ABSTRACT

DETECTION OF REACTIVE INTERMEDIATES FROM QUINOL ESTERS AND O-ARYL-N-METHANESULFONYL HYDROXYLAMINE

by Yue-Ting Wang

The aryloxenium ion 1 has been invoked to explain the products of synthetically useful electrochemical and chemical oxidations of phenols and oxidative phenolic couplings. Until recently mechanistic studies of 1 were limited. Prior to our investigations only a few highly stabilized aryloxenium ions were observed, but they have little in common with those proposed reactive intermediates. Focusing on the generation of less stabilized 1, this dissertation consists of three related projects.

Chapter 2, Decomposition of 4-Acetoxy-4-(4'-methylphenyl)-2,5-cyclohexadienone 2b addresses indirect and direct detection of 4'-methyl-4-biphenyloxyenium ion 1b during hydrolysis and photolysis of 2b. Indirect detection was accomplished by kinetic and product studies of the hydrolysis of 2b in the presence and absence of N3-. Attempted direct detection via laser flash photolysis (LFP) led to the observation of two transient species in aqueous buffer. They were identified as 1b with λmax 460 nm and aryloxy radical 5b with λmax 360 nm. The identity of 1b was confirmed by its reactivity with N3- and 5b was confirmed by its biphasic decay kinetics caused by reversible dimerization.

Chapter 3, Decomposition of O-(4-(4'-methylphenyl)phenyl)-N-methanesulfonylhydroxylamine 13b addresses kinetic studies, temperature studies, and product analyses of the hydrolysis of 13b over a wide range of pH. Oxenium ion 1b was generated during the hydrolysis of 13b, but it was not the only path for the hydrolysis reaction. Other pathways, including concerted rearrangement and base-catalyzed α-elimination, were demonstrated. LFP of 13b did not generate 1b but 5b.
Chapter 4, *Decomposition of 4-Acetoxy-4-(benzothiazol-2-yl)-2,5-cyclohexadien-1-one* 19 addresses studies of the decomposition of antitumor agent 4-(benzothiazol-2-yl)-4-hydroxy-2,5-cyclohexadien-1-one 20 and its putative metabolite quinol ester 19 in aqueous buffers. This is a preliminary test of our hypothesis that aryloxenium ion 21 is the reactive intermediate involved in the decomposition of 19. Evidence for the intermediacy of 21 for hydrolysis of 19 were obtained in kinetic studies and azide trapping experiments performed on 19 and 20. These kinetic and trapping results are consistent with what we observed for other quinol esters that generate aryloxenium ions.
DETECTION OF REACTIVE INTERMEDIATES FROM QUINOL ESTERS AND O-ARYL-N-METHANESULFONYL HYDROXYLAMINE

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</tr>
<tr>
<td>A</td>
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<td>B</td>
<td>Arylnitrenium ion</td>
</tr>
<tr>
<td>C</td>
<td>Arylcarbene</td>
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<td>4'-Methylbiphenyloxenium ion</td>
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</tbody>
</table>
$N$-(4-hydroxy-4'-methylbiphenyl-3-yl)methanesulfonamide

$N$-methoxymethanesulfonamide

4-(benzothiazol-2-yl)-4-hydroxy-2,5-cyclohexadien-1-one

4-(benzothiazol-2-yl)phenol

4-(6-azidobenzothiazol-2-yl)phenol

$N$-(benzothiazol-2-yl)-$O$-acetylhydroxylamine

methanesulfonylnitrene

methanesulfonamide

4-acetoxy-4-(benzothiazol-2-yl)-2,5-cyclohexadien-1-one

4-(benzothiazol-2-yl)phenyloxenium ion
2-(4-aminophenyl)benzothiazole

4-(benzothiazol-2-yl)phenyl nitrenium ion

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CHAPTER 1

Introduction
The aryloxenium ion 1 (Figure 1.1), in one of its canonical forms, is an oxygen-centered cation with a sextet of electrons on oxygen and one bond from oxygen to an aryl group. This structure (I) is in resonance with carbocation resonance structures (II) and (III) that are potentially more stable. Historically terms such as “phenoxyenium ion” and “phenoxyonium cation” have been used to describe this type of species, all implying that a positive charge might be residing on the oxygen atom. Aryloxenium ions are isoelectronic with arylcarbenium and arylnitrenium ions (Figure 1.2, A and B), as well as with neutral carbenes and nitrenes (Figure 1.2, C and D). These species have been known for a long time and are well studied. Compared to this, until recently the mechanistic studies of 1 were fairly limited.

Figure 1.1 Resonance structures of aryloxenium ion 1.

Figure 1.2 Carbenium and nitrenium ions, neutral carbenes and nitrenes.

