMS)phenyl triflate	DCM	N/A	4:1	SM slightly soluble, 1:3 Trip/SM product ratio by NMR
6	2-(TMS)phenyl triflate	DME	N/A	4:1	SM slightly soluble, 1:25 Trip/SM product ratio by NMR
7	2-(TMS)phenyl triflate	THF	Trace	4:1	SM slighty soluble

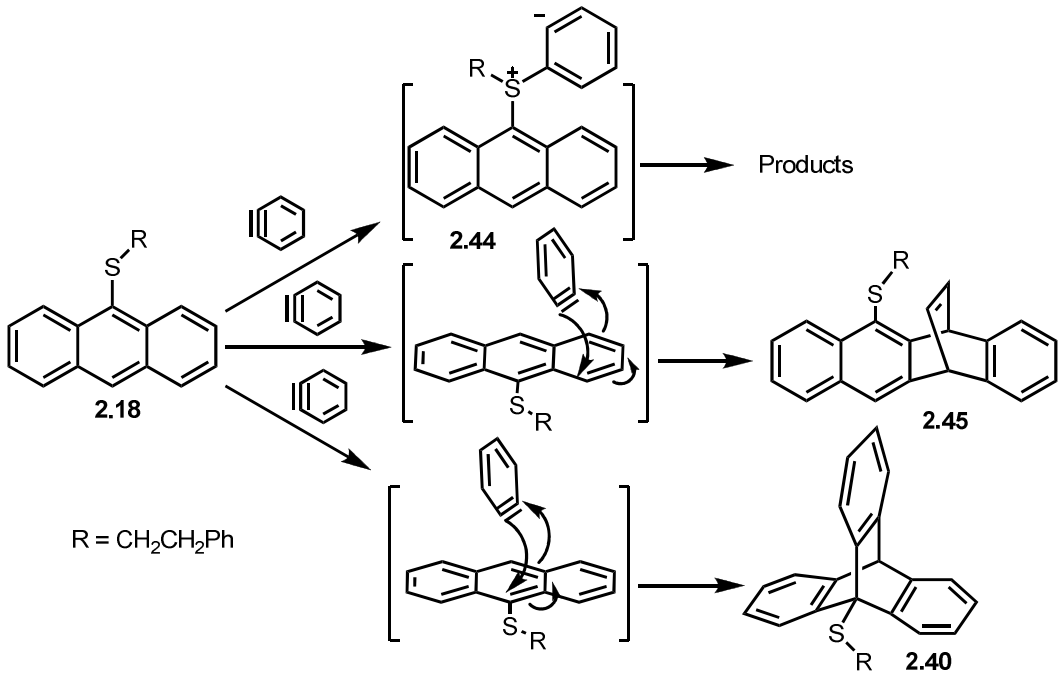
When we moved on to 9-(*tert*-butyl)thioanthracene as the benzyne acceptor we found that DCM was in fact the best solvent when using 2-(TMS)phenyl triflate as the benzyne precursor. However, the best yields came from isolating the benzenediazonium-2-carboxylate before adding it to 9-(*tert*-butyl)thioanthracene, and forming benzyne *in situ* by heating – which is why DCE was employed. This method was straightforward, cheap and gave the best yield, and was therefore used in all subsequent reactions.

Table 2.5. Survey of conditions for the [4+2] cycloaddition of 9-(*tert*-butylthio)anthracene with benzyne.

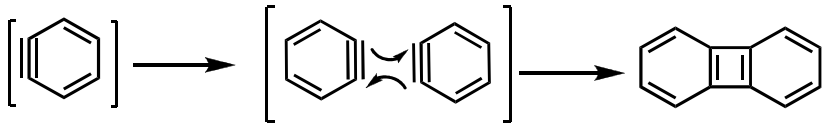
Trial	Benzyne Precursor	Solvent	Yield	Scale (g of SM)	Eq. SM : Eq. Benzyne Precursor	Comments
1	2-(TMS)phenyl triflate	DCM	48%	0.5	4:1	Stirred at RT overnight
2	2-(TMS)phenyl triflate	DCM	63%	1.7	4:1	Stirred at RT overnight
3	2-(TMS)phenyl triflate	DCE	33%	0.5	4:1	Refluxed for 2 hours
4	2-(TMS)phenyl triflate	DCE	4%	1.0	4:1	Refluxed overnight (no product after 2

						hrs)
5	Benzenediazonium-2-carboxylate	DCE	71%	0.2	1:3	Refluxed overnight
6	Benzenediazonium-2-carboxylate	DCE	63%	1.0	1:3	Refluxed overnight

Additionally we attempted the cycloaddition using 9-(phenylethylthio)anthracene as the benzyne acceptor, primarily because of the ease of coupling between 9-iodoanthracene and 2-phenylethyl thiol. Unfortunately, when the reaction was performed, the desired product could not be isolated from several byproducts that were formed during the cycloaddition. This is most likely due to the fact that the phenethylsulfide contains a sulfur atom that can undergo nucleophilic attack on benzyne.[85] Organic sulfides are well known to react with benzyne to produce sulfonium betaines (e.g. **2.44**) which collapse by elimination or rearrangement depending on the substituents on the sulfides.[101] This reaction could result in an additional side products to the possible triptycene adduct (**2.45**, Scheme 2.23)[85] and the self-reaction of benzyne (Scheme 2.24). The latter two side products would be typical for any reaction performed between benzyne and a 9-(alkylthio)anthracene thus formation of the sulfonium betaine (**2.44**) can account for the new side products associated with the reaction between benzyne and 9-(phenethylthio)anthracene. For the case with 9-(*tert*-butylthio)anthracene, the bulky *tert*-butyl group prevents this reaction from occurring.



Scheme 2.23. Possible outcomes for the reaction between 9-(phenylethylthio)anthracene and benzyne.

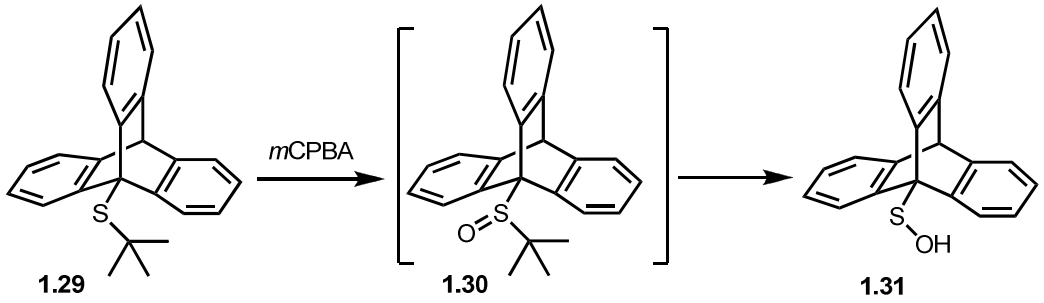


Scheme 2.24. Self-reaction of benzyne to form biphenylene.

2.2.4 Formation of 9-Triptycenesulfenic Acid

In general, oxidation of 9-(*tert*-butylthio)triptycene was done using the methods of Nakamura:[51] addition of a solution of *meta*-chloroperbenzoic acid dropwise to an ice-cooled solution of 9-(*tert*-butylthio)triptycene and stirred at room temperature overnight. The following morning there would consistently be two new spots by TLC analysis, one corresponding to the sulfenic acid, and

the other corresponding to what we believe to be the intermediate sulfoxide (Scheme 2.25) – but this was never indicated by Nakamura.



Scheme 2.25. Formation of 9-triptycenesulfenic acid going through sulfoxide intermediate.

Nakamura reports than when 9-(*tert*-butylthio)triptycene is treated with one equivalent of *m*CPBA, only the sulfenic acid (78%) and recovered starting material are isolated after preparatory TLC. In our experiences, there were always two new spots by TLC when the reaction was performed under the exact same conditions. Although full characterization data has not been obtained (various methods have been attempted to obtain a high resolution mass spectrum without success – presumably due to the lability of the C-S bond, and we are in the process of obtaining elemental analysis), we have obtained good evidence for the isolation of the sulfoxide intermediate by ^{1}H and ^{13}C NMR. The major difference when looking at the ^{1}H NMR for the sulfoxide (Figure 2.2) is that the protons on the triptycene backbone are no longer in a symmetrical environment so instead of the three distinct multiplets that are observed for both 9-(*tert*-butylthio)triptycene and 9-triptycenesulfenic acid (Figure 2.3), there are six distinct, complex splitting patterns. The reason for the six complex splitting patterns is that the sulfoxide is an asymmetric centre, as opposed to the thioether and the sulfenic acid, which are not. From the Newman projection in Figure 2.4, the hydrogen atoms on each of the aromatic rings of the

triptycene moiety are always in a different environment than the hydrogen atoms on the other two rings, which could account for the six splitting patterns.

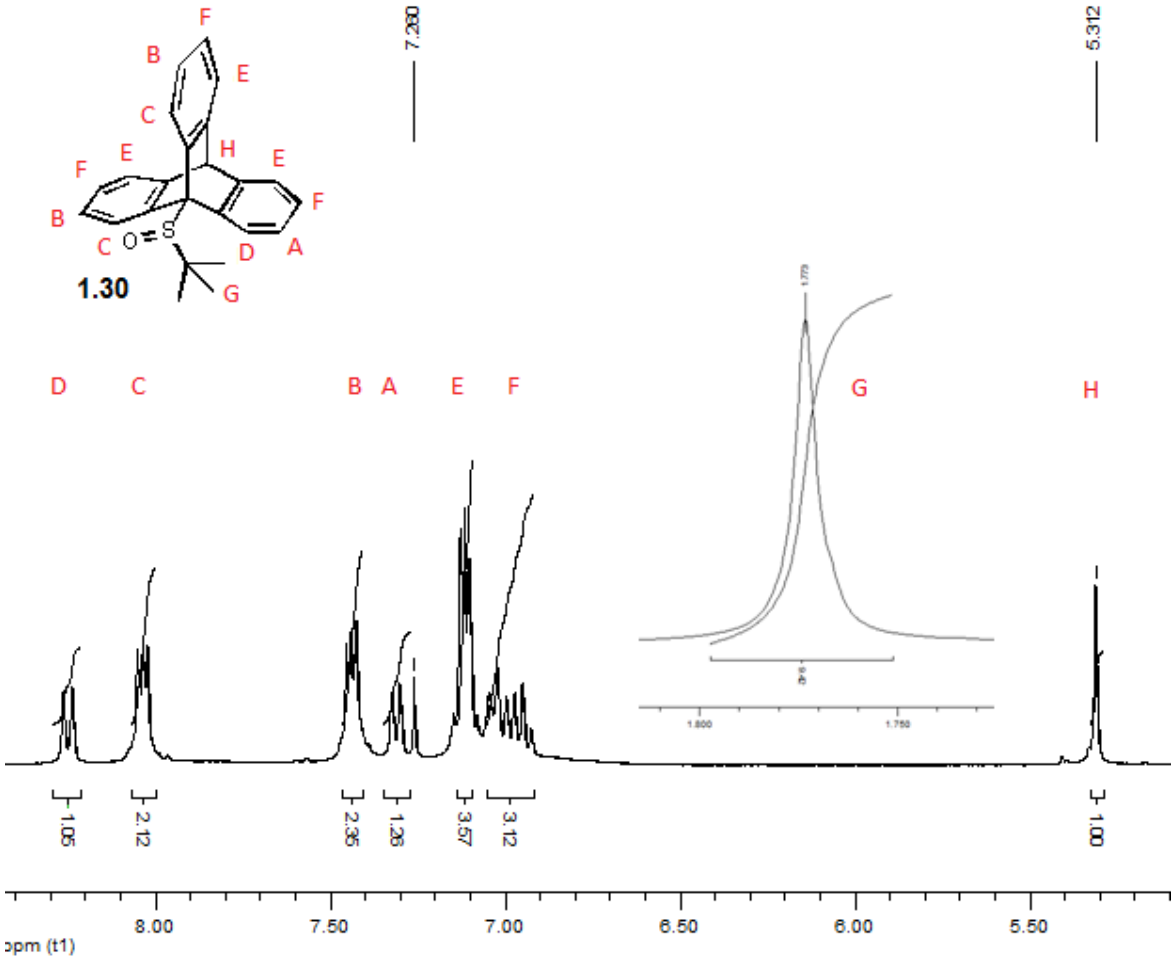


Figure 2.1. ^{1}H NMR for 9-triptycene-*tert*-butylsulfoxide in $CDCl_3$. Obtained at 400 MHz and chemical shifts recorded in ppm and referenced to $CDCl_3$ (7.26 ppm).

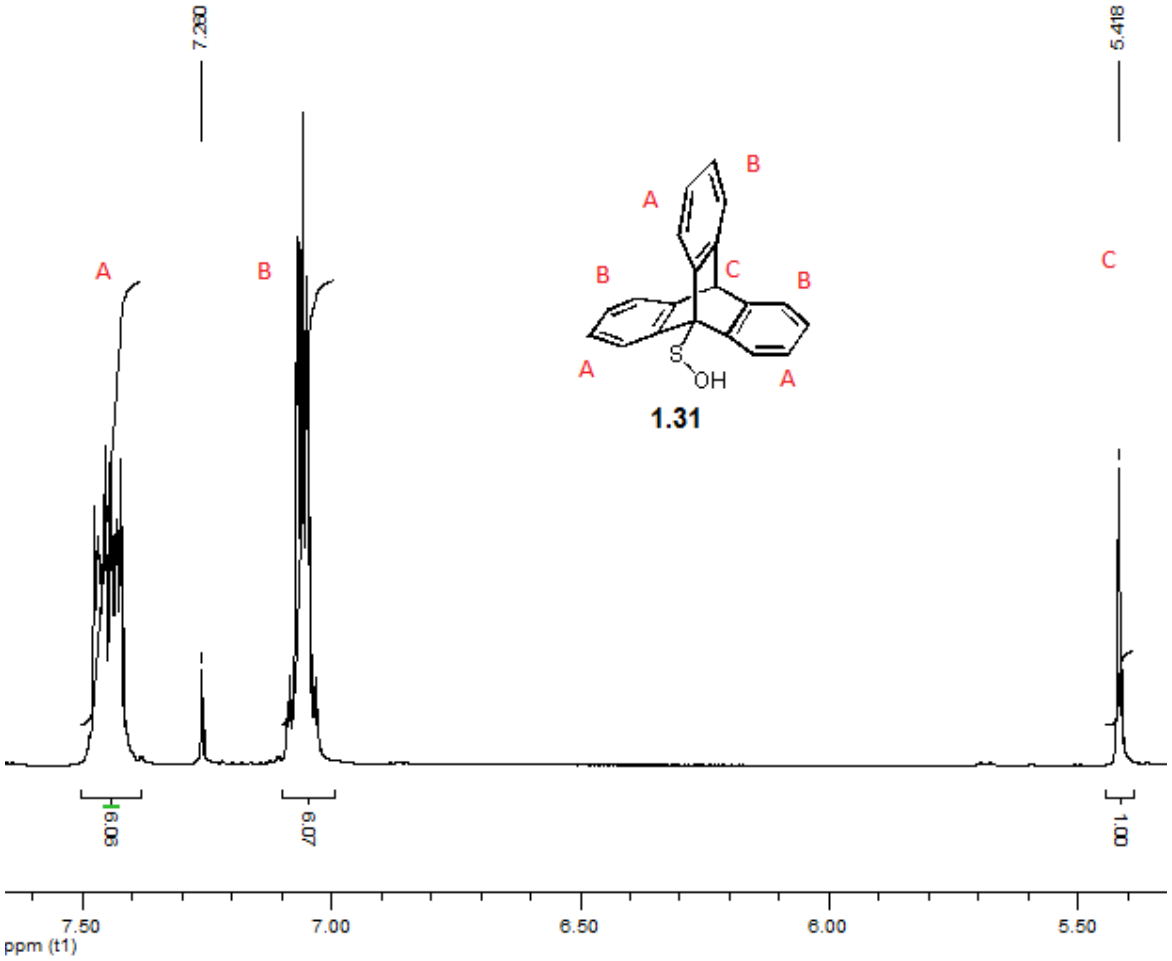


Figure 2.2. ^{1}H NMR for 9-triptycenesulfenic acid in $CDCl_3$. Obtained at 400 MHz and chemical shifts recorded in ppm and referenced to $CDCl_3$ (7.26 ppm).

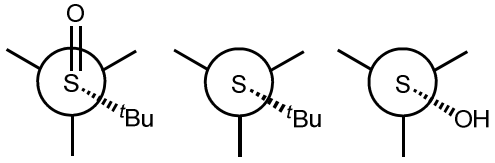


Figure 2.3. Simplified Newman projections of 9-triptycene-*tert*-butylsulfoxide compared to the corresponding 9-(*tert*-butylthio)ether and sulfenic acid.

It turns out that the sulfoxide is very difficult to separate from the sulfenic acid as their R_f values are very similar in a wide range of solvent systems. Nakamura purifies the sulfenic acid by preparatory TLC with 2:1 DCM/Hexanes as the eluent. When this method of purification was attempted, a mixture of sulfoxide and sulfenic acid were consistently obtained; however, Nakamura et al. did not provide a copy of their NMR spectra, so it cannot be verified that they had a single, pure compound. When 2:1 DCM/Hexanes was used with a very long column, the sulfenic acid still could not be separated from the sulfoxide. The only solvent system that was found to be effective in separating these two compounds was 2:1 DCM:Hexanes with 1% acetic acid which gave pure 9-triptycenesulfenic acid in 61% yield; the acetic acid presumably helps with the separation by hydrogen bonding with the sulfenic acid to facilitate its movement through the silica.

With the isolation of the sulfoxide, we were able to do some preliminary experiments to try and gain insight into the mechanism by which the sulfenic acid is formed via the sulfoxide intermediate (see Scheme 2.2). Initially, an experiment was performed to see if the sulfenic acid was formed by a thermally induced Cope elimination of the corresponding sulfoxide. A small amount of pure sulfoxide was dissolved in toluene and refluxed for a few hours and monitored by TLC. Over the course of a few hours, a new intense and easily oxidized spot was observed, which corresponded to the sulfenic acid. This lead to the belief, as other groups have shown,[53,54,60] that thermal elimination of the sulfoxide is in fact the mechanism by which the sulfenic acid is formed. We also set up experiments to test for the acid-catalyzed elimination pathway. Initially we subjected a mixture of sulfenic acid and sulfoxide (10:1 by ^{1}H NMR) to one equivalent of *m*CPBA, to see if the perbenzoic acid acts as both an oxidant and acid-catalyst in the reaction. Instead of pushing the reaction toward the desired sulfenic acid, new spots began to form by TLC

after stirring at room temperature overnight (same conditions were used as sulfenic acid formation from the thioether).

In attempt to figure out what new side products were being formed by the addition of acid, an experiment was set up in an NMR tube containing only the triptycenesulfenic acid, methanesulfonic acid and deuterated chloroform. After about an hour, new signals in the aromatic region were observed with significant sulfenic acid still present. The reaction was monitored by the relative integration of the sulfenic acid bridgehead proton (*) compared to the new bridgehead proton (a) over the span of a few days (See insert of Figure 2.5 and 2.6). The sulfenic acid was never fully consumed, but the ratio of new product to sulfenic acid grew slowly over time. This new product, we speculate, may be the condensation product of the sulfenic acid, the triptycene thiosulfinate (**2.46**, Scheme 2.26). The relative integration of the new bridgehead proton (insert, a) to the new aromatic signals (a) is 1:9. We would expect 1:12 based on thiosulfinate formation, however, some of the new aromatic signals (a) presumably overlap with the sulfenic acid aromatic signals (*).

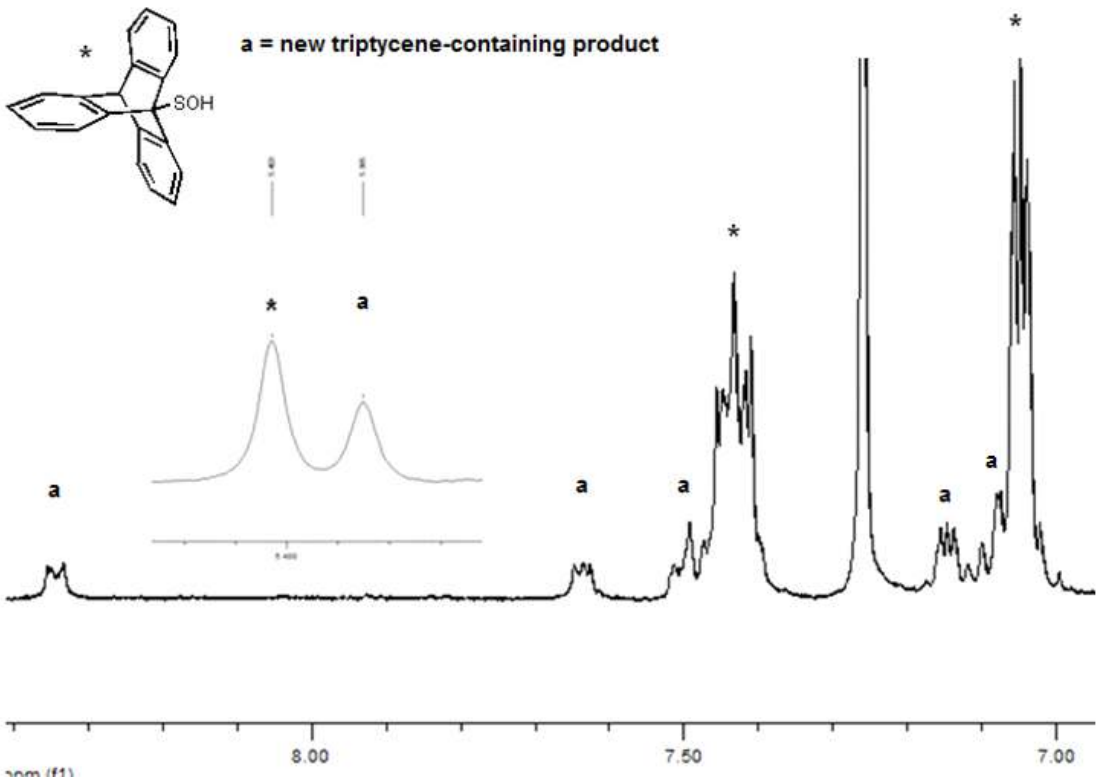


Figure 2.4. ^{1}H NMR for 9-triptycenesulfenic acid containing methanesulfonic acid in $CDCl_3$ after 5 hours showing the possible formation of di-triptycylthiosulfinate indicated by a new bridgehead signal (a) in addition to the sulfenic acid bridgehead signal (*). Spectrum obtained at 400 MHz and chemical shifts recorded in ppm and referenced to $CDCl_3$ (7.26 ppm).

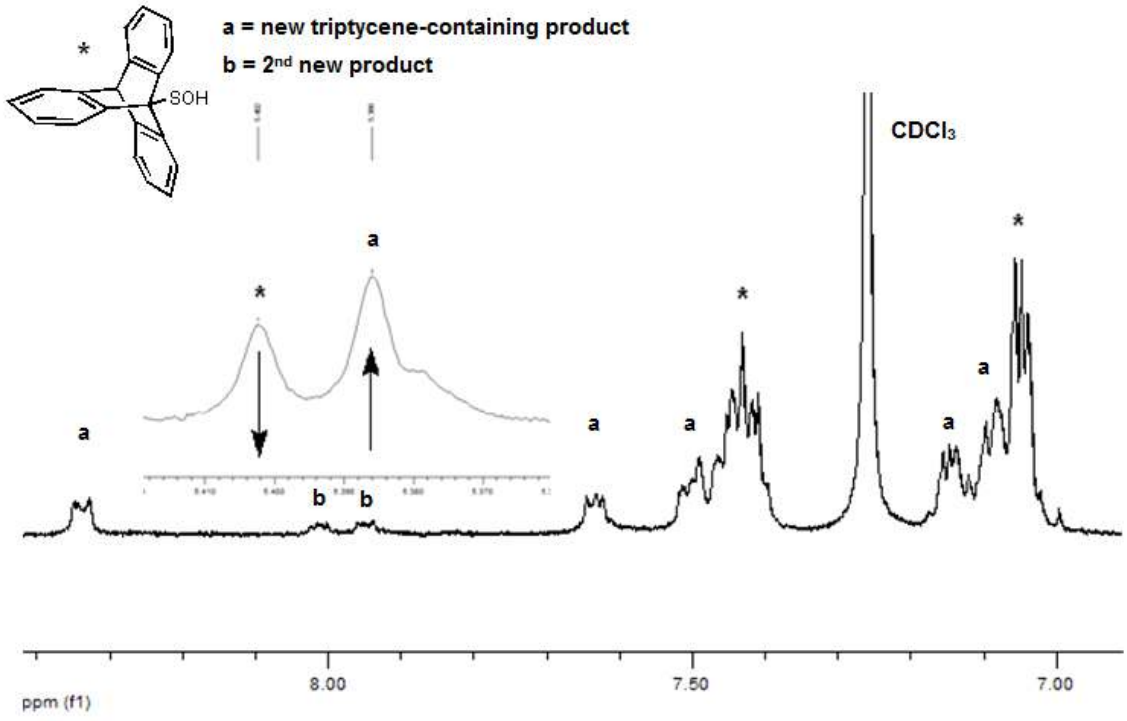
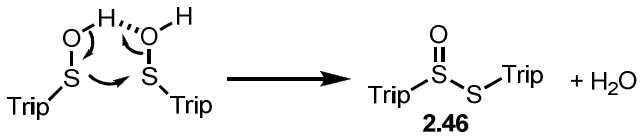


Figure 2.5. ^{1}H NMR for 9-triptycenesulfenic acid containing methanesulfonic acid in $CDCl_3$ after 24 hours showing the sulfenic acid bridgehead signal (*) getting smaller relative to the new bridgehead proton (a) and a new product forming (b). Spectrum obtained at 400 MHz and chemical shifts recorded in ppm and referenced to $CDCl_3$ (7.26 ppm).

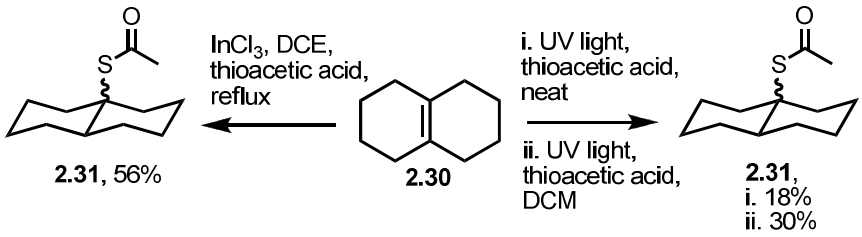


Scheme 2. 26 Mechanism for self-condensation of 9-triptycenesulfenic acid.

2.2.5 Preparation of *trans*-Decalin-9-sulfenic Acid by Modified Literature Procedure

The first efforts to prepare *trans*-decalin-9-sulfenic acid were made as reported in the literature,[52] to the best of our abilities, but without any experimental details (See Scheme 2.11). The initial

step was simply a Birch reduction of tetralin to form octalin; this worked successfully in 85% yield. The following step was the addition of thioacetic acid to octalin to form *trans*-9-decalyl thioacetate. Given that there were no experimental details or referenced procedure for this reaction, we surveyed the literature. The first attempts involved adding thioacetic acid to octalin and irradiating with a 400 W bulb in anticipation that the reaction would go by a radical addition of thioacetic acid to the alkene. This procedure was carried out in DCM and as a neat reaction mixture which produced 30 and 18% yields respectively. In attempt to optimize the reaction further, it was performed in the presence of $InCl_3$ in DCE and refluxed overnight.[102] This reaction gave 56% isolated yield of *trans*-9-decalyl thioacetate after column chromatography, and was the best we were able to achieve. Table 2.6 summarizes the attempted optimization of forming *trans*-9-decalyl thioacetate by addition of thioacetic acid to octalin.



Scheme 2.27. Attempted thioacetic acid additions to octalin.

Table 2.6. Conditions surveyed for preparation of *trans*-9-decalyl thioacetate.

Trial	Conditions	Yield
1	Irradiate with 400 W bulb, neat	18 %
2	Irradiate with 400 W bulb, 0.1 M DCM	30 %
3	$InCl_3$ (5 mol%), DCE, reflux 24 hrs	56 %

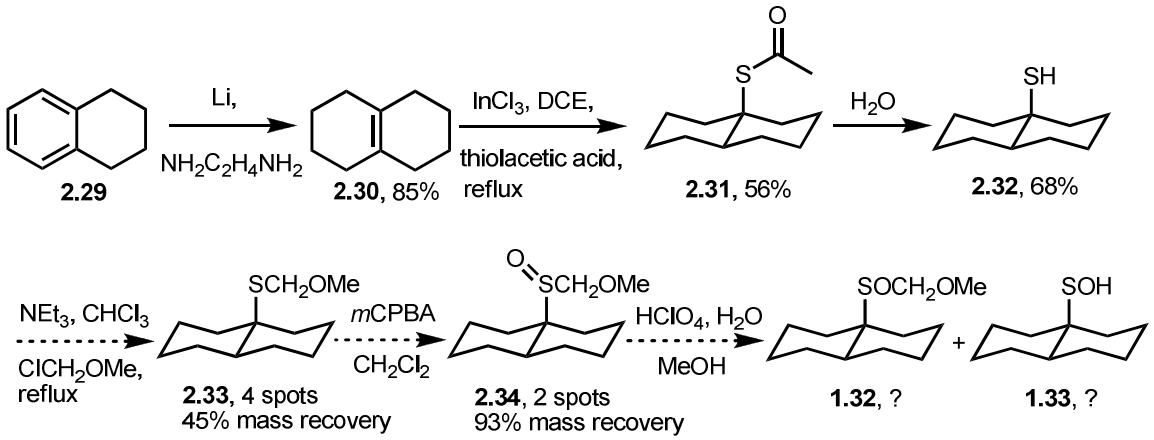
The next step in the literature synthesis was hydrolysis of the thioacetate to prepare the corresponding thiol. Therefore, the thioacetate was refluxed in 1:1 ethanol:water, in the absence of oxygen (to prevent disulfide formation), to form a foul smelling oil in 68% yield. Typically, TLC analysis indicated that the starting material was consumed and one new spot, identified as the thiol, was formed and isolated without further purification. By ^{1}H NMR the methyl signal from the thioacetate group was clearly gone and several signals in the alkyl region were observed. Formation of *trans*-9-decalyl thiol was confirmed by GC-MS, which contained a signal corresponding to the thiol as the major product, along with small amounts of unknown impurities.

Surprisingly, protection of the thiol by chloromethyl methyl ether (MOMCl) and other protecting groups (chlorobenzylmethylether, BOMCl) posed significant problems; which ultimately lead to the abandonment of the literature route. Table 2.7 summarizes the attempts made toward protecting *trans*-9-decalyl thiol. Basically, the products, methylmethoxy, or methylbenzyloxy sulfide, were never isolated as pure compounds; the best purification was actually the isolation of four spots by TLC. However, it was decided to carry this mixture on to be oxidized anyways, to see if the byproducts could be separated out later.

Table 2.7. Conditions and results of attempted reactions to prepare MOM and BOM protected *trans*-9-decalyl thiol.

Trial	Conditions	Mass Recovery	Comments
1	Pyridine, $Cl(CH_2)_2OMe$ in CH_2Cl_2, reflux overnight	94% crude	NMR and TLC plates are a mess
2	MeONa, $Cl(CH_2)OBn$ in MeOH, reflux overnight	N/A	NMR did not show product, TLC a mess
3	$N(Et)_3$, $ClCH_2OMe$ in $CHCl_3$, reflux for 1 day	45% (4 spots)	4 spots isolated show significant product by NMR
4	$N(Et)_3$, $Cl(CH_2)OBn$ in $CHCl_3$, reflux overnight	13% (4 spots)	4 spots isolated

Next, a solution of *m*CPBA in DCM was added to an ice-cooled solution of the four isolated spots derived from the thiol protection. After five minutes, TLC showed that two of the four spots had cleanly converted to two new spots, while the other two spots remained unchanged. This was encouraging, as the two spots that appeared to be consumed could have potentially been two isomers of the MOM-protected thiol. Upon work-up and solvent removal in ice, two spots were isolated by TLC. At this point no NMR was taken to avoid decomposition, which would result in formation of sulfenate **1.32**. Finally, the two spots which were believed to be two isomers of the decalyl sulfoxide were subjected to 7% perchloric acid in 1:2 water:methanol and stirred at room temperature overnight. Both of the starting material spots disappeared by TLC and two new spots became visible. No concrete information could be obtained from the NMR, as again it was a mess of signals in the alkyl region. If the product had been made on a larger scale, proper characterization data could have been obtained however, due to the difficulties with thiol protection it was decided to move on to a new synthetic route.



Scheme 2.28. Summary of attempt to synthesize *trans*-decalin-9-sulfenic acid by modified literature preparation

2.2.6 Preparation of *trans*-Decalin-9-sulfenic Acid by Other Methods

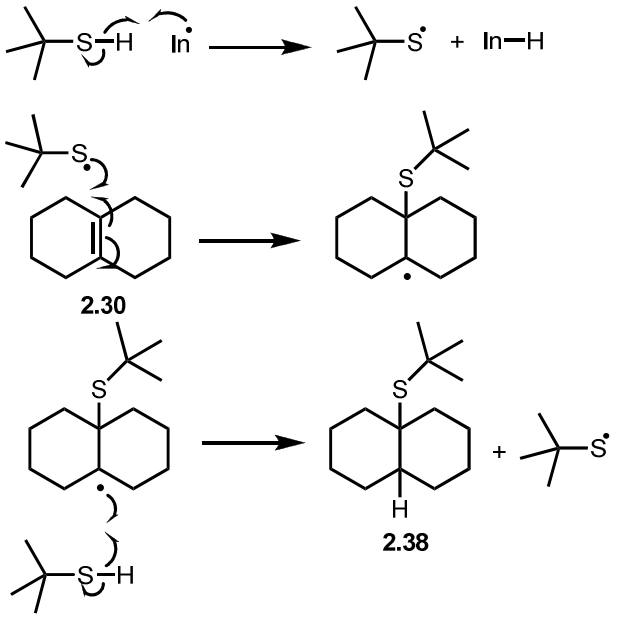
A new route for preparing *trans*-decalin-9-sulfenic acid was by methods similar to that of preparing 9-triptycenesulfenic acid; that is, preparing the *tert*-butylthioether, followed by *m*CPBA oxidation to form the sulfenic acid. Our first endeavour then, was synthesizing the *trans*-decalin-9-*tert*-butylthioether. Hence, neat *trans*-9-decalyl thiol was treated with *tert*-butylchloride and a strong Lewis acid, $AlCl_3$.[103] After stirring at room temperature for a day, no reaction had occurred, and by NMR, starting material and disulfide were identified. Unfortunately, the Lewis acid appeared to catalyze the self-reaction instead of the desired alkylation reaction.

Moving forward, we thought that the radical addition of *tert*-butyl thiol to octalin might be a good option,[104] considering that octalin could be made easily on very large scale. The general reaction procedure follows: thiol, initiator, and freshly distilled solvent were added to a Schlenk flask and subjected to a minimum of three freeze/pump/thaw cycles to remove oxygen from the reaction. The reaction was then heated to decompose the initiator and monitored by TLC. Table

2.8 summarizes the conditions attempted for this reaction. Entry 3 was performed by the procedure described above only in the absence of initiator (the idea being that trace amounts of oxygen may initiate the chain) and entry 4 was performed in an open atmosphere. Scheme 2.29 provides the mechanism for the anticipated radical chain reaction between *tert*-butylthiol and octalin. Since entry 2 appeared to be the cleanest reaction, flash chromatography with hexanes was performed on the reaction mixture and the desired product was isolated in 9% yield.

Table 2. 8. Reaction conditions for the radical chain reaction to between *tert*-butylthiol and octalin.

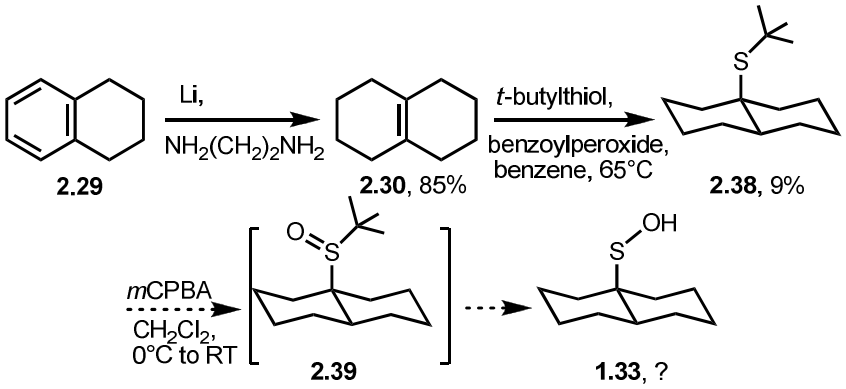
Trial	Solvent	Initiator	Temperature (°C)	Yield	Comments
1	Benzene (1M)	AIBN	65	N/A	>7 spots after stirring for 1 day
2	Benzene (1M)	Benzoyl Peroxide	65	9%	3-4 new spots after stirring overnight
3	Benzene (1M)	None	RT	0%	Stirred overnight
4	Neat	UV light	Heat from bulb	N/A	4 new spots after irradiating for 3 days with a 200 W bulb.



Scheme 2.29. Radical chain reaction between *tert*-butyl thiol and octalin.

Although only very small quantities of the *trans*-decalin-9-thioether were isolated, it was subjected to *m*CPBA under similar conditions to the reaction with the analogous triptycene compound to see if the sulfenic acid could be made. By TLC, the starting material was consumed and three new spots were observed. After column chromatography with 5% ethyl acetate, one spot was isolated, which was believed to be either the sulfoxide or sulfenic acid. By ^{1}H NMR, the *tert*-butyl singlet from the thioether shifted from 1.36 to 1.45 ppm indicating the possibility that the corresponding sulfoxide had formed. However, the alkyl region integrated for approximately twice the anticipated protons in comparison to the *tert*-butyl signal, which potentially indicated the presence of a 1:1 mixture of sulfoxide and sulfenic acid. Although the desired product may have been made (probably as a mixture with the sulfoxide), there is no definite evidence for its preparation. After attempting a few other methods to make the *trans*-decalin-9-*tert*-butylthioether in effort to obtain a better yield (see discussion below), we decided to focus our attention on 9-

triptycenesulfenic acid for further investigation, as we had much more success with its synthesis and purification.



Scheme 2.30. Summary of most successful attempt to synthesize *trans*-decalin-9-sulfenic acid by sulfoxide elimination.

As shown in Scheme 2.13 and 2.14, the thioether could be installed by forming the *trans*-decalin-9-alcohol followed by S_N1 substitution by *tert*-butyl thiol. There were two ways that we attempted to synthesize the alcohol: the first was oxidation by MTO and H_2O_2[94] and the second was *m*CPBA oxidation to form the epoxide, followed by reduction to the alcohol by $LiAlH_4$.[95] The first procedure did not appear to yield any product at all, probably due to small amounts of water killing the catalyst. The second route was more successful as octalin was readily oxidized to the epoxide by *m*CPBA to give a mixture of two isomers in 40% yield. Next, the epoxide was reduced to the alcohol in near quantitative yield by refluxing with $LiAlH_4$ in ether. Finally, the alcohol, followed by the thiol, was added slowly to an ice-cooled solution of 2:1 H_2SO_4/H_2O. The reaction was warmed to room temperature but no new products were observed by TLC. As one last attempt at the substitution reaction, the alcohol and thiol were added to a mixture of acetic acid, perchloric acid and acetic anhydride and stirred at room temperature overnight. By TLC, the starting material appeared to be consumed; however, the crude NMR was a mixture of octalin and

another new unidentifiable byproduct. No *tert*-butyl singlet was observed in the NMR, which suggests that no desired thioether was made. Evidently, under these conditions, the alcohol undergoes elimination to reform octalin.

2.3 Experimental Procedures

General Procedures for 9-Triptycenesulfenic Acid (**1.31**). All reagents were obtained from commercial sources and used without further purification unless specified. Anhydrous dioxane was purchased from Sigma-Aldrich and distilled from benzophenone ketyl immediately prior to use. Dry toluene and dichloromethane were obtained from a PureSolv solvent system. Column chromatography was performed using flash silica gel (60Å 40-63 μm, 500 m^2/g). ^1H NMR and ^{13}C NMR were obtained on 300 and 400 MHz spectrometers at 298 K and referenced to $CDCl_3$ (δ 7.26 ppm and 77.36 ppm, respectively). High resolution mass spectrometry was obtained by Qq-TOF.

9-Iodoanthracene (**2.17**). To a mixture of CuI (29.6 mg, 0.16 mmol), NaI (934 mg, 6.23 mmol), and 9-bromoanthracene (800 mg, 3.11 mmol) in a dry Schlenk flask (evacuated and purged with nitrogen) was added dry dioxane (3.11 mL, 1 M) and N,N'-dimethylethylene diamine (0.02 mL, 0.16 mmol) and heated to 110°C overnight. The reaction was monitored by GC-MS and was found to be 80-90% complete after 24 hrs. The reaction was cooled to room temperature, quenched with aq. NH_4OH and then water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product could not be separated from the starting material and so the crude product was carried on to the next step.

Alternatively, to a mixture of CuI (185 mg, 0.97 mmol), NaI (5.53 g, 36.9 mmol), and 9-bromoranthracene (5 g, 19.4 mmol), in a dry microwave tube (evacuated and purged with nitrogen) was added dry dioxane (19.4 mL, 1 M) and N,N'-dimethylethylene diamine (0.1 mL, 0.97 mmol) and sealed in a glove bag. The reaction was heated to 160°C in a microwave reactor for 7 hours, at which point the reaction had gone to 100% conversion by GC-MS. The reaction mixture was then quenched with aq. NH_4OH, followed by water, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 9-iodoanthracene (5.52 g, 93%). ^{1}H NMR ($CDCl_3$) δ 7.48-7.51, 7.57-7.60 (2 m, 4 H, aromatic H's), 7.96 (d, J = 8.36, 2 H, aromatic H's), 8.45 (s, 1 H, 10-C), 8.47 (d, J= 8.98, 2H, aromatic H's); ^{13}C NMR ($CDCl_3$) δ 105.1 (9-C), 125.8, 127.9, 128.8, 129.0, 132.2, 133.4, 134.0 (aromatic C's); HRMS (EI^+) calculated (M) 303.9749, observed 303.9742. Spectral data are in accordance with literature values.[105]

9-tert-Butylthioanthracene (**2.4**). To a mixture of CuI (240 mg, 1.26 mmol), NaO*t*-Bu (910 mg, 9.47 mmol), 1,10-phenanthroline (227 mg, 1.26 mmol), and 9-iodoanthracene (1.92 g, 6.31 mmol), in a dry microwave tube (evacuated and purged with nitrogen) was added dry toluene (16 mL, 0.4 M) and *t*-butylthiol (0.78 mL, 6.94 mmol) and sealed. The reaction vessel was heated to 160°C in a microwave reactor for 10 hours, at which point the reaction had gone to complete conversion by GC-MS. The reaction mixture was then washed through celite with ethyl acetate to remove salts, and purified by flash chromatography (eluent: hexanes) to afford 9-(*tert*-butylthio)anthracene (1.43 g, 85%). ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H, t-butyl), 7.47-7.50 (m, 2 H, aromatic H's), 7.53-7.57 (m, 2 H, aromatic H's), 8.01 (d, J = 8.42, 2 H, aromatic H's), 8.51 (s, 1 H, 10-C), 9.08 (d, J = 8.42, 2 H, aromatic H's); ^{13}C NMR ($CDCl_3$) δ 32.2 (Me C's of *t*-butyl),

50.7 (quaternary C of *t*-butyl), 125.6, 126.3, 128.9, 129.0, 129.7, 132.1, 136.9 (aromatic C's); HRMS (EI^+) calculated (M) 266.1129, observed 266.1132.

9-tert-Butylthiotriptycene (**1.29**). To a suspension of anthranilic acid (440 mg, 3.22 mmol) in THF (3.2 mL, 1 M) at 0°C was added trichloroacetic acid (26.1 mg, 0.16 mmol) followed by isoamyl nitrite (0.71 mL, 5.28 mmol) slowly. The reaction was warmed to room temperature and stirred for 1-2 hours or until a tan precipitate formed. The benzenediazonium-2-carboxylate was then collected by suction filtration with a glass fritted funnel and washed with cold THF until the washings were colorless and washed with DCE to displace the THF (note: care should be taken to avoid letting the salt become dry as it is known to detonate violently upon being heated or scraped). The solvent-wet salt was washed with DCE (5 mL, 0.15 M) into a round bottom flask containing 9-(*tert*-butylthio)anthracene (200 mg, 0.75 mmol) and equipped with a reflux condenser. The reaction was heated to 60°C and a mildly exothermic reaction occurred after about 5-10 minutes. The reaction was then heated overnight and concentrated in vacuo. The product was purified using a long column and 5 % DCM/Hexanes as the eluent to give 9-(*tert*-butylthio)triptycene (181 mg, 70%). Note: the product was the last spot to come off the column and will bleed unless washed with DCM, typically the yield ranged from 50-70%. ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 9 H, *t*-butyl), 5.33 (s, 1 H, 10-C), 6.98-7.06 (m, 6 H, aromatic), 7.34-7.37 (m, 3 H, aromatic), 7.80-7.83 (m, 3 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 34.5 (Me C's of *t*-butyl), 47.4 (quaternary C of *t*-butyl), 54.4 (10-C), 65.9 (9-C), 123.3, 124.2, 124.8, 125.6 (aromatic C's with H), 145.6, 146.5 (aromatic ipso-C's); HRMS (EI^+) calculated (M) 342.1442, observed 342.1449. Spectral data are in accordance with literature values.[51]

Alternatively, to a solution of 9-*tert*-butylthioanthracene (1.68 g, 6.34 mmol) was added 1 M tetrabutylammoium fluoride (TBAF) (2.37 mL, 2.37 mmol) followed by 2-(TMS)phenyl

triflate (0.38 mL, 1.58 mmol). The reaction was monitored by TLC and additional TBAF was added to the reaction until the 2-(TMS)phenyl triflate was consumed. After stirring overnight at room temperature, the reaction was extracted with DCM and the combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash chromatography using 5% DCM/Hexanes as the eluent to give pure 9-(*tert*-butylthio)triptycene (340 mg, 63%).

9-Bromotriptycene (**2.7**). Prepared as 9-(*tert*-butylthio)triptycene only using 9-bromoanthracene (500 mg, 1.94 mmol) as the benzyne acceptor. The product was purified by flash chromatography with 5% DCM/Hexanes to afford pure 9-bromotriptycene (481 mg, 74%).^{1}H NMR ($CDCl_3$) δ 5.44 (s, 1 H, 10-C), 7.05-7.08 (m, 6 H, aromatic), 7.37-7.40 (m, 3 H, aromatic), 7.78-7.81 (m, 3 H, aromatic).

9-Triptycenesulfenic acid (**1.31**). To an ice-cooled solution of 9-(*tert*-butylthio)triptycene (**1.29**, 1.79 g, 5.23 mmol) in DCM (122 mL, 0.043 M) in a dry rbf (evacuated and purged with nitrogen before solvent added) was added a 0.086 M solution of 77% *m*CPBA (1.17 g, 5.23 mmol) dropwise via a syringe. The reaction was then stirred overnight at room temperature and concentrated in vacuo. The white solid was subject to a very long column using 2:1 DCM/Hexanes with 1% acetic acid as the eluting solvent to afford pure **1.31** (970 mg, 61%). **1.31** was further purified to remove trace impurities by recrystallizing from isopropanol and hexanes before experiments were conducted. ^{1}H NMR ($CDCl_3$) δ 3.09 (brs, 1 H, OH), 5.42 (s, 1 H, 10-C), 7.03-7.08 (m, 6 H, aromatic), 7.42-7.48 (m, 6 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 54.3 (10-C), 65.9 (9-C), 122.5, 124.1, 125.6, 126.0 (aromatic C's with H), 143.2, 143.7 (aromatic ipso-C's);

HRMS (EI^+) calculated (M) 302.0765, observed 302.0769. Spectral data in accordance with literature values.[51]

Isolation of 9-triptycene-tert-butylsulfoxide (**1.30**). The reaction between 9-(*tert*-butylthio)triptycene and *m*CPBA always gave three isolable products: small amounts of starting material, the desired product, **1.31**, and another product, which we believe to be the intermediate sulfoxide through which the sulfenic acid is formed via Cope elimination. In previous reports this intermediate had been proposed but never isolated. ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 9 H, t-butyl), 5.32 (s, 1 H, C-10), 6.95 (dt, J = 7.60, 7.48, 1.10 Hz, 1H), 7.02 (ddd, J = 9.07, 5.48, 1.61 Hz, 2 H), 7.10-7.13 (m, 4 H), 7.31 (dd, J = 7.11, 1.16 Hz, 1H), 7.43-7.46 (m, 2 H), 8.02-8.05 (m, 2 H), 8.26 (d, J = 7.80 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.9 (Me C's of t-butyl), 55.0 (quaternary C of *t*-butyl and 10-C), 73.9 (9-C), 126.8, 125.7, 125.6, 125.4, 125.0, 124.9, 123.9 (aromatic C's with H), 145.9, 145.5, 142.5, 142.3, 140.6 (aromatic ipso-C's).

Di(phenethyl) disulfide. To a stirred solution of benzeneethanethiol (0.11 mL, 0.79 mmol) in hexafluoroisopropanol (HFIP) was added 35% H_2O_2 (0.08 mL, 0.87 mmol) and stirred at room temperature for one hour. The reaction was added to a mixture of ether and water and extracted with ether three times. The combined extracts were washed with brine, dried with $MgSO_4$ and concentrated in vacuo to afford di-phenethyl disulfide (155 mg, 71%). ^{1}H NMR ($CDCl_3$) δ 2.92-3.02 (m, 8 H, ethyl H's), 7.19-7.24 (m, 6 H, aromatic), 7.32 (t, 4 H, aromatic). ^{13}C NMR ($CDCl_3$) δ 36.1, 40.6 (ethyl C's), 126.8 (aromatic *p*-C's), 128.9, 129.0 (aromatic *o*- and *p*-C's), 140.4 (aromatic ipso-C's). Spectral data in accordance with literature values.[106]

Di-tert-butyl thiosulfinate. To an ice-cooled solution of di-*tert*-butyl disulfide (4.3 g, 24 mmol) in DCM (10 mL, 2.2 M) was added a 0.62 M solution of 77% *m*CPBA (6.0 g, 27 mmol) dropwise. The reaction was then warmed to room temperature and stirred overnight. It was then poured into a mixture of DCM and saturated $NaHCO_3$ and extracted three times with DCM. The combined organic extracts were washed three times with saturated $NaHCO_3$ and brine followed by drying over $MgSO_4$ and concentrating in vacuo. The white solid was purified by column chromatography using 2% ether/pentanes to remove impurities, followed by flushing with ether to afford pure di-*tert*-butyl thiosulfinate (4.6 g, 98%). ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-butyl), 1.56 (s, 9 H, *t*-butyl). Spectral data in accordance with literature values.[98]

General Procedures Towards trans-Decalin-9-sulfenic Acid (**1.33**). All reagents were obtained from commercial sources and used without further purification unless specified. Ethylenediamine and benzene were purchased from Sigma-Aldrich and distilled from NaOH pellets and benzophenone ketyl respectively immediately prior to use. Dry 1,2-dichloroethane was obtained from Sigma-Aldrich in a sure-seal bottle. Column chromatography was performed using flash silica gel (60Å 40-63 μm, 500 m^2/g). ^{1}H NMR and ^{13}C NMR were obtained on 300 and 400 MHz spectrometers at 298 K and referenced to CDCl3 (δ 7.26 ppm and 77.36 ppm, respectively). High resolution mass spectrometry was obtained by Qq-TOF.

Octalin (**2.30**). In a three-necked, round bottom flask (rbf) fitted with a glass stopper and a reflux condenser closed with a calcium chloride tube were added ethylenediamine (75 mL, 1.12 mol) and tetralin (10 g, 75.6 mmol). Clean lithium wire (3.1 g, 0.45 mol) was cut into small pieces, measured out into a flask of hexanes, and added to the reaction is small portions. Note: sometimes

heat was needed to initiate the reaction. After the first few portions of lithium had reacted, the rest was added over a period or ~30 minutes to an hour. Near the end of lithium addition, the reaction turned deep blue and upon stirring for an additional hour the reaction faded to blue-grey. The reaction was then slowly quenched with 40 mL ethanol and poured into ~350 mL ice water. The mixture was extracted with hexanes and the combined extracts were washed with 5% H_2SO_4, water and brine followed by drying over $MgSO_4$. The solvent was removed in vacuo to afford pure octalin (8.8 g, 85%). ^{1}H NMR ($CDCl_3$) δ 1.60 (bm, 8 H, CH_2's), 1.86 (bm, 8 H, CH_2's). ^{13}C NMR ($CDCl_3$) δ 23.7, 30.8 (CH_2 C's), 128.28 (alkene C's). Spectral data are in accordance with literature values.[107]

Trans-9-decalyl thioacetate (**2.31**). To a solution of octalin (9.3 g, 68 mmol) and $InCl_3$ (75.4 mg, 3.41 mmol) in dry DCE (68 mL, 1 M) under nitrogen, was added thioacetic acid via a dropping funnel. The reaction was heated to 80°C and refluxed for 24 hrs. The reaction mixture was purified by a short column using hexanes as the eluent to afford *trans*-9-decalyl thioacetate (8.1 g, 56%).^{1}H NMR ($CDCl_3$) δ 0.87-1.83 (m, 17 H, decalyl), 2.30 (s, 3 H, thioacetyl). ^{13}C NMR ($CDCl_3$) δ 22.8, 26.4, 26.5, 31.1, 33.7, 34.2, 34.7, 38.7, 46.3, 47.7 (decalyl C's), 195.9 (thioacetyl C).

Trans-9-decalyl thiol (**2.32**). *Trans*-9-decalyl thioacetate (**2.31**, 9.2 g, 43 mmol) was dissolved in a 10% KOH solution in 1:1 H_2O/EtOH (56 mL, 0.77M) and heated at reflux for 8 hours under nitrogen. The reaction was then quenched with glacial acetic acid and extracted with hexanes. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo over ice to afford the *trans*-9-decalyl thiol (7.38 g, 68%). Note: the thiol has a very foul smell and all glassware used

should be rinsed with a bleach solution before leaving the fumehood. ^{1}H NMR ($CDCl_3$) δ 2.00 (bs, 1 H, thiol), 1.29-1.76 (m, 17 H, decalyl).

4aα,8aα-epoxy-decahydronaphthylene (**2.39**). To an ice-cooled solution of octalin (447 mg, 3.28 mmol) in DCM (0.5 mL, 1.6 M) was added a 0.33 M solution of 77% *m*CPBA (238 mg, 1.06 mmol) in DCM (3.2 mL) dropwise. The reaction was stirred for 2 hours at room temperature, washed with water and 5% $NaHCO_3$ (x3) and dried with KCO_3. DCM was concentrated in vacuo to afford a mixture of two isomeric forms of 4a,8a-epoxy-decahydronaphthylene (200 mg, 40%).^{1}H NMR ($CDCl_3$) δ 1.21-1.30 (m, 4 H), 1.43-1.50 (m, 4 H), 1.58-1.65 (m, 4 H), 1.83-1.90 (m, 4 H). Spectral data are in accordance with literature values.[108]

4aα,8aα-decahydronaphthalen-4a-ol (**2.38**). To a stirred suspension of $LiAlH_4$ (187 mg, 4.92 mmol) in dry ether (2.45 mL, 2 M) was added a 0.27 M solution of the epoxides (300 mg, 1.97 mmol) in dry ether (7.3 mL). The reaction was heated under reflux overnight, cooled in an ice bath and quenched with 0.2 mL H_2O, 0.2 mL aqueous 15% NaOH solution and finally 0.6 mL H_2O. The resulting mixture was filtered and the filtrate was washed with water and brine and dried with $MgSO_4$. The solvent was concentrated in vacuo to afford 4aα,8aα-decahydronaphthalen-4a-ol (305 mg) in quantitative yield. ^{1}H NMR ($CDCl_3$) δ 1.20-1.70 (m, 17 H). Spectral data are in accordance with literature values.[109]

Chapter 3

The Redox Chemistry and Antioxidant Activity of Sulfenic Acids

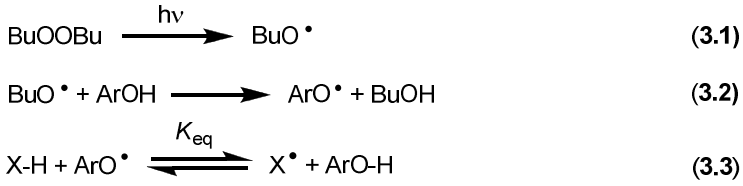
3.1 Introduction

As introduced in Chapter 1, sulfenic acids have been detected in cells and have been assigned prominent roles in cellular processes such as redox signalling. However, the mechanisms by which formation and reaction of cysteine sulfenic acids occur remains unclear. For this reason, we were intent on discovering the chemical transformations of the sulfenic acid functionality, to gain insight into what reactions cysteine sulfenic acids undergo in cells. Furthermore, sulfenic acids are proposed to be key intermediates in the biosynthesis of thiosulfinates in *Allium* species, such as garlic, onions, leeks and shallots.[39,110] Recently, our group has shown indirectly that allylsulfenic acid (**1.24**) may be responsible for garlic's potent antioxidant activity. This radical trapping ability was reflected in the prediction that various alkylsulfenic acids may react with peroxyl radicals at diffusion controlled rates and that their O-H BDE's are some of the lowest known (~68 kcal mol^{-1}).[45] By comparison, their isoelectronic counterparts, alkylhydroperoxides, have much lower inhibition rates (on the order of 10^2-10^3 $M^{-1}s^{-1}$)[47] and higher O-H BDEs (~86 kcal mol^{-1}).[45] With these applications in mind, performing experiments to measure the k_{inh}, SO-H BDE, pK_a, and electrochemical properties of sulfenic acids and comparing them to analogous hydroperoxides would be useful in gaining insight into the role of the sulfur atom in various chemical transformations as they apply to biological situations.

3.1.1 Determination of O-H BDEs by Radical Equilibration EPR

The most reliable method for determining X-H bond dissociation enthalpies (BDEs) is the EPR radical equilibration technique.[111] For example, commonly cited values of the O-H bond dissociation enthalpies of phenols[30,112-114] as well as N-H BDE's of aromatic amine antioxidants[115] have been determined using this approach. This technique is based on the equilibrium constant for H-atom transfer between the antioxidant, i.e. a phenol, ArOH (with an unknown BDE), and an

appropriate reference compound, X-H (whose BDE is known, Equation 3.3).[112] In general, the two equilibrating radicals are generated in the cavity of an EPR spectrometer by continuous photolysis of deoxygenated solutions containing small amounts of a radical photoinitiator, such as di-*tert*-butylperoxide, and both the antioxidant and reference compound. The molar ratio of the two equilibrating radicals is obtained by comparing the EPR spectrum recorded to the computer-simulated spectra. The equilibrium constant, K_{eq}, is then determined according to Equation 3.4, by taking into consideration the initial concentrations of both the antioxidant and reference compound. A reference compound appropriate for the experiments is chosen based on the prediction that it has a very similar BDE (i.e. within 2-3 kcal/mol) to that of the unknown antioxidant such that the H-atom exchange between the two species is a rapid equilibrium.



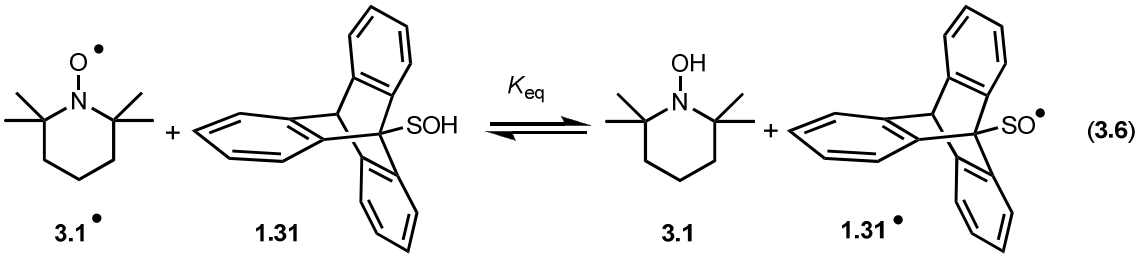
Scheme 3.1. Simplified reaction scheme of an EPR experiment for determination of the BDE for a phenolic antioxidant showing formation of a radical initiator (Equation 3.1), formation of a phenoxyl radical (Equation 3.2) and equilibration of H-atom transfer between the reference compound and phenoxyl radical (Equation 3.3).

$$K_{eq} = \frac{[ArO^{\bullet}]\,[X\text{-}H]}{[X^{\bullet}]\,[ArOH]} \qquad (3.4)$$

To ensure H-atom transfer occurs rapidly relative to the decay of the radicals derived from both the antioxidant and reference compound, measurements are done at different initial concentrations of the reactants and peroxide initiator. The BDE of the antioxidant of interest can then be calculated by means of Equation 3.5 with the assumption that the entropic change for H-atom transfer is negligible.

$$\mathrm{BDE(ArOH)} = \mathrm{BDE(X\text{-}H)} - RT\ln K_{eq} \qquad \textbf{(3.5)}$$

A requirement for using this technique to determine the BDE of our model compound, **1.31**, is that the sulfinyl radical is sufficiently persistent such that its concentration can be accurately determined. We predict this will be the case, due to the steric hindrance imparted on the sulfinyl radical by the triptycene moiety. High-level theoretical calculations, carried out previously in our laboratory, suggest that the O-H BDE of alkyl sulfenic acids are ca. 69 kcal/mol. This is much lower than those in the reference compounds that are typically used in equilibration experiments (i.e. phenols, which have O-H BDEs ranging from 77-87 kcal/mol). The only compounds that have O-H bonds that are similarly weak are hindered hydroxylamines. For example, TEMPO-H (**3.1**, N-hydroxy-2,2,6,6,-tetramethylpiperidine) has an O-H BDE of 69.6 kcal mol^{-1},[116] making it an ideal choice for a reference compound (Equation 3.6).



(3.6)

3.1.2 Determinination of Electrochemical Behavior by Cyclic Voltammetry

As discussed in Chapter 1.3.4, sulfenic acids are involved in a variety of cellular processes, including signaling transduction whereby they act as important intermediates that respond to the redox state of the cell and modulate gene transcription accordingly.[70] Given that very little information is known about the mechanisms by which redox signaling in cells occurs, determining the electrochemical transformations of sulfenic acids could give valuable insight into understanding them. Additionally, formal H-atom transfer between sulfenic acids and peroxyl radicals may occur by sequential proton transfer followed by electron transfer (see SPLET mechanism in Chapter 1.2.3). Although it has been predicted computationally that these reactions go by PCETs, performing electrochemical experiments on sulfenic acids will tell us if H-atom transfer has the potential to occur by SPLET; that is, if the sulfenate anion is sufficiently reducing (in conjunction with the RSO-H atom being sufficiently acidic) this mechanism may prevail. The fundamental parameter reflecting the redox reactivity of compounds in general is the electrochemical potential, that is, the driving force with which they lose or gain electrons; this can be determined by cyclic voltammetry.

Ideally, due to the predicted persistence of the sulfinyl radical, the oxidation potential of a sulfenic acid would be reversible such that the standard reduction potential (E°) could be obtained (Equation 3.7). In a reversible cyclic voltammogram (Figure 3.1), E° is equal to the midpoint between E_{pc} and E_{pa}, representing the cathodic (reduction) and anodic (oxidation) electrochemical potentials respectively.

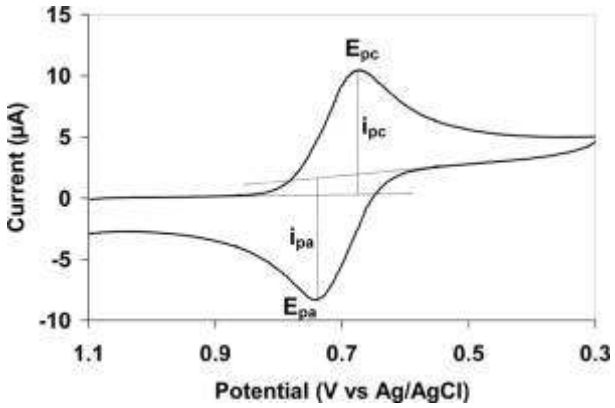


Figure 3.1. General cyclic voltammogram showing a fully reversible oxidation/reduction process

$$RSOH \overset{E^\circ}{\rightleftharpoons} RSO^\bullet + e^- + H^+ \qquad (3.7)$$

In order to find conditions for our electrochemical experiments, it would be useful if analogous experiments had been performed on an isoelectronic compound, such as a hydroperoxide; however, to our knowledge no such experiments exist. Thorough electrochemical studies have been performed on α-tocopherol and although it is not isoelectronic with a sulfenic acid, we anticipate that its cyclic voltammograms may exhibit the same general trends.

The electrochemical behavior of α-tocopherol and other simple phenols were investigated by Williams *et al.* in 2004 and this work is summarized in Figure 3.2.[78] In aprotic solvents such as acetonitile or dimethylformamide, most substituted phenols were oxidized at positive potentials by two-electron processes (black lines, Figure 3.2). In the presence of one molar equivalent of an organic soluble base, such as Et_4NOH, the phenolate anions undergo one-electron oxidations between approximately 1.2 and 1.8 V less than their corresponding phenols to produce phenoxyl radicals (Equation 3.8 and 3.9, blue lines, Figure 3.2). Electrochemical experiments have demonstrated that phenoxyl radicals containing bulky substituents in the 2-, 4-, and 6- positions

are the most stable towards irreversible biomolecular reactions but commonly undergo rapid reversible reactions to form dimers. Cyclic voltammetry experiments performed on solutions of hindered phenolate anions (blue line, Figure 3.2 *b* and *c*) show fully reversible oxidation potentials indicating that the associated phenoxyl radicals are more stable compared with their less bulky counterparts (blue lines, Figure 3.2 *a* and *d*) which show only a small reverse peak. In fact, it has been reported that the phenoxyl radicals derived from the phenols shown in Figure 3.2 *b* and *c* are stable in acetonitrile for several hours at room temperature.[117]

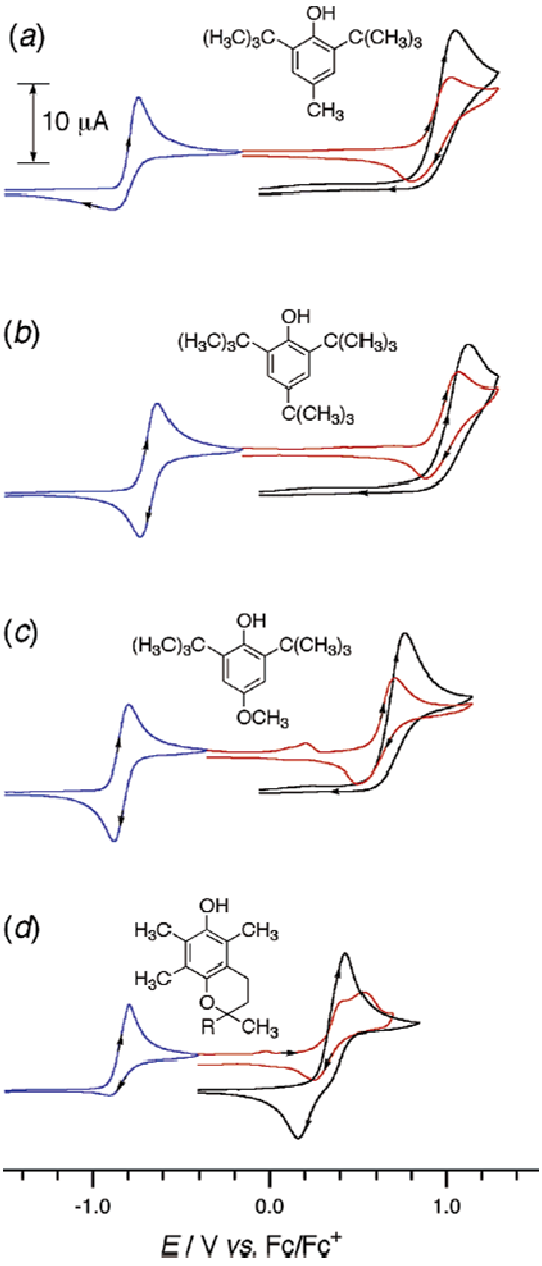


Figure 3.2. Cyclic voltammagrams recorded at 25°C at a scan rate of 0.1 Vs^{-1} with a 1.6 mm diameter Pt electrode in CH_3CN with 0.25 M Bu_4NPF_6 and 2.0 mM substrate. The two-electron oxidation of the substituted phenols (PhOH, Black lines). The one-electron oxidation of the phenolate anion (PhO^-) prepared by the addition of 2 mM Et_4NOH to the same solutions of PhOH (Blue line). The further oxidation of the phenoxyl radicals (PhO•) (Red line).

$$PhOH + Et_4NOH \rightleftharpoons PhO^- + Et_4N^+ + H_2O \quad (3.8)$$

$$PhO^- \rightleftharpoons PhO^{\bullet} + e^- \quad (3.9)$$

In a subsequent paper, Webster went on to perform a series of experiments on α-tocopherol in the absence and presence of acid or base to assist with the identification of the intermediates formed in the electrochemically induced transformations.[79] In acetonitrile, in the absence of acid or base, α-tocopherol can be voltammetrically oxidized at approximately +0.5 V vs Fc/Fc^+ by one electron to from the highly unstable $\alpha\text{-}TOH^{+\bullet}$ (Equation 3.10) which quickly dissociates into $\alpha\text{-}TO^{\bullet}$ and H^+ (Equation 3.15). $\alpha\text{-}TO^{\bullet}$ is further oxidized by one electron to form the phenoxonium cation, $\alpha\text{-}TO^+$ (Equation 3.13) because it is approximately 0.4 V easier to oxidize than α-TOH; thus the voltammogram shows one process corresponding to a two-electron oxidation (green line, Figure 3.3).

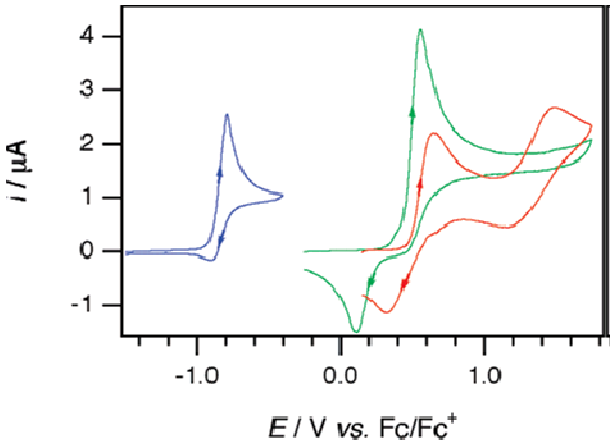
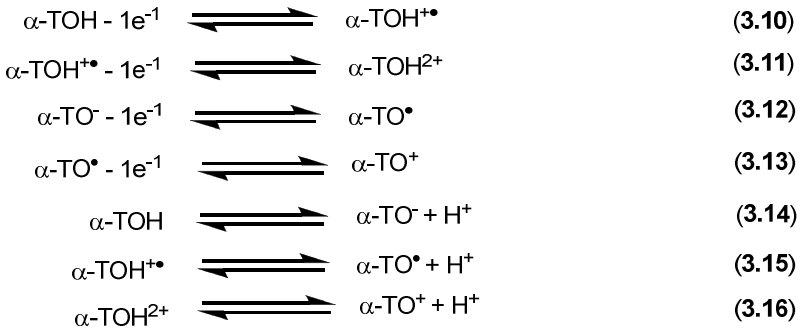


Figure 3.3. Cyclic voltammograms of samples containing 2 mM substrate at a scan rate of 100 mV s^{-1} at a 1 mm diameter planar Pt electrode in CH_3CN with 0.25 M Bu_4NPF_6: α-TOH (green line); α-TOH with 0.1 M CF_3SO_3H (red line); $\alpha\text{-}TO^-$ prepared by reacting α-TOH with 2 mM Et_4NOH (blue line).



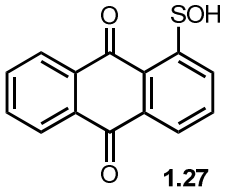
(3.10)
(3.11)
(3.12)
(3.13)
(3.14)
(3.15)
(3.16)

In the presence of a strong acid, CF_3SO_3H, the equilibrium in Equation 3.15 shifts towards the protonation reaction and α-$TOH^{+\bullet}$ becomes increasingly persistent; in fact at sufficiently high concentrations of acid, the voltammogram appears as a one-electron, chemically reversible process at ~+0.6 V vs Fc/Fc^+ (Equation 3.10) due to the complete inhibition of deprotonation (Equation 3.15, red line, Figure 3.3). Under acidic conditions, α-$TOH^{+\bullet}$ is further oxidized by one electron to form the dication, α-TOH^{2+}, at ~+1.4 V vs Fc/Fc^+ (Equation 3.11). The dication is not detectable in non-acidic conditions due to the rapid deprotonation of the intermediate monocation.

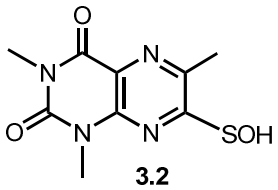
As stated, in the presence of an organosoluble base, such as Et_4NOH, the phenolate anion is immediately formed (α-TO^-) and can be oxidized in two sequential steps to form α-TO^+ (Equations 3.12 and 3.13). α-TO^- is more easily oxidized than α-TOH by ~-1.5 V resulting in a substantial shift in the peak potential and decrease in the oxidation peak current due to the change from a two- to one-electron process. A relatively small reversible peak is observed when the scan direction is reversed at slow scan rates, as the phenoxyl radical of α-tocopherol is not overly stable, as mentioned previously (blue line, Figure 3.3).

3.1.3 Determiniation of the pK_a of Sulfenic Acids

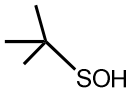
To our knowledge, the pK_a values of three sulfenic acids have been determined: that of 1-anthraquinonesulfenic acid (**1.27**)[75] and 1,3,6-trimethyllumazine-7-sulfenic acid (**3.2**),[118] two persistent sulfenic acids, and the comparatively non-persistent 2-methyl-2-propanesulfenic acid (**3.3**).[77] Table 3.1 provides the acid dissociation constants for these sulfenic acids as well as the analogous 2-methyl-2-propanehydroperoxide for comparison.



1.27



3.2



3.3

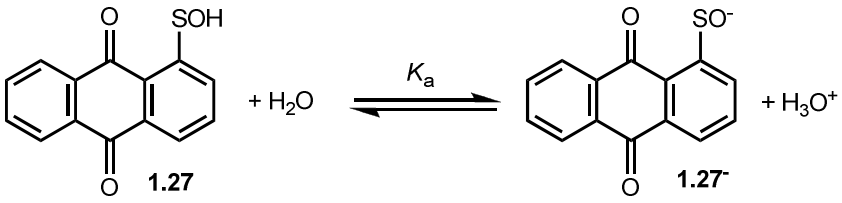
Table 3.1. Reported acid dissociation constants for sulfenic acids and one corresponding hydroperoxide with associated conditions.

Acid	pK_a	Conditions
1.27	7.51	15% CH_3CN/H_2O, 25°C
3.2	4.84	N/A
3.3	10.47	20% CH_3CN/H_2O 14°C
Me_3COOH	12.8[119]	H_2O 20°C

The pK_a of **1.27** was determined to be surprisingly low despite suggested intramolecular hydrogen bonding. The pK_a of **3.2** is sufficiently lower than that of **1.27** probably due to the decrease in strength of its hydrogen bond to the pyrazine nitrogen compared to the carbonyl oxygen in **1.27**; both compounds stabilize the sulfenate anion to a large extent through resonance. Not surprisingly, **3.3** has a relatively higher pK_a due to the lack of additional stabilizing effects on

the deprotonated form; this value is most likely the best estimate for an acid dissociation constant for a sulfenic acid thus far.

The pK_a measurement obtained by Kice *et al.* proved to be fairly simple due to the clear difference between the ultraviolet-visible spectra of **1.27** and its anion, **1.27**$^-$ (Equation 3.17). It was found that a solution of **1.27** in 85:15 acetonitrile/water had a λ_{max} of 462 nm, and upon addition of sufficient NaOH solution λ_{max} shifted to 676 nm, demonstrating conversion to its anion. Upon acidification the anion was converted back to its protonated form showing the instantaneous equilibrium shown in Equation 3.17. The fraction of **1.27** converted to **1.27**$^-$, *f*, was determined by measuring the optical density of a 10^{-4} M solution of **1.27** in the presence of a series of buffers ranging from pH 7.5-8.7 (Equation 3.18). The pK_a at each buffer was then calculated by equation 3.19 and the average was taken to give a value of 7.51 ± 0.06.[75]



(**3.17**)

$$\frac{[\mathbf{1.27^-}]}{[\mathbf{1.27}]} = \frac{f}{(1-f)} \qquad (\mathbf{3.18})$$

$$pK_a = pH - \log \frac{[\mathbf{1.27^-}]}{[\mathbf{1.27}]} \qquad (\mathbf{3.19})$$

Although *tert*-butylsulfenic acid is absent of any electronic or hydrogen bonding effects, it is not a persistent sulfenic acid, and has to be generated by flash vacuum pyrolysis (FVP) of di-*tert*-butyl sulfoxide, followed by deposition of the product on a cold finger cooled with liquid

nitrogen and stored as a solution at -196°C. The lifetime of **3.3** in dilute, neutral aqueous solution was found to be considerably long and the second-order rate constant for the self-condensation reaction was found to be 5 x 10^{-4} M^{-1} s^{-1} at 35°C. The pK_a was determined by adding 30 μL of a stock solution of **3.3** in acetonitrile to 3 mL of an aqueous buffer solution containing 20 vol % acetonitrile. The absorbance at 240 nm was recorded and extrapolated to the time of mixing to obtain the initial absorbance A_0. Absorbances in neutral and 0.1 M NaOH were used for the conjugate acid and base respectively. The pK_a was obtained by using the Henderson-Hasselbalch equation, pK_a = pH + log ([HA]/[A^-]).[77]

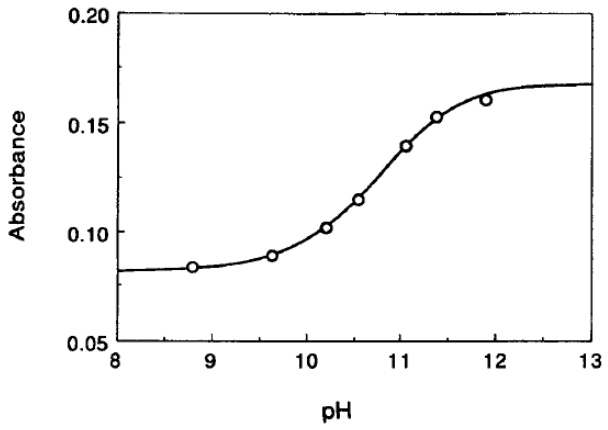


Figure 3.4 The initial absorbance of 3.6 in alkaline solution measure at 240 nm and 14°C.

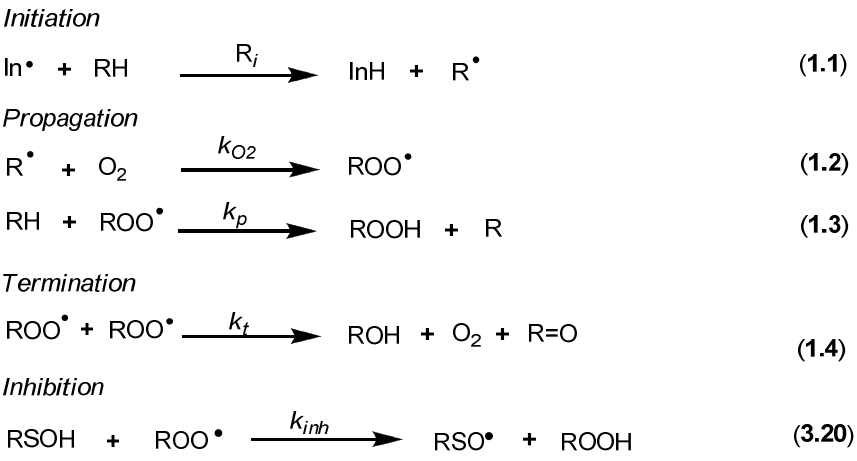
When initial experiments were performed to see if λ_{max} would shift for 9-triptycenesulfenic in its protonated and deprotonated forms, it was established that its chromophore was independent of basicity and hence the pK_a could not be calculated similar to that for the previous two examples. Therefore, other methods were considered: one such method

was to perform titrations using an autotitrator and finding the pH at half-neutralization from a pH curve such that the pH = pK_a (See Results and Discussion).

It is interesting to compare the acidity of the sulfenic acid functional group to the isoelectronic hydroperoxide. It is known that hydroperoxides are much more acidic than their alcohol counterparts and that by inserting the oxygen atom, the acidity is typically enhanced by 4-6 pK_a units. By inserting a sulfur atom, the effect should be greater still, due to the negative charge being delocalized to a greater extent onto the sulfur. This expectation is supported by the comparison of **3.3** and $(CH_3)_3COOH$ (Table 3.1), assuming that the solvent and temperature effects are negligible, and that the estimated value for **3.3** is reliable.

3.1.4 Determination of Inhibition Rate Constant

As introduced in Chapter 1.2.2, the inhibition rate constant (k_{inh}) for the reaction between a given H-atom donor and peroxyl radicals reflects its antioxidant activity. This rate can be determined by inhibited autoxidation experiments performed on an oxidizable hydrocarbon, as long as the chain is initiated by an initiator with a known rate of radical generation (R_i) and the rate of chain propagation is also known (k_p).



Scheme 3.2. General mechanism of hydrocarbon autoxidation and inhibition by a sulfenic acid.

The rate of inhibited autoxidation in which all RSO• are destroyed by reacting with other radical species and do not go on to propagate the chain, can be represented by Equation 3.21. It should be noted that Equation 3.21 is only valid when $d[O_2]/dt$ is at least 5-10 times greater than R_i (i.e. the kinetic chain length is at least 5-10), such that the reaction is a legitimate chain reaction. The rate can be measured as a function of oxygen consumption, or alternatively, hydroperoxide production.

$$-d[O_2]/dt = d[ROOH]/dt = \frac{k_p[RH]R_i}{nk_{inh}[ArOH]} \quad (3.21)$$

Inhibition rate constants are only easily determined when a clear inhibition period is observed. The duration of this inhibited period, τ, can be used to determine the stoichiometric factor (n) as in Equation 3.22. The stoichiometric factor is the number of peroxyl radicals trapped

by each molecule of antioxidant, and is 2 for most phenolic antioxidants, owing to Equations 1.5 and 1.9 (see Chapter 1.2.2).[120] Once the stoichiometric factor is known, it can be used in Equation 3.22 to determine k_{inh}.

$$\tau = n[\mathrm{ArOH}]/R_i \qquad \textbf{(3.22)}$$

A normal curve for oxygen uptake during autoxidation in the absence of an antioxidant consists of no inhibition period (solid line, Figure 3.5). In the presence of an antioxidant, an inhibition period appears, followed by an increase in rate of oxygen consumption which occurs when the antioxidant source has been completely depleted (broken line, Figure 3.5). [121]

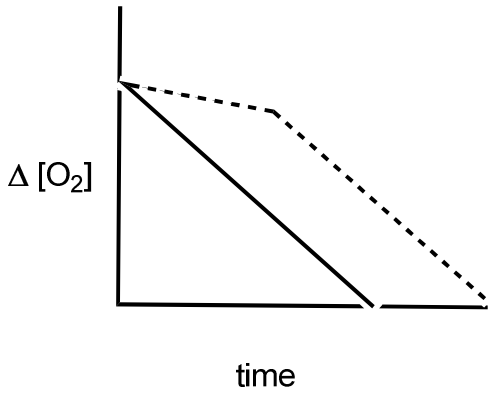
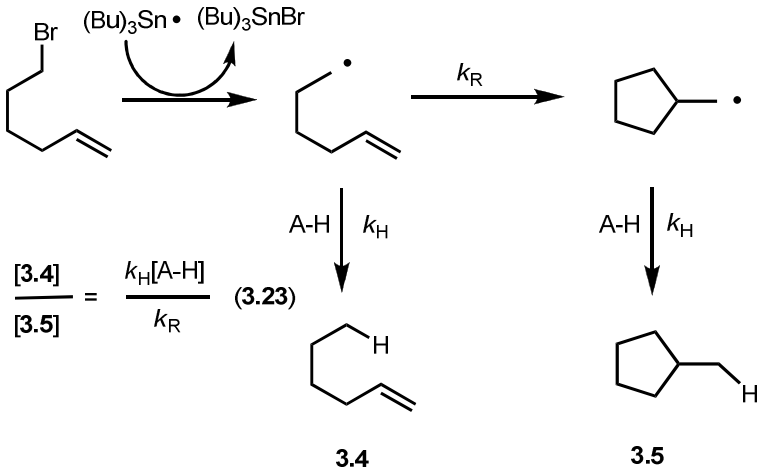


Figure 3.5. Oxygen consumption profile comparing autoxidations in the presence and absence of an antioxidant.

Recently, Porter et al. have designed "radical clock" approaches for determining rate constants for reactions with peroxyl radicals that requires less specialized equipment than the oxygen consumption experiments. Radical clocks are an indirect method for determining the

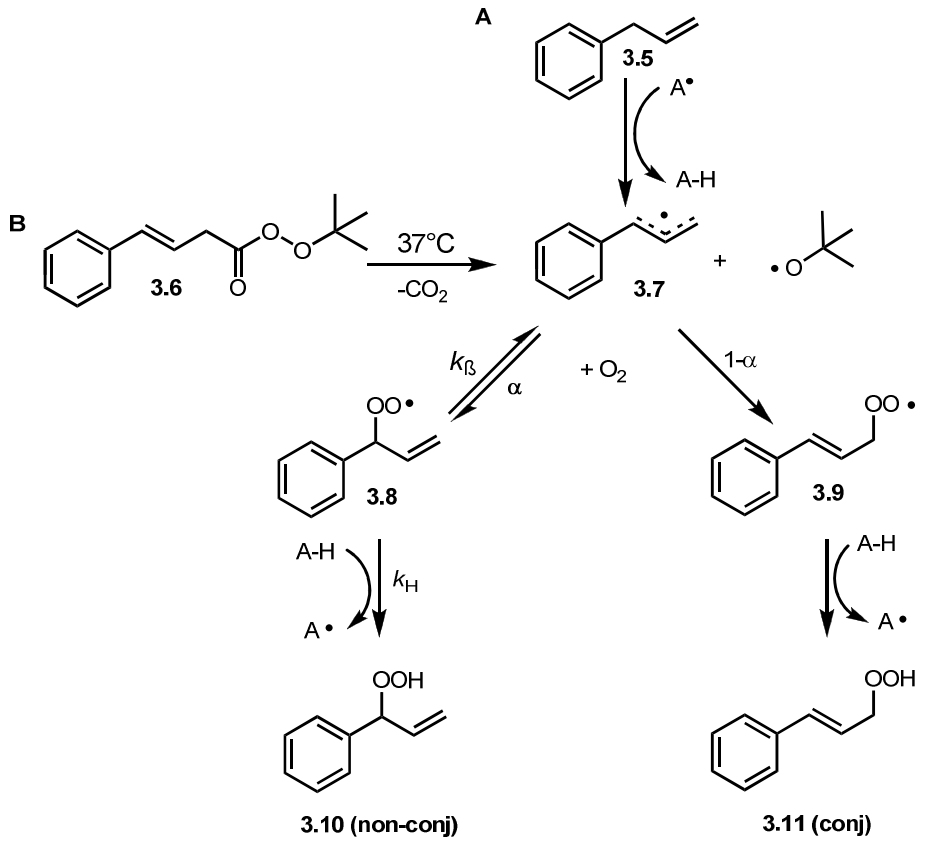
kinetics for a radical-molecule reaction by competition between a unimolecular reaction having a known rate constant and a bimolecular reaction with an unknown rate constant. A prototypical example is the 5-hexenyl radical cyclization which utilizes the competition between a 5-*exo*-trig cyclization (k_R) and abstraction of a hydrogen atom from a substrate, A-H (k_H) (Scheme 3.3). Using the product ratio and the known cyclization rate, k_R, k_H, can be determined via Equation 3.23. Using this general methodology, dozens of clocks have been designed to measure rates ranging from 10^{-1} to 10^{12} $M^{-1}s^{-1}$.



Scheme 3.3. 5-hexenyl radical cyclization clock.

Porter *et al.* report the development of a series of peroxyl radical clocks based on the competition between a unimolecular peroxyl radical rearrangement (k_β) and bimolecular H-atom transfer (k_H) where k_H refers to compounds that may propagate (k_p) or inhibit (k_{inh}) the chain (see Scheme 3.4). The clocks were based on two substrates, methyl linoleate (see Scheme 1.2) and allylbenzene (see path A, Scheme 3.4), and are amenable to measuring H-atom transfers ranging from 10^0 to 10^7 $M^{-1}s^{-1}$.[20] An alternative and perhaps superior method to measuring inhibition rate

constants for antioxidants was suggested in a 2008 paper by Jha and Pratt using a novel peroxyester-based radical clock. They were interested in the kinetic competition approach suggested by Porter *et al.*, but were dissatisfied with a major limitation: the radical generated from A-H ($A^{\bullet}$) must propagate the chain reaction. This poses a problem for H-atom donors that yield sufficiently persistent or highly stabilized radicals (i.e. Butylated hydroxy toluene[20] and 6-amino-3-pyridinols[122] respectively). In addition, because the rate of chain propagation (k_p) is so slow, a large concentration of substrate is required so that sufficient oxidation products are formed for accurate analysis, which makes it impossible to consider any solvent effects on the observed kinetics.



Scheme 3.4. Mechanism of a peroxyl radical clock derived from allyl benzene in the presence of a radical initiator (A) or a homoconjugated peroxyester (B) in the presence of an H-atom donor, A-H where k_H = rate of H-atom transfer, and k_β = 1.7 (±0.1) x 10^5 s^{-1} at 37°C.

In an attempt to overcome the limitations mentioned, a homoconjugated peroxyester (**3.6**) was prepared as a source of delocalized carbon-centered radical (**3.7**) which can became oxidized and trapped by an H-atom donor to form non-conjugated (**3.10**) and conjugated products (**3.11**, Scheme 3.4). Using this methodology, values for k_β and α were obtained in good agreement to the experiments using allylbenzene; in addition, only 10 mM peroxyester precursor was needed in comparison to 2.6 M of allylbenzene precursor or 0.2 M methyl linoleate.[20,123] Using known k_H values for the reaction between α-tocopherol and cumyl peroxyl radicals in a variety of solvents

using laser flash photolysis,[124] the kinetic solvent effects (KSE) on β-fragmentation of **3.8** were determined and validated by measuring k_{inh} values for a number of known antioxidants.[33]

Recently, our group has further refined this approach, by simply replacing the phenyl group in the perester with a naphthyl moiety.[125] This methodology is an improvement from the phenyl peroxyester primarily due to better resolution of the products by GC analysis. The clock works similar to compound Scheme 3.4 and we plan to measure the k_{inh} for our model 9-triptycene sulfenic acid, **1.31**, this way using Equation 3.24.

$$\frac{[\text{non-conj}]}{[\text{conj}]} = \frac{k_H\,[\mathbf{1.31}]}{k_\beta} \bullet \frac{\alpha}{1-\alpha} + \frac{\alpha}{1-\alpha} \qquad (\mathbf{3.24})$$

3.2 Results and Discussion

3.2.1 The O-H BDE of 9-Triptycenesulfenic Acid[126]

Before conducting the experiments for determining the O-H BDE for **1.31**, as described in Chapter 3.1.2, it was of interest to find out the persistence of the sulfinyl radical under similar reaction conditions to see if in fact the EPR equilibration technique is useful for our compound. Thus, a deoxygenated solution of **1.31** and 5-10% v/v di-*tert*-butylperoxide in benzene was placed in an EPR cavity and irradiated with UV light for 30 seconds. Under these conditions, an intense, single line spectrum was observed with a field centre at g = 2.0114 (black line, Figure 3.6). The persistence of the 9-triptycenesulfinyl radical is an interesting result, as other simple alkyl sulfinyl radicals (i.e. *tert*-butylSO•[127] and MeSO•[128]) have not displayed this property under similar conditions. In fact, *tert*-butylsulfinyl radicals were found to undergo bimolecular self-reactions at $2k = 6 \times 10^7$ $M^{-1}s^{-1}$ at -100ºC.[127] Remarkably, in addition to the sulfinyl radical

derived from **1.31** being more persistent than other alkylsulfinyl radicals, it was found to be stable to oxygen. When the sample was exposed to air, significant broadening of the signal was observed (the line width increased from less than 0.4 G to approximately 1.8 G, (red line, Figure 3.6) due to the paramagnetism of oxygen, and upon sparging with nitrogen, the original peak formed (blue line, Figure 3.6).

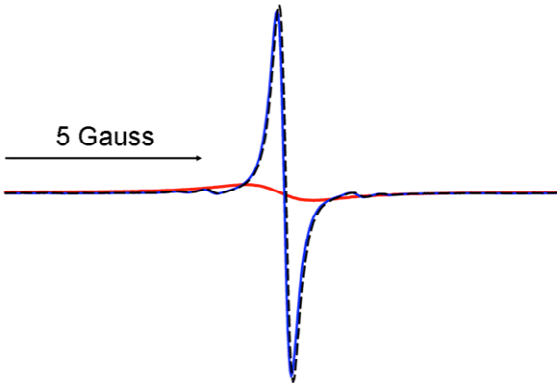


Figure 3.6. EPR spectrum of 1.17$^{\bullet}$ obtained following irradiation of **1.31** in benzene containing 5-10 mol% di-*tert*-butylperoxide in the absence of O_2 (black dashed line), following exposure to air (red line) and after being sparged with N_2 to remove O_2 (blue line).

Because the triptycenesulfinyl radical was sufficiently persistent as anticipated, we could move forward and perform our radical equilibration experiments with TEMPO-H (**3.1**). Thus, a deoxygenated solution of di-*tert*-butylperoxide, **1.31** and **3.1** in benzene was added to an EPR cavity and irradiated to yield the spectrum shown in Figure 3.7. The relative amounts of the two equilibrating radicals were determined as described in Chapter 3.1.1, and confirmed by double integration of the first line of the spectrum of TEMPO (**3.1$^{\bullet}$**) compared to the double integration of the signal corresponding to the sulfinyl radical. The relative amounts of the two radicals we plugged into Equation 3.4 (replacing ArOH with **1.31** and X-H with **3.1** along with the

corresponding radicals) to obtain the equilibrium constant (K_{eq} = 0.022 ± 0.010) which was subsequently used in Equation 3.5 to obtain the BDE for **1.31** (71.9±0.3 kcal/mol).

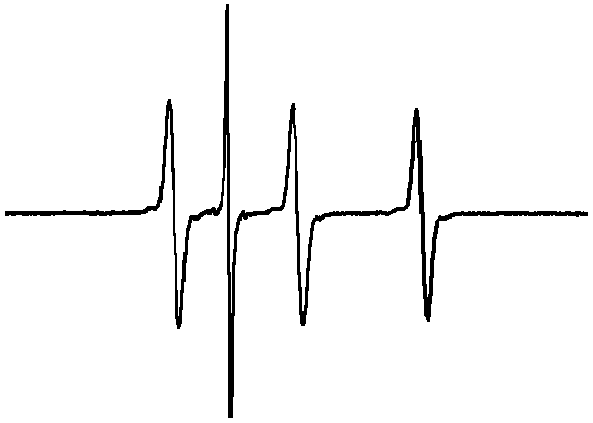


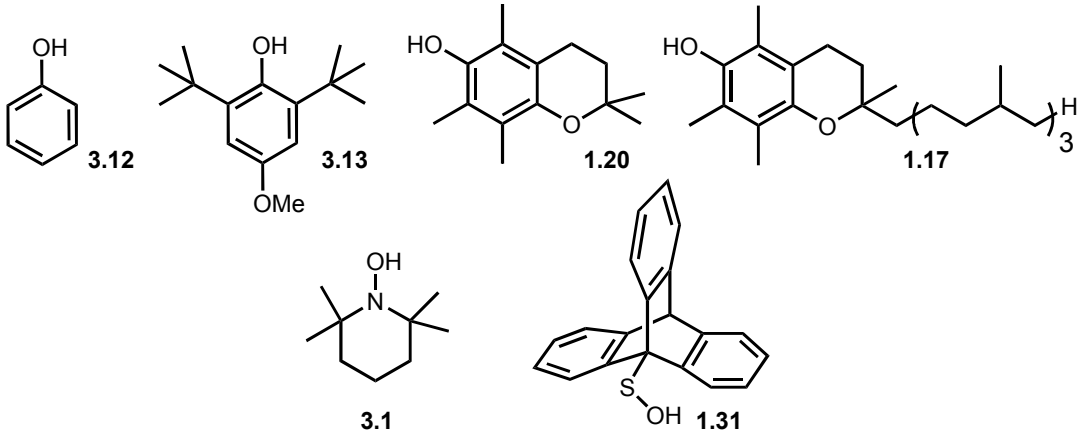
Figure 3.7. EPR spectrum obtained from the equilibration of the sulfinyl radical **1.31**$^{\bullet}$ and **3.1**$^{\bullet}$ shown in Equation 3.4.

The BDE obtained for **1.31** is the first obtained for a sulfenic acid experimentally and is in good agreement with that predicted by Vaidya *et al*. for other alkylsulfenic acids (68.4-68.6 kcal mol^{-1}).[45] For a perspective on the utility of this value, it is useful to compare the BDE measured for **1.31** to phenolic antioxidants, such as α-tocopherol, and justify its antioxidant activity accordingly. Table 3.2 compares the O-H BDE of phenol (**3.12**) to some of the lowest BDEs determined for substituted phenolic antioxidants (**3.13**, **1.20**, **1.17**),[30] as well as the hydroxylamine, TEMPO-H (**3.1**),[46] and our model sulfenic acid, 9-triptycenesulfenic acid (**1.31**). Based on our measurement, 9-triptycenesulfenic acid has a lower BDE than phenols and slightly higher than TEMPO-H, which is the lowest known O-H BDE for a hydroxylamine.[116] Although a great deal of effort has been made to decrease the O-H BDE of phenolic compounds to enhance their reactivity towards peroxyl radicals, the all-natural α-tocopherol still remains one of the best.

However, it turns out that the sulfur atom of a sulfenic acid stabilizes the radical to a much greater extent than the variously substituted phenyl groups.

Table 3.2. BDEs for selected phenolic antioxidants, TEMPO-H and 9-triptycenesulfenic acid.

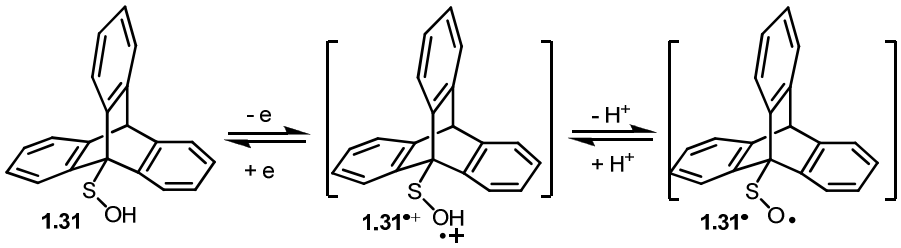
Phenol	BDE (kcal M^{-1})
3.12	88.3 ± 0.8
3.13	78.31 ± 0.13
1.20	78.25 ± 0.18
1.17	78.23 ± 0.25
1.31	71.9 ± 0.3
3.1	69.6



3.2.2 The Electrochemical Behavior of 9-Triptycenesulfenic Acid

For our electrochemical experiments with 9-triptycenesulfenic acid, we used conditions similar to that used for experiments done with α-tocopherol as it was expected that there would be

similarities between their electrochemical behaviors. Initially it was expected that when a potential was applied to a solution of **1.31**, it would undergo a one electron oxidation to form an intermediate radical cation species (**1.31**$^{+\bullet}$) which would most likely dissociate rapidly to form the sulfinyl radical (**1.31**$^{\bullet}$) and H^+ (Scheme 3.5). Since we observed that **1.31**$^{\bullet}$ was highly persistent during the EPR experiments, it was anticipated that when a potential was applied with the reverse polarity that a fully reversible reduction peak would be observed. However, when a potential was applied to a solution of **1.31**, a broad oxidation (anodic) peak was revealed at 1.46 V versus NHE[129] (Figure 3.8) and when the polarity of the potential applied was reversed, no reversible reduction (cathodic) peak was observed. Apparently the triptycenesulfinyl radical cation undergoes subsequent chemistry on the time scale of the experiment such that we cannot observe it being reduced back to its original form. Alternatively, the reverse reduction occurs much slower than the initial oxidation event and equilibrium cannot be established during the time of the experiment.



Scheme 3.5. Predicted electrochemically induced one-electron oxidation of **1.31** in a neutral environment.

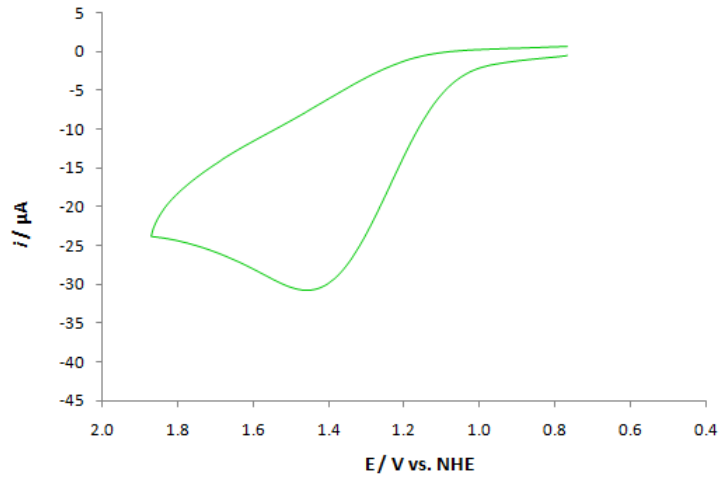


Figure 3.8. Cyclic voltammagram corresponding to the oxidation of 5 mM **1.31** in CH_3CN containing 0.1 M Bu_4NPF_6 as supporting electrolyte and no additive at a scan rate of 100 mV/s.

Next we attempted the experiment in the presence of a strong acid, CF_3SO_3H. Again we saw an irreversible peak, the difference being that upon titrating in acid, the peak sharpened and shifted towards higher potentials eventually becoming constant at 1.57 V vs NHE (red line, Figure 3.9). This observation could be attributed to the equilibrium between $\mathbf{1.31}^{\bullet+}$ and $\mathbf{1.31}^{\bullet}$ being shifted completely towards the protonated radical cation. Again, the radical cation is not stable enough to undergo a reversible one-electron reduction and so the sharp irreversible peak is observed.

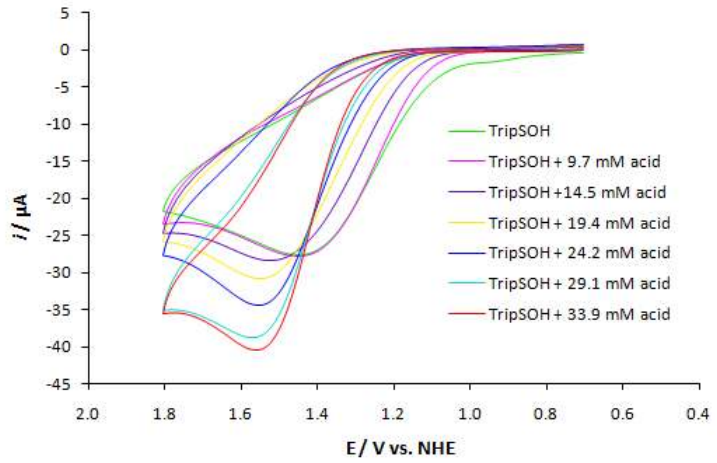


Figure 3.9. Cyclic voltammagrams corresponding to the oxidation of 5 mM **1.31** in CH_3CN containing 0.1 M Bu_4NPF_6 as supporting electrolyte and 9.7-33.9 mM CF_3SO_3H at a scan rate of 100 mV/s.

Finally, we added base to our sulfenic acid to learn about the electrochemical transformations of the sulfenate anion. After adding half an equivalent of base, a new peak began to form at a much lower potential (~0.79 V) while the peak at 1.46 V remained present, but its current reduced. After addition of a full equivalent of base (or slightly more to make sure all the sulfenic acid had been deprotonated) the peak at 1.46 V had disappeared completely and only the new, more easily oxidized peak was observed (Figure 3.10).

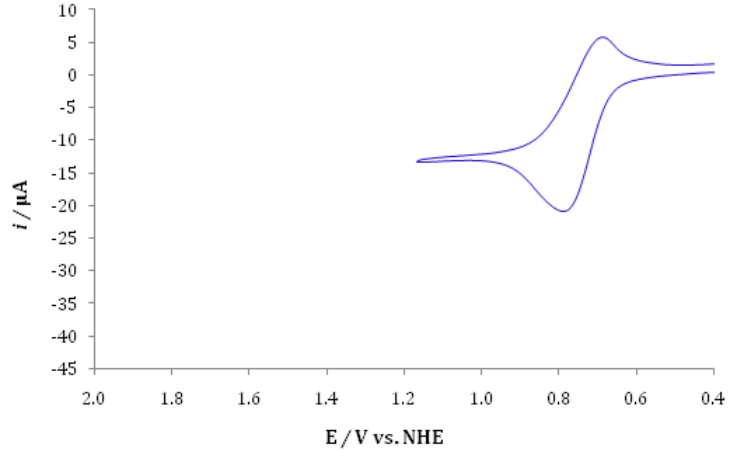
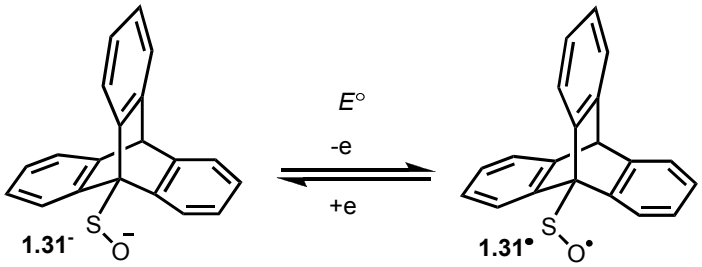


Figure 3.10. Cyclic voltammogram corresponding to the quasi-reversible oxidation of 5 mM **1.31** in CH_3CN containing 0.1 M Bu_4NPF_6 as supporting electrolyte and 5 mM Bu_4NOH at a scan rate of 100 mV/s

As well, this peak showed quasi-reversible behavior indicating that in basic media the sulfinyl radical is sufficiently stable and can be reduced back to its anionic form. In essence, quasi-reversibility indicates that on the time scale of the experiment, equilibration has not been fully established such that not all of the oxidized sulfenic acid has been reduced back to its original form. There are two characteristic features for a fully reversible process. One is that the peak currents of the oxidation and reduction events are the same height, indicating the same number of electrons being transferred. The other is that the distance between the peaks is 63 mV. We did not observe either of these traits for the sulfenate anion; however, we did attempt to decrease the scan rate to see if full reversibility was possible. Unfortunately at significantly lower scan rates, other chemistry began to occur as indicated by the appearance of new peaks. At a scan rate of 25 mV s^{-1} we did obtain a peak difference as low as 69 mV.



(**3.25**)

Since this transformation showed quasi-reversibility, the standard electrochemical potential ($E°$) for the transformation between the sulfenate anion and the sulfinyl radical could be calculated (0.74 V, Equations 3.25 and 3.26) and should serve as a viable estimate for the actual value. In comparison, $E°$ for the $ROO^{\bullet}/ROO^{-}$ couple under neutral conditions is estimated to be 1.05 V[130] indicating that the sulfenate anion is more easily oxidized than its peroxide anion counterpart. This corresponds adequately to our idea that the sulfinyl radical is stabilized to a large degree by delocalization onto the internal sulfur atom when an electron is removed from the terminal oxygen.

$$E^{\circ} = E_{1/2} = \frac{E_a + E_c}{2} \qquad (\mathbf{3.26})$$

3.2.3 pK_a Determination for a Sulfenic Acid

A series of half-neutralizations were performed on the sulfenic acid where the samples were made up of 10 mM **1.31** and 5 mM NaOH in 1 mL of 8:2 $CH_3CN:H_2O$ and the pH measured under oxygen-free conditions. Table 3.3 shows the eleven trials that we did to determine the ${}^{S}_{S}\mathrm{p}K_a$ of

1.31 using the half-neutralization method and the average value was calculated to be 12.55 ± 1.27. Although this may be a good estimate, the standard deviation is too large for the value to be reliable. Based on the report by Okuyama and coworkers, we were expecting our triptycenesulfenic acid to have a ${}^{s}_{s}\mathrm{p}K_{\mathrm{a}}$ higher than 10.47. Due to the different solvent conditions used for the two experiments, a quantitative comparison cannot be made (for **3.3**, 2:8 $CH_3CN:H_2O$ was used); however our value follows the expected trend that the ${}^{s}_{s}\mathrm{p}K_{\mathrm{a}}$ in 4:1 $CH_3CN:H_2O$ would be higher than in 2:8 $CH_3CN:H_2O$. The reasoning for this being that the anion would be stabilized less in a less polar solvent (4:1 $CH_3CN:H_2O$), thus the equilibrium would be more towards the protonated form.

Table 3.3. ${}^{s}_{s}\boldsymbol{p}\mathbf{K}_{\mathbf{a}}$ values determined by half-neutralizations of 10 mM **1.31** with 5 mM NaOH in 4:1 (v:v) CH_3CN/H_2O at 25°C.

Trial	Solvent	${}^{s}_{s}\mathrm{p}K_{\mathrm{a}}$ [131]
1	$CH_3CN:H_2O$	12.15
2	$CH_3CN:H_2O$	14.45
3	$CH_3CN:H_2O$	14.55
4	$CH_3CN:H_2O$	13.28
5	$CH_3CN:H_2O$	13.17
6	$CH_3CN:H_2O$	13.42
7	$CH_3CN:H_2O$	11.16
8	$CH_3CN:H_2O$	11.47
9	$CH_3CN:H_2O$	11.51
10	$CH_3CN:H_2O$	11.51
11	$CH_3CN:H_2O$	11.34
Average		12.55 ± 1.27

Using an autotitrator, we were able to obtain three pH curves from which we could extract pK_a values for **1.31**. From Figure 3.11, the point on the curve corresponding to one half of an equivalent of base (or half neutralization) is the pK_a. The average value of the three trials after correction was found to be 12.5 ± 0.1 (Table 3.4), which is not only in good agreement with our average value from the half-neutralization experiments, but also has a much better standard deviation, making it a great deal more reliable.

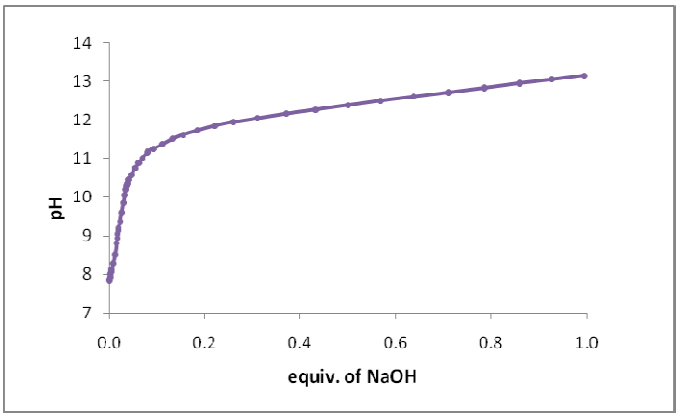


Figure 3.11. Titration of 20 mL of 1 mM **1.31** with 19 mM NaOH in 4:1 (v:v) CH_3CN/H_2O at 25°C.

Table 3.4. $^{s}_{s}\mathbf{pK_a}$ values obtained from autotitrations of 1 mM **1.31** in 4:1 (v:v) CH_3CN/H_2O at 25°C where the slope of the line was linearly interpelated to 0.5 eqivalents of NaOH (i.e. at 0.53 mL of 19 mM NaOH solution).

Trial	Solvent	$^{s}_{s}pK_a$ [131]
1	$CH_3CN:H_2O$	12.6
2	$CH_3CN:H_2O$	12.4
3	$CH_3CN:H_2O$	12.4
Average		12.5 ± 0.1

In addition, we performed titrations on *tert*-butylhydroperoxide in 4:1 CH_3CN:H_2O to confirm that in fact the tertiary sulfenic acid is more acidic than the tertiary hydroperoxide in the same solvent system. In water, the pK_a for *tert*-butylhydroperoxide was reported as 12.8;[119] using the autotitrator and 4:1 CH_3CN:H_2O as the solvent, we measured an average value of 13.9 ± 0.1 (Table 3.5). It should be noted that the maximum reliable value of ${}^{s}_{s}$pH our probe can measure is approximately 14 and as a result the ${}^{s}_{s}\mathrm{p}K_a$ of *tert*-butylhydroperoxide is ≥ 14 and at least 1.5 pK_a units higher than the sulfenic acid.

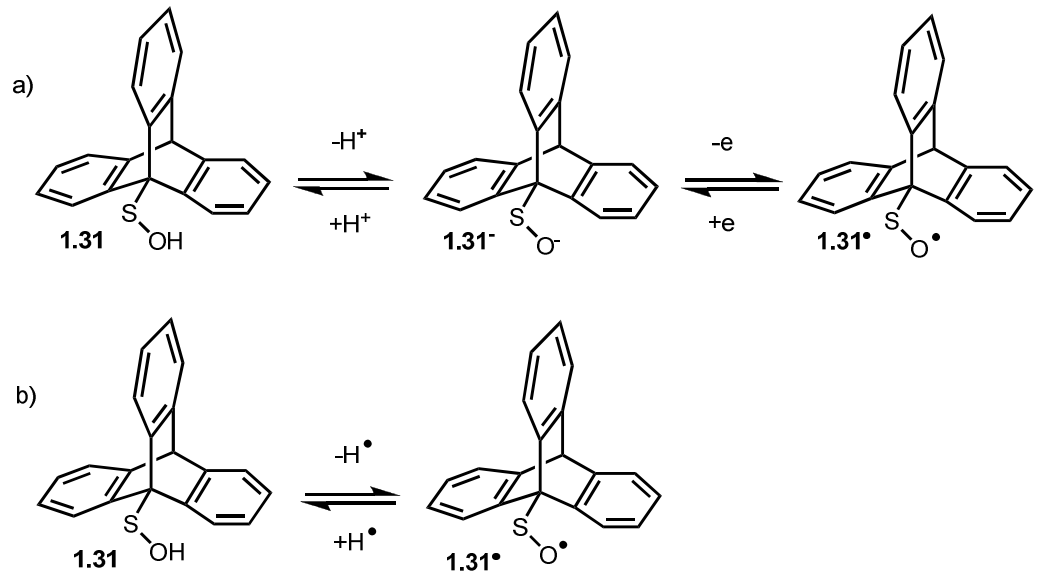
Table 3.5. $\mathbf{{}^{s}_{s}pK_a}$ values obtained from autotitrations of 1 mM *tert*-butylhydroperoxide 4:1 (v:v) CH_3CN/H_2O at 25°C where the slope of the line was linearly interpelated to 0.5 eqivalents of NaOH (i.e. at 0.53 mL of 19 mM NaOH solution).

Trial	Solvent	${}^{s}_{s}\mathrm{p}K_a$ [131]
1	CH_3CN:H_2O	14.0
2	CH_3CN:H_2O	14.0
3	CH_3CN:H_2O	13.7
4	CH_3CN:H_2O	13.9
Average		13.9 ± 0.1

The pK_a difference between the sulfenic acid and hydroperoxide is relatively small compared to the difference in $E°$ between the $ROO^{\bullet}/ROO^{-}$ and $RSO^{\bullet}/RSO^{-}$ couples; thus, lability of the O-H bonds in sulfenic acids is probably derived more from the stability of the sulfinyl radical than the sulfenate anion. The pK_a values will be based largely on the stability of either the sulfenate or peroxide anions in solution; since these values are relatively similar, the internal sulfur and oxygen must stabilize the terminal oxygen anion to a similar extent. In contrast, the

internal sulfur atom must have a much greater stabilization effect on the sulfinyl radical compared to the internal oxygen on a peroxyl radical.

The potential energy diagram shown in Figure 3.12 presents a thermodynamic cycle of deprotonation (based on pK_a) and electron transfer (based on $E°$) versus homolytic bond cleavage (based on the BDE, Scheme 3.6). As mentioned, the BDE of the TripSO-H bond was found to be 71.9 kcal mol^{-1}, which is 12.9 kcal mol^{-1} lower than the predicted BDE for the *tert*-buOO-H bond (84.8 kcal mol^{-1}). If we quantitate the difference in the $E°$ values between the ROO$^{\bullet}$/ROO^{-} and RSO$^{\bullet}$/RSO^{-}couples and the pK_a values between the ROO^{-}/ROOH and RSO^{-}/RSOH couples using common units, the energy required to remove an electron from **1.31**$^{-}$ and for deprotonation of **1.31** could be compared. Each pK_a unit is worth essentially 1.36 kcal mol^{-1}, and each volt worth 23.1 kcal mol^{-1}; the values are derived from the Gibbs free energy relation and Nernst equation respectively. Therefore, the E° difference between the RSO$^{\bullet}$/RSO^{-} and ROO$^{\bullet}$/ROO^{-} couples (ca. 300 mV), corresponds to 7 kcal mol^{-1}. The pK_a difference between the RSO^{-}/RSOH and ROO^{-} /ROOH couples (approximately 1.5 pK_a units) corresponds to 2.1 kcal mol^{-1}. Thus the lability of the O-H bond is based more on formation of the highly stabilized sulfinyl radical, **1.31**$^{\bullet}$.



Scheme 3.6. O-H bond cleavage via a) deprotonation followed by electron transfer and b) homolytic bond breaking.

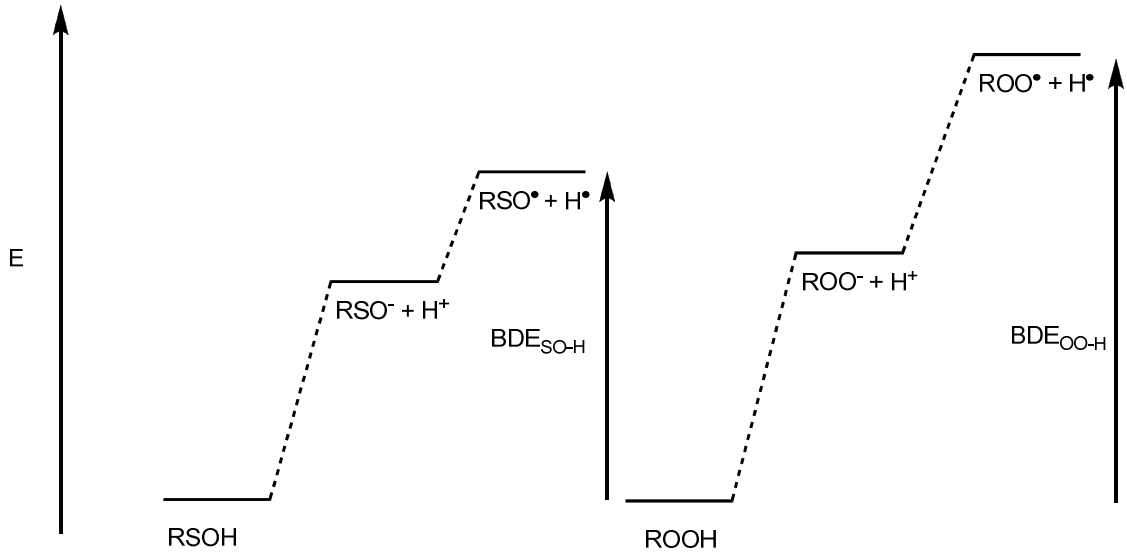
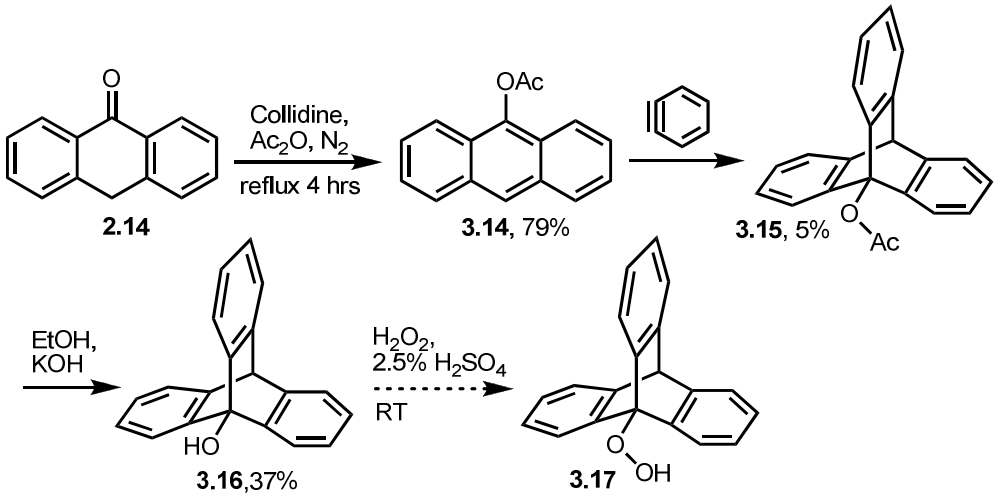


Figure 3.12. Potential energy diagram comparing homolytic bond cleavage (Energy gap from RSOH to $RSO^{\bullet} + H^{\bullet}$, reflected by BDE) to deprotonation (RSOH to $RSO^{-} + H^{+}$, reflected in pK_a) followed by electron transfer ($RSO^{-} + H^{+}$ to $RSO^{\bullet} + H^{\bullet}$, reflected in $E°$) for both a sulfenic acid and hydroperoxide.

It should be noted that if the differences for deprotonation and electron transfer are combined, the value obtained is significantly smaller than 12.9 kcal mol^{-1}, the difference between the O-H BDEs. The discrepancy may result from the fact that we are comparing substrates with different sidechains (i.e. the sulfenic acid is attached to a triptycyl moiety and the hydroperoxide to a *tert*-butyl group) and that the values were not measured under the exact same reaction conditions (i.e. the pK_a for *tert*-butylhydroperoxide and the $E°$ for the corresponding *tert*-$BuOO^{\bullet}$/*tert*-$BuOO^{-}$ couple were measured in water while the parallel sulfenic acid measurements were made in acetonitrile and 8:2 acetonitrile:water respectively).

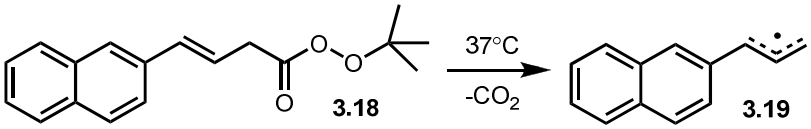
Although comparing our pK_a value for 9-triptycenesulfenic acid to that of *tert*-butylhydroperoxide is useful, it would be more reliable to compare it to the pK_a for the analogous 9-triptycenehydroperoxide (**3.17**). Thus, the synthesis of 9-triptycene hydroperoxide was attempted (Scheme 3.7), but due to time constraints, was never completed. Although some yields were poor, the first three steps of the synthesis were relatively straightforward. The final step was oxidation of 9-triptycenealcohol using 2.5% sulfuric acid and 35% hydrogen peroxide. Even when the concentration of hydrogen peroxide was increased to 50%, the reaction failed to occur, and eventually the synthesis was put on hold. Although there are other reports for oxidation of tertiary alcohols using this method,[132] the 9-triptycene alcohol may be less reactive due to the steric bulk surrounding the alcohol. For future endeavors, we could also acquire a pH probe reliable to reading $^{S}_{S}$pH = 15 to make our comparison quantitative.



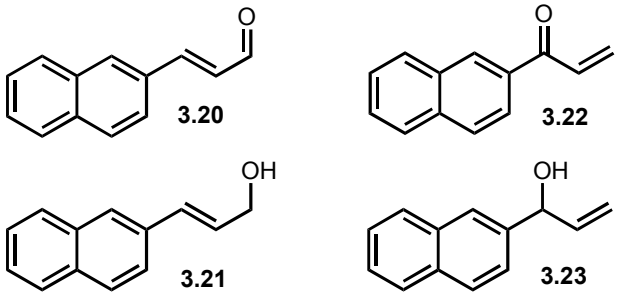
Scheme 3.7. Attempted synthesis of 9-triptycenehydroperoxide from anthrone.

3.2.4 The Inhibition Rate Constant for 9-Triptycenesulfenic Acid.

To determine the inhibition rate constant, k_{inh}, for **1.31** we used the naphthyl perester clock methodology[133] which works analogously to Scheme 3.5.[33] The homoconjugated naphthyl peroxyester, **3.18**, (15 mM) was combined with 10-100 mM **1.31** in chlorobenzene and heated to 37°C overnight. When heated, the peroxyester decomposed to form the naphthyl analogue to the carbon centered radical (**3.19**) shown in Scheme 3.4. In the presence of oxygen, the conjugated and non-conjugated hydroperoxides are formed. Eventually, the reactions were quenched with triphenylphosphine and diluted to be analyzed by GC. Upon reduction, the hydroperoxides can form four products: two conjugated (conjugated aldehyde, **3.20**, and alcohol, **3.21**) and two non-conjugated products (non-conjugated ketone, **3.22**, and alcohol, **3.23**).[133] Figure 3.13 shows a typical chromatogram showing mainly **3.20** and **3.23** as products. Figure 3.14 illustrates a plot of the conjugated / non-conjugated products versus 1 / [**1.31**] corresponding to one set of data from which k_{inh} can be extracted.



(3.27)



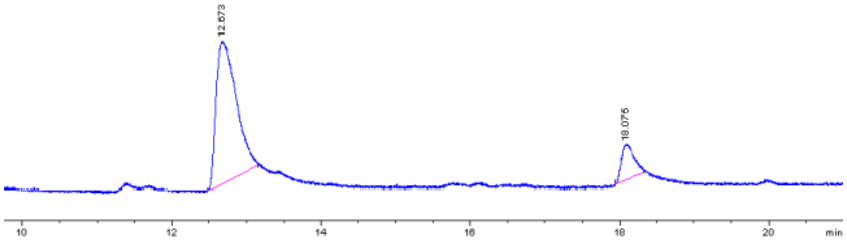


Figure 3.13. Sample GC chromatogram of **3.19** oxidation containing 100 mM of antioxidant **1.31** and 15 mM **3.18** showing the non-conjugated alcohol (**3.23**, 12.7 min) and conjugated aldehyde (**3.20**, 18.1 min); the other two products (**3.21**, 19.6 min and **3.22**, 12.3 min) are negligible.

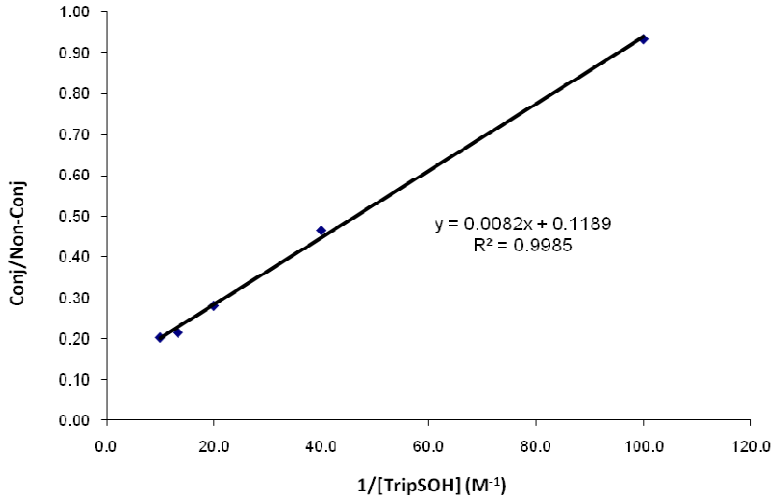


Figure 3.14. Oxidation profile of naphthyl oxidation products as a ratio of conjugated/non-conjugated versus 1/[**1.31**]. Oxidations were carried out in chlorobenzene with 15 mM **3.18**, 10-100 mM **1.31** at 37°C overnight. The hydroperoxide products were reduced by PPh_3 and alcohol and aldehyde or ketone products were analyzed by GC.

According to our experiments, the inhibition rate constant for the reaction between a peroxyl radical (derived from **3.18**) and 9-triptycenesulfenic acid is 1.06 x 10^7 $M^{-1}s^{-1}$ as calculated according to Equation 3.24. Although this is not the diffusion controlled reaction we were expecting, it is still a considerably fast reaction and is approximately three times faster than the reaction between α-tocopherol and peroxyl radicals derived from **3.6** in benzene, which is 3.4 x 10^6 $M^{-1}s^{-1}$.[33]

Additionally, inhibited autoxidations of styrene were performed in the presence of **1.31** to corroborate the k_{inh} derived from our naphthyl perester-based radical clock method. Experiments using this method were performed by measuring the rate of oxygen consumption as a function of time as introduced in 3.1.4. Figure 3.15 shows the oxygen consumption over time, in the presence of **1.31** in both chlorobenzene (ClBz) and acetonitrile (MeCN). In ClBz, there is a clear induction

period in which very little oxidation occurs, followed by a rapid increase in the rate of oxygen consumption (solid line, Figure 3.15). In contrast, the experiment in acetonitrile is absent of an obvious induction period (broken line, Figure 3.15) indicating that autoxidation has been retarded to a much lesser extent. These results are consistent with the solvent effect observed on allicin-inhibited autoxidations, which was ascribed to the hydrogen bonding interaction between acetonitrile and allicin's decomposition product, allylsulfenic acid (see Scheme 1.6).[45] Likewise, presumably acetonitrile ties up 9-triptycenesulfenic acid by accepting a hydrogen bond from the SO-H group, thus inhibiting formation of the pre-transition state hydrogen bonded complex required for a PCET to occur.

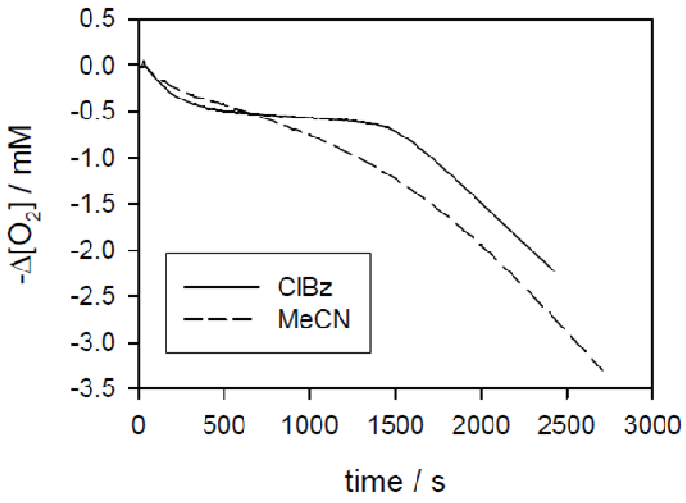


Figure 3.15. Oxygen consumption observed during the autoxidation of styrene (4.3 M) initiated by AIBN (0.05M) at 303 K in the presence of sulfenic acid, **1.31**, in chlorobenzene ([**1.31**]=2.4x10^{-5} M) or acetonitrile ([**1.31**]=3.6x10^{-5} M).

The inhibition rate constants of the reaction between **1.31** and styrene-derived peroxyl radicals in both ClBz and MeCN were calculated via Equation 3.21; the stoichiometric factors, *n*,

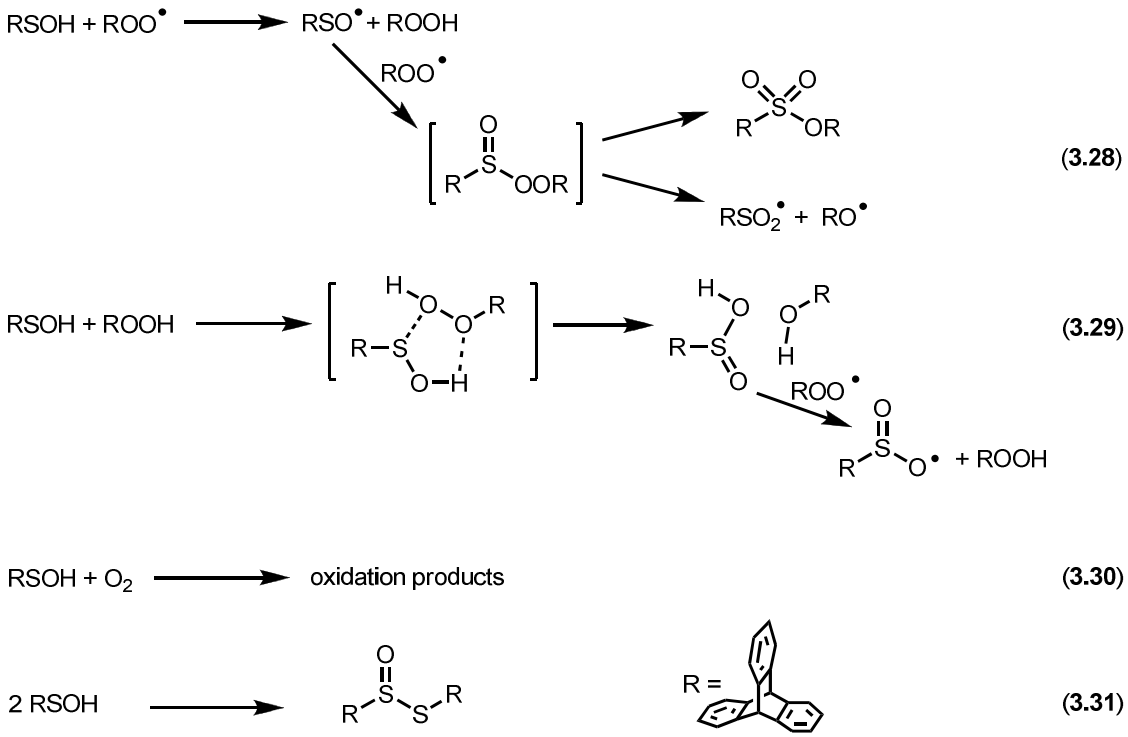
were determined by Equation 3.22 (Table 3.6). As expected, the inhibition rate for **1.31** is lower in a hydrogen bond accepting solvent, MeCN, than in ClBz. This decrease in rate conflicts with the SPLET mechanism, as SPLET mechanisms would become faster in more ionizing solvents. As well, the k_{inh} in ClBz using this method corresponds to the value obtained for the naphthyl perester clock method within a factor of ten.

In Chapter 1.3.2 we introduced that sulfenic acids were predicted computationally to react with peroxyl radicals at diffusion controlled rates. The exact numerical value for this predicted rate could be determined based on the Arrhenius equation ($k = Ae^{-Ea/RT}$). However, the pre-exponential factor (A) for this reaction is not known. Since the barrier to reaction is expected to be zero, the rate simplifies to $k = A$. It might be expected that the pre-exponential factor for H-atom transfer between phenol and *tert*-butylhydroperoxide ($A = 10^{7.2}$) would be comparable to that for the analogous reaction between a sulfenic acid and peroxyl radical. Under this assumption, our experimentally determined k_{inh} rate is in very good agreement with this value. Any discrepancy could be due to the bulkiness of the triptycene backbone in comparison to the relatively smaller substituents on the sulfenic acids used for computation.

Table 3.6. Inhibition rate constants derived from the autoxidation of styrene in the presence of **1.31** as shown in Figure 3.15 and stiochiometric factors, *n*.

Conditions	k_{inh}	N
Styrene/ClBz	(3.0±0.3) x 10^6	0.37±0.03
Styrene/CH_3CN	(3.5±0.4) x 10^5	0.35±0.02

Furthermore, the computations do not take into consideration the possible fates of the sulfenic acid and sulfinyl radical. Each sulfinyl radical derived from H-atom donation from a sulfenic acid to a peroxyl radical may go on to react with another peroxyl radical to ultimately form a sulfonic ester or sulfonyl and alkoxy radical (Equation 3.28). The problem is that the alkoxy radical may go on to propagate the chain by abstracting H-atoms from the hydrocarbon-based substrates. Thus, the rate of inhibition of autoxidation may be reduced due to the fact that for each inhibition action by the sulfenic acid, a chain-propagating species is formed. Another reason for a reduced inhibition rate is the formation of sulfinic acids by either the reaction between sulfenic acids and hydroperoxides (Equation 3.29) or oxygen (Equation 3.30). The sulfinic acid would be expected to be much less reactive toward peroxyl radicals due to electron density being withdrawn from the sulfur atom by the sulfinyl oxygen, resulting in less stabilization of the radical by sulfur and reduced inhibition rates.



Scheme 3.8. Possible fates of 9-triptycenesulfenic acid in the autoxidation of styrene.

It is perhaps unexpected that the *n* value for **1.31** (*n* = 0.37 in ClBz) is quite low in comparison to that for most phenolic antioxidants (*n* = 2).[32] The fact that *n* < 1 indicates that each molecule of **1.31** traps less than one peroxyl radical. One explanation for this is that sulfenic acids may react very quickly with hydroperoxides and be transformed into sulfinic acids (Equation 3.29). Thus, each hydroperoxide that is formed via H-atom donation from a sulfenic acid to a peroxyl radical (Equation 3.28), may subsequently react with another sulfenic acid molecule to form a sulfinic acid (Equation 3.29). If everything in the experiment was perfectly pure, and every ROOH formed from an inhibition step reacted with a sulfenic acid molecule, a value of *n* = 0.5 may be expected. The fact that experimental value is *n* = 0.37 indicates that other possible

fates of species derived from the sulfenic acid, or the sulfenic acid itself must be taken into consideration. Not only can the sulfenic acid react with hydroperoxides, but also with oxygen, to form higher oxidation products such as sulfinic and sulfonic acids (Equation 3.30), and itself, to form thiosulfinates (Equation 3.31). These reactions, if occurring at comparable rates, could provide rationalization for $n < 0.5$. A final reason for $n < 0.5$ could be, as explained above, that one of the fates of a sulfinyl radical could be an alkoxy radical, which would initiate a new chain, thus causing the number of peroxyl radicals the sulfenic acid 'appears' to trap to be misrepresented.

Based on the results obtained from the inhibited autoxidation experiments performed, some interesting conclusions can be made. First, the rate constant for the reaction with our model sulfenic acid, **1.31**, with peroxyl radicals was found to be 1.06×10^7 $M^{-1}s^{-1}$ using the peroxyl radical clock technique and 3.0×10^6 $M^{-1}s^{-1}$ by inhibited autoxidations of styrene in ClBz. These values did not correspond to the diffusion controlled rate we were expecting based on our calculations, but are still substantially high inhibition rates, which compare to α-tocopherol in benzene. This may be considered a lower bounds for reactions of sulfenic acids with peroxyl radicals due to the steric hindrance that must be overcome to achieve the predicted *syn* PCET transition state. The stoichiometric factor, or number of peroxyl radicals trapped by each molecule of antioxidant for **1.31** was found to be surprisingly low ($n = 0.37$) in comparison to most phenolic antioxidants ($n = 2$), but this was probably due to the sulfenic acid undergoing other transformations at comparable rates to H-atom donation to a peroxyl radical. Since the allyl sulfenic acid that derives from allicin is formed in situ, autoxidations inhibited by allicin presumably display greater stoichiometric factors (ca. 1) due to the lesser contribution of these competing reactions.

3.3 Experimental Procedures

Preparation of 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPO-H, **3.1**). TEMPO-H was prepared from TEMPO according to the literature.[134,135] Briefly, a dichloromethane solution was vigorously stirred under N_2 with an aqueous solution of excess $Na_2S_2O_4$ at r.t. for 1 hour. The organic layer was separated, dried over Na_2SO_4, concentrated in vacuo, and then completely removed under a stream of nitrogen. The crude hydroxylamine was purified by sublimation. ^{1}H NMR (CD_3CN); δ 1.1 (s, 12H), 1.5 (s, 6H), 4.3 (br s, 1H); IR: ν_{OH} 3595 cm^{-1} (CCl_4).

EPR spectra. EPR spectra were recorded at 25°C in a Bruker Ellexsys 500 X-band spectrometer, equipped with a standard temperature control unit. A Solution of **1.31** in benzene, containing 1-10% v/v di-*tert*-butyl peroxide, was irradiated by a short (10-30s) unfocused beam of a 500 W high-pressure Hg lamp, in the cavity of the spectrometer. Oxygen was removed by sparging with nitrogen. The built-in gauss-meter and frequency-counter were used for the determination of the *g*-factor, which was corrected with respect of the known value of 2,2,6,6-tetramethylpiperidine-N-oxyl radical in benzene (g = 2.0064). Radical persistency in the absence/presence of oxygen was monitored for 4 hours by double integration of EPR spectra recorded at time intervals on the same sample (without additional irradiation) subjected to repeated sparging with N_2 or air.

Determination of the O-H bond dissociation enthalpy (BDE). Radical equilibration experiments[30,112,136] were performed by short irradiation in the cavity of the EPR spectrometer of benzene solutions (containing 5% v/v di-tert-butylperoxide) and sulfenic acid **1.31** (10-50 mM) with TEMPO-H (2-20 mM) in variable ratio. About 30 seconds after irradiation, the EPR spectrum was recorded and the relative amount of the two equilibrating radical species was

determined by iterative fitting of simulated to experimental spectra, and confirmed by double integration of the first line of the spectrum of TEMPO compared to the double integration of the signal of the sulfinyl radical.

Cyclic Voltammetry. The sulfenic acid **1.31** was synthesized and purified using the methods in Chapter 2.3 and stored under nitrogen at -35°C between experiments. Bu_4NPF_6 was obtained from TCI America and recrystalized from ethanol and dried over P_2O_5 under a vacuum for a few days prior to use. Et_4NOH (35 wt. % in water) was obtained from Sigma-Aldrich and concentrated in vacuo to remove the bulk of the water (the rest of the water was removed by pumping under vacuum overnight) to afford a clear, colorless liquid which was stored under nitrogen between experiments. CF_3SO_3H (>99%) was obtained from Sigma-Aldrich as an ampoule and opened under a blanket of nitrogen immediately before use. HPLC grade acetonitrile was distilled from calcium hydride and deoxygenated immediately prior to experiments. Voltammetric experiments were done using a computer-controlled CH Instuments potentiostat.

Deoxygenated solutions of **1.31** (5 mM) and supporting electrolyte Bu_4NPF_6 (0.1 M) in CH_3CN were made up in the electrochemical cell via syringe and maintained oxygen-free by a blanket of argon. Et_4NOH and CF_3SO_3H were added neat via a microsyringe inserted into the cell through a small hole in the cell lid. The cell was equipped with a platinum working electrode, a platinum wire counter electrode and a non-aqueous Ag/Ag^+ reference electrode (10 mM $AgNO_3$ in CH_3CN). The cell was enclosed in a Faraday cage with a picoamp booster connected to the electrochemical analyzer. All experiments were done at room temperature and results are recorded at scan rates of 100 mV/s. All sets of experiments were immediately preceded by a

verification of the voltammetric properties of the ferrocene/ferrocenium$^+$ couple, which was used as a reference.

pK_a Determination. The sulfenic acid **1.31** was synthesized and purified using the methods described in Chapter 2.3 and stored under nitrogen at -35°C between experiments. *tert*-Butylhydroperoxide (5.5 M solution in pentanes) and NaOH were obtained from Sigma-Aldrich. HPLC grade acetonitrile and Milli-Q water were deoxygenated for a few hours prior to use. Titrations were conducted using a Metrohm 798 MPT Titrino autotitrator. NaOH solutions were prepared in Milli-Q water and deoxygenated for a few hours before use. The base solution was maintained oxygen free by a blanket of Argon. 1 mL of N/50 HCl was combined with 19 mL water to make up a 20 mM solution of HCl into which the NaOH solution was titrated to neutral pH so that its exact concentration could be determined.

For the experiments performed, the concentration of NaOH was found to be 19 mM. Samples were made up as 20 mL of 1 mM **1.31** (or *tert*-butylhydroperoxide) in 80:20 (v:v) CH_3CN/H_2O and were added to an Argon purged cell via syringe and maintained oxygen free by a blanket of Argon. Measurements were taken with an Accument Electrode microprobe and referenced to Ag/Ag^+. The pH in 4:1 (v:v) CH_3CN/H_2O was obtained by adding 0.897 to the measured value as suggested in reference.[131] The slope of the line was linearly interpelated to 0.5 eqivalents of **1.31** (i.e. at 0.53 mL of 19 mM NaOH solution), such that when half of **1.31** was neutralized pH=pK_a.

*k_{inh} Determination by naphthylperester clock method***.** The sulfenic acid **1.31** was prepared and purified using methods described in Chapter 2.3 and stored under nitrogen at -35°C between experiments. The naphthyl perester clock was synthesized according to unpublished methods by

the Pratt lab[125] and stored in the absence of light at -35°C. HPLC grade chlorobenzene and triphenylphosphine were obtained from sigma-aldrich.

Solutions made of sulfenic acid **1.31** (10-100 mM) and naphthyl perester **3.18** (15 mM) in chlorobenzene were made up in GC vials and diluted to 100 μL. Samples were incubated at 37°C overnight, quenched with 50 μL of 1.0 M PPh_3 and diluted to 1.8 mL with benzene. The samples were analyzed by GC as the conjugated aldehyde, non-conjugated ketone, conjugated and non-conjugated alcohol. k_{inh} was determined according to Equation 3.24.

k_{inh} Determination by inhibited autoxidation experiments. Experiment performed according to the experimental details in the literature by Luca Valgimigli.[29,137]

General Procedures for 9-triptycenehydroperoxide (**3.17**). All reagents were obtained from commercial sources and used without purification unless specified. Anhydrous dioxane was purchased from Sigma-Aldrich and distilled from benzophenone ketyl immediately prior to use. Dry toluene and dichloromethane were obtained from a PureSolv solvent still system. Column chromatography was performed using flash silica gel (60Å 40-63 μm, 500 m^2/g). ^1H NMR and ^{13}C NMR were obtained on 300 and 400 MHz spectrometers at 298 K and referenced to CDCl3 (δ 7.26 ppm and 77.36 ppm, respectively).

9-Anthryl acetate (**3.14**). Anthrone (3.34 g, 17.2 mmol) was dissolved in collidine (22.4 mL, 0.17 mol) and acetic anhydride (5.47 mL, 57.9 mmol) and refluxed under nitrogen for 4 hours. The reaction was cooled to room temperature, poured into 140 g of ice and quenched with 24.6 mL concentrated HCl. The crude product was recrystallized from ethanol to form 9-anthryl acetate (4.1 g, 79%). ^1H NMR ($CDCl_3$) δ 2.64 (s, 3 H, OAc), 7.46-7.53 (m, 4 H, aromatic), 7.94 (d,

J=8.41, 2H, aromatic), 8.02 (d, J=7.58, 2 H, aromatic), 8.38 (s, 1 H, 10-C). Data in accordance with the literature.[138]

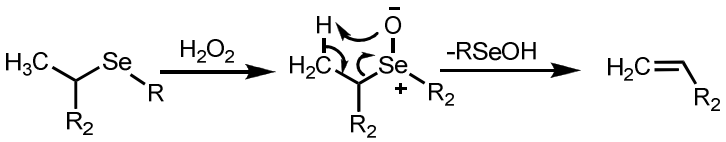
9-Triptycyl acetate (**3.15**). Reaction performed as 9-(*tert*-butylthio)triptycene only using 9-anthryl acetate (3.03 g, 22.2 mmol) as the benzyne acceptor. The product was purified by flash chromatography using a hexanes/ethyl acetate gradient (product came out in 5% ethyl acetate:hexanes) to afford pure 9-triptycyl acetate (362 mg, 5%).^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3 H, OAc), 5.38 (s, 1 H, 10-C), 7.01-7.04 (m, 6 H, aromatic), 7.30-7.32 (m, 3 H), 7.38-7.40 (m, 3 H). Data in accordance with the literature.[139]

9-triptycyl alcohol (**3.16**). 9-triptycyl acetate (362 mg, 1.16 mmol) and KOH (1.24 g, 22.1mmol) were dissolved in ethanol (7.3 mL, 0.16 M) and heated to reflux for 3 hours. The reaction was then added to ice and extracted with DCM. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo to afford the crude product which was recrystallized from methanol to give pure 9-triptycyl alcohol (313.6 mg, 37%).^{1}H NMR ($CDCl_3$) 5.40 (s, 1 H, 10-C), 7.05 (dtd, J_1=1.16, J_2=7.50, J_3=24.0, 6H, aromatic), 7.38 (d, J=7.11, 3 H, aromatic), 7.54 (d, J= 6.87, 1 H, aromatic). Data in accordance with the literature.[139]

Appendix A
Selenenic Acids: Preliminary Work

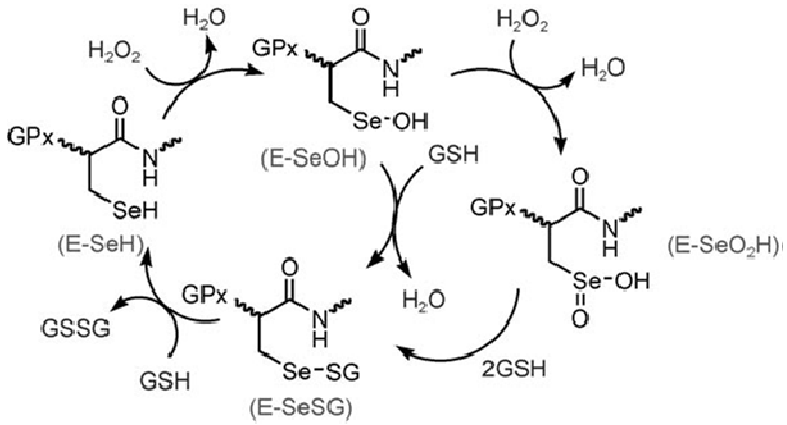
A1 Introduction

In addition to our interest in the role of sulfenic acids in the antioxidant activity in plant-derived thiosulfinates, such as allicin (from garlic), and as important intermediates in cellular processes, the analogous selenenic acids are also of interest. Indeed, selenenic acids are well-recognized as important intermediates in organic and biochemical reactions. For example, the *syn*-elimination of selenoxides is an important organic reaction for preparing alkenes (Scheme A-1).



Scheme A-1. Cope elimination of a selenoxide to form an α,β-unsaturated compound.

Furthermore, selenenic acids derived from selenocysteine (the so-called 21st amino acid), are important in enzymatic processes, and possibly, cell-signalling. The archetypical example, glutathione peroxidase (GPx), protects various organisms from oxidative damage by catalyzing the reduction of harmful peroxides in the presence of glutathione (GSH).[140] The selenenic acid intermediate (E-SeOH) is formed upon oxidation of the catalytically active selenol (E-SeH) by hydrogen peroxide. The selenenic acid then reacts with a thiol containing cofactor (GSH) to generate the key intermediate selenenyl sulfide (E-SeSG). This intermediate is subsequently attacked by a second GSH to regenerate the active site selenol and the cofactor is released in its oxidized form, GSSG (Scheme A-2).[140]



Scheme A-2. Proposed catalytic mechanism of GPx, involving selenol, selenenyl sulfide, and selenenic acid intermediates. In the absence of thiols, the selenenic acid undergoes overoxidation to produce the seleninic acid species.

Many organoselenium compounds (e.g. Ebselen,[141-143] benzoselenazolinones,[144] selenenamides,[145] diaryl diselenides,[146] and the semisynthetic enzyme selenosubtilisin[147,148]) have interesting biological activities, which are often consistent with antioxidant properties, prompting the supposition that they act as glutathione peroxidase mimics; reducing hydroperoxides that may otherwise decompose to form toxic byproducts and/or reactive oxygen species that can cause further damage to the cell. Another possibility may be through the intervention of selenenic acids, formed from elimination of selenoxides. To the best of our knowledge, this has neither been suggested, nor explored. It is also interesting from a fundamental perspective to consider the properties and reactivities of selenenic acids as compared to sulfenic acids and hydroperoxides, but no physicochemical or kinetic data are available.

For initial comparison, the O-H BDE's for some selected selenenic acids were calculated and compared to the analogous sulfenic acids. As shown in Table A-1, the BDEs for selenenic acids are significantly higher than those of the sulfenic acids; this may simply be because the selenium atom does not stabilize the radical as well as the sulfur atom, owing to the much longer

Se-O bond in selenenyl radicals as compared to the S-O bond in sulfinyl radicals (i.e. for the sulfinyl radical the unpaired electron is delocalized 50:50 on the sulfur and oxygen atoms while for the seleninyl radical the unpaired electron is delocalized 70:30, similar to a peroxyl radical).

Table A-1. Calculated O-H BDEs (in kcal mol^{-1}) for selected selenenic acids compared to analogous sulfenic acids using CBS-QB3 level of theory.

Selenenic Acid	O-H BDE	Sulfenic Acid	O-H BDE
HSeO-H	86.5	HSO-H	73.1
MeSeO-H	81.9	MeSO-H	68.4

Using computational methods, the rate at which alkylselenenic acids react with peroxyl radicals was also predicted. Similar to the sulfenic acid, the cisoid transition state between the selenenic acid and peroxyl radical was found to be lower in energy than the transoid alternative (Figure A-1). In addition, the energy of the cisoid transition state was computed to be lower in energy than the separated reactants, indicating that despite its much higher BDE, selenenic acids may still react with peroxyl radicals at diffusion controlled rates. This can be rationalized on the basis of the transition states for these reactions, which are characterized by substantial orbital overlap between the internal oxygen atom on the peroxyl radical and the Se atom of the selenenic acid, thereby facilitating a proton-coupled electron transfer reaction.

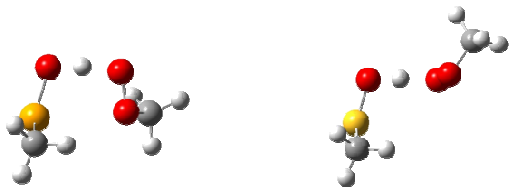
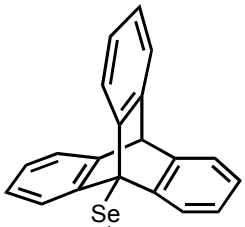


Figure A-1. Cisoid and Transoid transition state structures for the MeSeOH/˙OOMe reaction.

Table A-2. Activation energies (in kcal mol^{-1}) for H-atom transfers between methylselenenic (and sulfenic) acids and peroxyl radicals using CBS-QB3 level of theory.

Selenenic /Sulfenic Acid	E_a (cisoid TS)	E_a (transoid TS)
MeSeO-H/˙OOMe	3.0	15.1
MeSO-H/˙OOMe	4.6	11.0

We sought to prepare compound **A1** in a similar manner to **1.31** (see Chapter 2) such that its redox chemistry and reactivity could be explored as we have done for **1.31** as detailed previously.

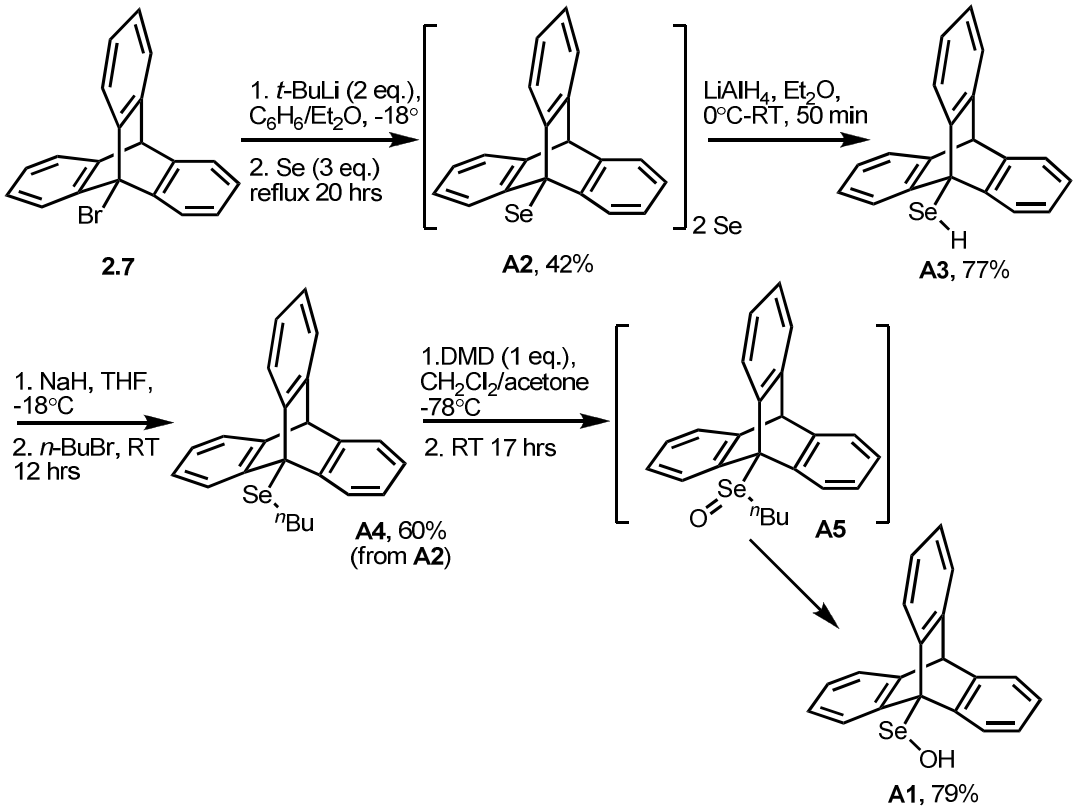


A1

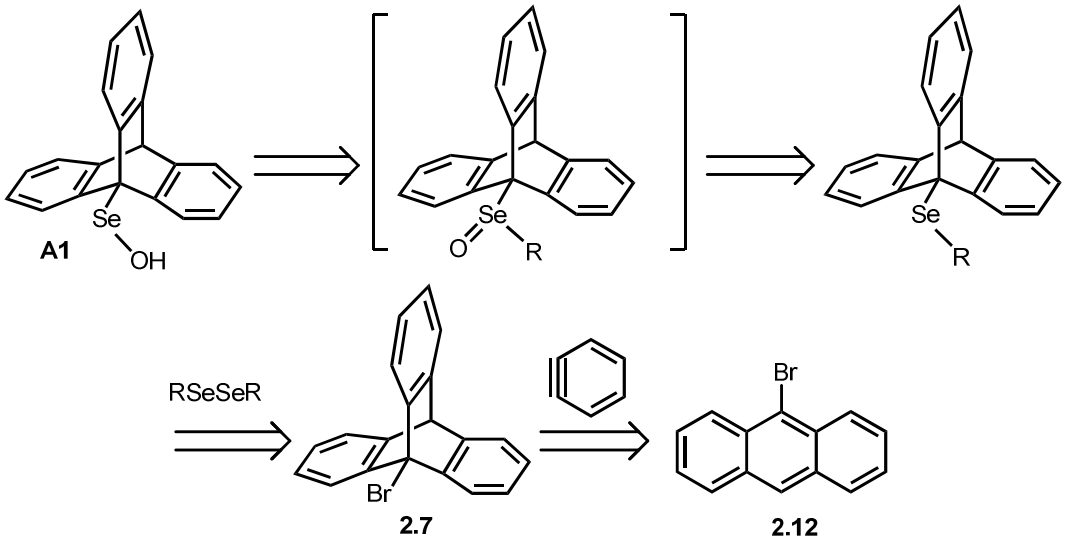
A2 Synthetic Approach towards 9-Triptycene Selenenic Acid

Despite our eventual success in synthesizing 9-tripycene sulfenic acid, less time was spent on preparing the analogous selenenic acid and thus the optimization of its preparation was comparatively much less thorough. However, we were able to make some progress towards the end product (**A1**) and further physiochemical studies may be pursued at a later date.

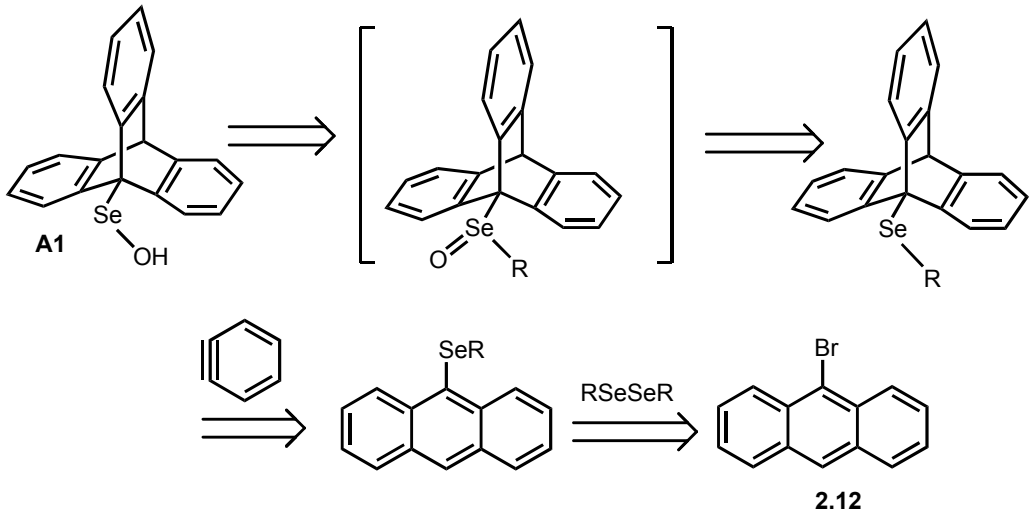
The literature preparation of 9-triptyceneselenenic acid is shown in Scheme A-3. Although seemingly this route would be attempted first, we opted to use our own route which was inspired by the synthetic work towards 9-triptycenesulfenic acid. Scheme A-4 illustrates the retro-synthetic analysis using our method towards 9-triptyceneselenenic acid from 9-bromotriptycene. From Chapter 2.2.3, the reaction between 1-triptycyllithium and various disulfides proved to be quite useless, however, due to the increased length of the Se-Se bond in the diselenide in comparison to the S-S bond in the disulfide, this reaction may actually occur more readily. In fact other groups have shown that 9-anthryllithium can be quenched with diselenides, al beit in low yields.[149] Thus, our third approach was starting with 9-bromoanthracene and quenching with a diselenide, followed by the triptycene backbone installation (Scheme A-5). Basically this is a very similar pathway to Scheme A-4 except that the first two steps are reversed.



Scheme A-3. Literature preparation of 9-triptyceneselenenic acid from 9-bromotriptycene.



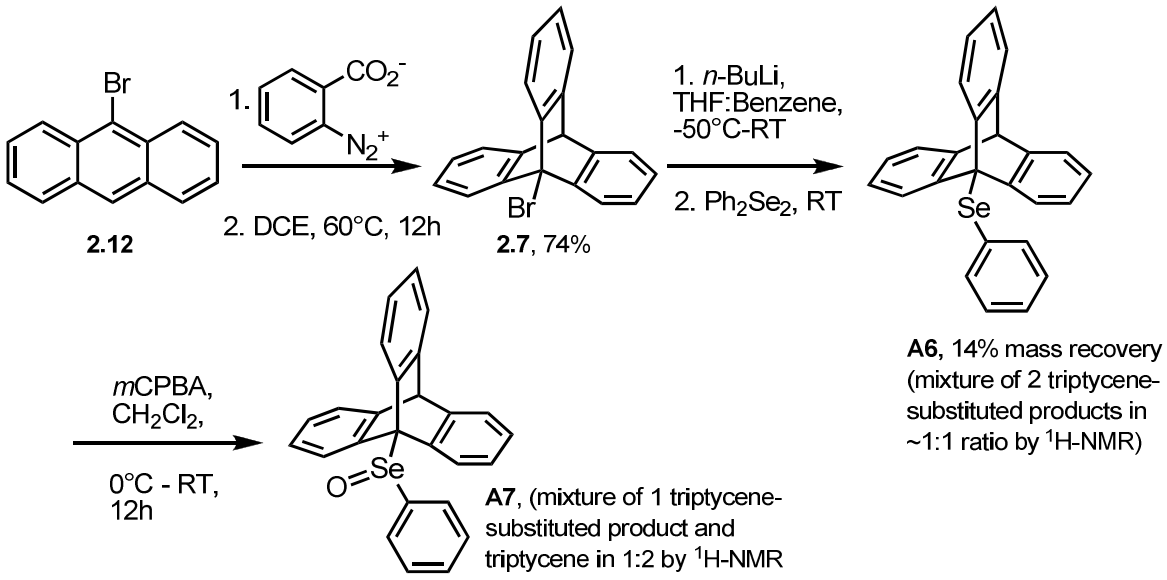
Scheme A-4. Synthetic approach to 9-triptyceneselenenic acid via lithium-halogen exchange of 9-bromotriptycene followed by diselenide quenching.



Scheme A-5. Synthetic approach to 9-triptyceneselenenic acid via lithium-halogen exchange on 9-bromoantrhacene followed by diselenide quenching.

A3 Results and Discussion

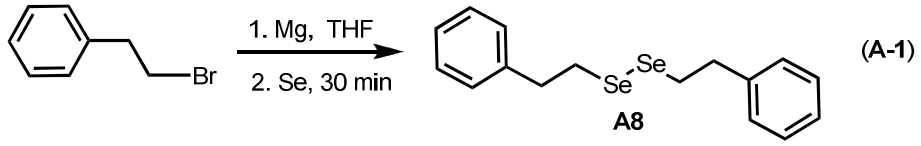
For our first experiments, we tested the lithium-halogen exchange on 9-bromotriptycene and subsequently quenched with a commercially available diselenide, diphenyldiselenide. Eventually, the corresponding selenenic acid cannot be prepared from the phenylselenide (due to lack of an eliminable β-hydrogen) but at least we can discover if the chemistry works without wasting a diselenide that had to be prepared manually. Scheme A-6 summarizes the work done towards preparation of the phenylselenoxide.



Scheme A-6. Summary of work towards preparation of 9-triptycenephenylselenoxide by lithium-halogen exchange on 9-bromotriptycene followed by quenching with diphenyldiselenide.

Since we had evidence that the lithium-halogen exchange followed by diselenide quenching would work successfully (or at least that a new 9-substituted triptycene compound had been prepared), it was decided to move on and prepare the appropriate diselenide with a β-

hydrogen so that ultimately we could actually make the desired selenenic acid. We sought out to synthesize two diselenides, di-*tert*-butyldiselenide and bis(2-phenylethyl)diselenide and found two potentially useful routes towards these compounds in the literature.[150,151] The method by Block *et al.* seemed to work the best which involved making a Grignard reagent from the alkylbromide and adding in Se powder slowly (Equation A-1). For preparation of the phenylethyl diselenide, the ethyl protons shifted considerably upfield in the ^{1}H NMR from two triplets at 3.57 and 3.17 ppm for the bromide to a triplet at 2.68 and a multiplet at 1.72 ppm in the diselenide which is consistent with what would be expected. Although the yield was fairly low ~>20%, we are quite confident this method is reliable for making diselenides and can be optimized with more effort. Attempts to make the di-*tert*-butyldiselenide were less successful and only small amounts of impure product were isolated.



(A-1)

Although the progress towards the desired 9-triptyceneselenenic acid is quite preliminary, some useful experiments have been performed. First, we believe that it is possible to form an alkylselenide via diselenide quenching of 1-triptycyllithium, contrary to what we found with the corresponding reaction with disulfides (see Chapter 2.2.3). According to ^{1}H-NMR, after purification to one spot by TLC, the product was a mixture of two compounds corresponding to two bridgehead protons with chemical shifts that did not match triptycene. Presumably these could be 9-phenylselenyltriptycene and the corresponding selenenoxide. A diselenide is in fact

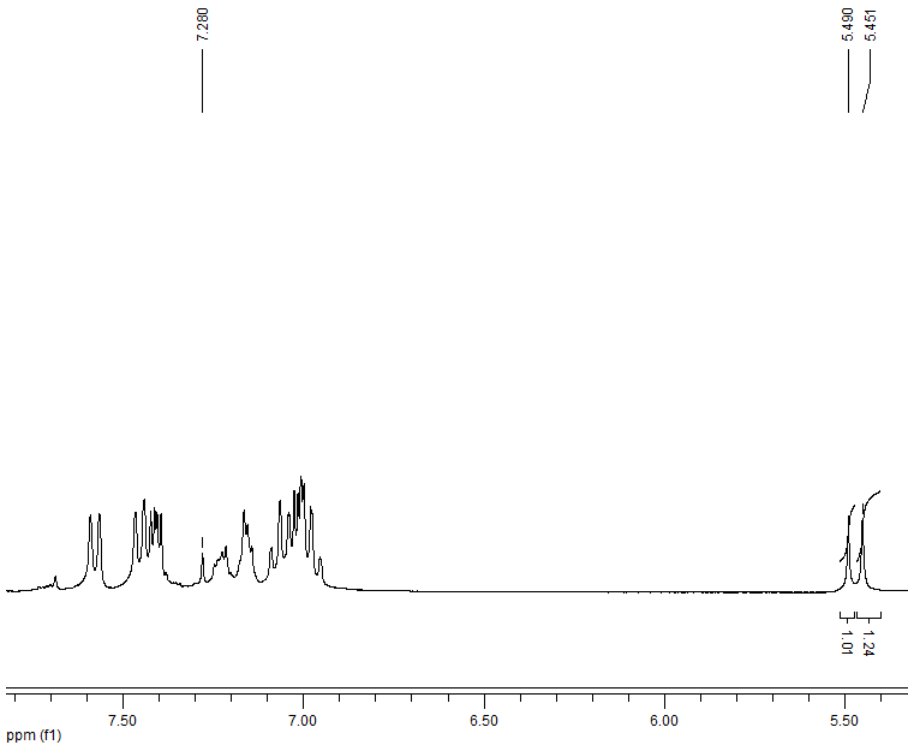
less electrophilic than a disulfide, however, the longer Se-Se bond may allow for approach by 1-triptycyllithium. Because of the low electrophilicity of the diselenide, we again should not rule out that this reaction may go by a radical mechanism. To test this theory, this reaction should be performed in an inert solvent (i.e. α,α,α-trifluorotoluene) to see if the yield can be improved upon. If this test is successful, the low mass recovery obtained is likely due to abstraction of a H-atom from THF by 1-triptycyllithium rather than low electrophilicity of the diselenide.

Second, it would seem that it is possible to oxidize the triptycylselenide with *m*CPBA to form the corresponding selenoxide and hopefully, with the presence of a β-proton, the selenenic acid can be formed. The ^{1}H-NMR after oxidation and chromatography shows a mixture containing two triptycyl compounds corresponding to one of the bridgehead protons from the starting mixture and triptycene. Finally, a reliable route towards making diselenides has been established, although optimization needs to be executed.

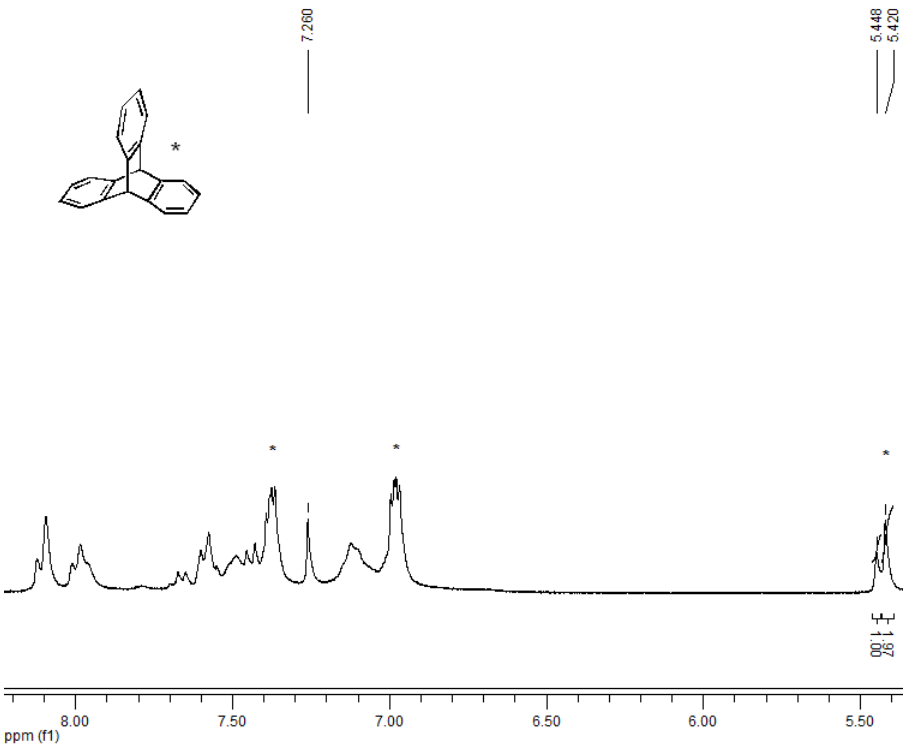
A4 Experimental Procedures

General Procedures. All reagents were obtained from commercial sources and used without purification unless specified. Magnesium turnings were washed with dilute HCl followed by ethanol and ether and dried over P_2O_5 under vacuum overnight before use. Dry THF was obtained from a PureSolv solvent still system. Column chromatography was performed using flash silica gel (60Å 40-63 μm, 500 m^2/g). ^{1}H NMR and ^{13}C NMR were obtained on 300 and 400 MHz spectrometers at 298 K and referenced to CDCl3 (δ 7.26 ppm and 77.36 ppm, respectively).

Phenylselenyltriptycene (**A6**). To a solution of 9-bromotriptycene (**2.7**, preparation in Chapter 2.3, 100 mg, 0.30 mmol) in 2:1 THF:Benzene (18 mL, 0.017 M) cooled to -50°C was added *n*-BuLi as a 1.24 M solution in hexanes (0.29 mL, 0.36 mmol) slowly. The reaction was stirred at -50°C for 30 minutes and one hour after removal of the cold bath. Diphenyldiselenide was added as a concentrated solution in benzene over 10-15 minutes and the reaction was stirred at room temperature overnight. The reaction was then quenched with H_2O, extracted with ether. The combined ether extracts washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The crude product was subjected to flash chromatography using 20% DCM:Hexanes as the eluent to afford phenylselenyltriptycene in 14% mass recovery as a mixture containing two triptycene substituted products in a 1:1.24 ratio by ^{1}H NMR, which were carried on in the subsequent step. ^{1}H NMR ($CDCl_3$) See below.



Phenyl-triptycenyl selenoxide (**A7**) To an ice-cooled solution of phenylselenyltriptycene (as a 2:1 mixture to triptycene, 11 mg, 0.027 mmol) in DCM (0.63 mL, 0.043 M) was added a 0.086 M solution of 77% *m*CPBA (6 mg, 0.027 mmol) dropwise. The reaction was stirred at room temperature overnight and small spatula tips of *m*CPBA were added over 2 hours until a new product spot was seen. The reaction was then poured into a mixture of DCM and saturated $NaHCO_3$ and extracted three times with DCM. The combined organic extracts were washed three times with saturated $NaHCO_3$ and brine followed by drying over $MgSO_4$ and concentrating in vacuo to afford a new substituted triptycene compound as a mixture with triptycene in a 1:2 ratio. ^1H NMR ($CDCl_3$) See below.



Bis(2-phenylethyl)diselenide (**A8**). To a three-neck round bottom flask equipped with an inlet, and containing Mg turnings (394 mg, 16.2 mmol) and dry THF (8.1 mL, 2 M) under a blanket of nitrogen was added (2-phenylethyl)bromide (2.19 mL, 16.2 mmol). The reaction was heated

slightly until all the Mg had gone into solution and then Se powder (1.15 g, 16.2 mmol) was added in small portions over approximately 30 minutes. The reaction was stirred at room temperature overnight then cooled to 0°C and quenched with aqueous NH_4Cl (8.1 mL), and aqueous KI_3, prepared by combining KI (26 g, 104 mmol) and I_2 (4.11 g, 16.2 mmol) in 13.5 mL H_2O. The mixture was then extracted with ether and the combined organic extracts were washed with 10% sodium thiosulfate and NH_4Cl solution and dried over $MgSO_4$. The solvent was concentrated in vacuo and the product was purified by flash chromatography (eluent: hexanes) to afford bis(2-phenylethyl)diselenide. ^{1}H NMR ($CDCl_3$) δ 1.70-1.73 (m, 4 H, ethyl), 2.68 (t, J=6.87, 4H, ethyl), 7.29-7.33 (m, 6H, phenyl), 7.21 (dd, J=5.12, J=7.08, 4H, phenyl); ^{13}C NMR ($CDCl_3$) δ 31.4, 36.2 (Me C's of ethyl), 126.0 (*para*-C's of phenyl), 128.6, 128.8 (*ortho*- and *para*- C's of phenyl), 142.9 (quaternary C's of phenyl).Data is in accordance with the literature except in the ^{1}H NMR the shifts for the ethyl protons are at 3.06 and 3.18 ppm.[152]

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