This situation is surprising since 1 has been widely invoked to explain certain synthetically useful reactions that lead to the formation of new carbon-carbon bonds or carbon-oxygen bonds. The most discussed reaction categories that possibly involve 1 as the reactive intermediate are two electron electrochemical and chemical oxidations of phenols (particularly with hypervalent iodine compounds such as phenyliodonium dicarboxylates (PhI(OCOR)₂) in chemical oxidation).¹⁻³² Electroanalytic investigations revealed that oxenium ion 1 may be obtained from
the starting phenol via two routes depending on the presence or absence of base (Scheme 1.1).6,7,11 These oxenium ions, especially those generated from sterically hindered phenols (Figure 1.3), reported by Rieker and co-workers, can react with O-nucleophiles (e.g., sugar OH-group, carboxyl OH-groups in amino acids)8,9 or NH-nucleophiles (amino acid derivatives)10 to give cyclohexadienyl-protected nucleophiles. It was also claimed that the 4-acyloxy substituted aryloxenium ions can transfer the acyl group to nucleophiles.11-13 A synthesis of dipeptides and glycoamino acids based on this principle was developed by Rieker et al.11-13

**SCHEME 1.1.** Two routes for electrochemical oxidation of phenols.11

![Scheme 1.1](image)

**Figure 1.3** Anodically produced oxenium ions used for protection of O- or N-nucleophiles.11

Swenton et al. used 4-(2-alkenylphenyl)phenols as model systems to investigate their electrochemical oxidation reactions.14-16 They proposed that the intramolecular cyclization product spirocyclic 2,5-cyclohexadienones arise from trapping of the oxenium ion E by the alkenyl side chain. (Scheme 1.2)
SCHEME 1.2. Electrochemical oxidation of 4-(2-alkenylphenyl)phenols.

Chemical phenolic oxidations and oxidative couplings in which hypervalent iodine compounds have been used extensively, were thought to give rise to the generation of aryloxenium ions as well.\textsuperscript{18-27} As part of the work mentioned above, 4-(2-alkenylphenyl)phenols were treated with phenyliodonium diacetate (PIDA) and the same spiro dienones were produced possibly through the intermediacy of aryloxenium ion E.\textsuperscript{16} In fact in many biomimetic syntheses of natural compounds containing a spirocycle framework, the generation of aryloxenium ion was considered to be the key step. In the oxidation of tyrosine by two-electron oxidants such as NBS or PIDA, aryloxenium ion F was proposed as the intermediate that cyclizes to yield spiro lactones (Scheme 1.3).\textsuperscript{24}

SCHEME 1.3. Oxidation of tyrosine derivatives.\textsuperscript{24}

In the preparation of cularine-type alkaloids, Rodrigues and Abramovitch \textit{et al.} suggested that an intramolecular cyclization involving aryloxenium ion G resulted in the formation of the new C-O bond in the target compound (Scheme 1.4).\textsuperscript{25}
Regarding the synthesis of natural alkaloids bearing a spirocyclohexadienone moiety, Honda et al. developed a facile synthetic procedure by employing an oxidative enamide-phenol coupling of an isoquinoline derivative with PIDA as the key step for the synthesis of (±)-stepharine and its derivative pronucipherine (Scheme 1.5), and the first total synthesis of (±)-annosqualine (Scheme 1.6). In both cases aryloxenium ions H and I were proposed as the important intermediate that leads to the final spri dienone core.

**SCHEME 1.4.** Synthesis of cularine alkaloids.25

![Scheme 1.4](image)

**SCHEME 1.5.** Key step of the synthesis of proaporphine alkaloids (±)-stepharine and (±)-pronucipherine.26

![Scheme 1.5](image)
SCHEME 1.6. Key step of the synthesis of isoquinoline alkaloid (±)-annosqualine.27

In addition to being involved in natural product syntheses, 1 was also proposed to be responsible for the formation of commercially useful polymers.28-32 For example, the oxidative coupling of 2,6-dimethylphenol (DMP) catalyzed by copper-amine complexes ultimately yields the linear poly(phenylene ether) (PPE) as an important engineering plastic. Baesjou et al suggested a mechanism where a nucleophilic attack of a phenol or phenolate on an aryloxenium ion J at the para-carbon leads to the polymerization of DMP (Scheme 1.7).30,31

SCHEME 1.7. Oxidative coupling of DMP to form PPE.30,31

However, there is controversy about the involvement of 1 in those reactions mentioned above. Many of the electrochemical reactions were shown to be two-electron processes by coulometry, but that does not require an oxenium ion intermediate.1,2,14-17 Evidence for these ions is either indirect (lack of chiral induction by chiral iodonium compounds, correlation of product structures with calculated charge distributions of the cations in the example presented in Scheme 1.7) or altogether lacking: in those natural product syntheses examples the generation of aryloxenium ions were only conceived pathways without any support from actual mechanistic
studies. In many cases alternative mechanisms such as radical or concerted processes cannot be excluded.

There are a few examples of stable or isolatable aryloxenium ions. The lifetimes of electrochemically generated aryloxenium ion K and L, and the metal-stabilized cation M (Figure 1.4) are long enough to allow isolation and characterization by electrochemical or spectroscopic methods.

**Figure 1.4** Stable isolatable aryloxenium ions (one resonance structure displayed for each species).

Another species in the same category is generated from chemical or electrochemical oxidation of α-tocopherol, the most active component of Vitamin E. Webster and co-workers have demonstrated that aryloxenium ion N (Figure 1.5), derived from the naturally occurring compound Vitamin E, is stable in CH$_3$CN for at least several hours and leads to 9-hydroxy-α-tocopherone in the presence of water.

**Figure 1.5** Tocopherol and the stable aryloxenium ion α-TO$^+$ (N)
But, these highly stabilized aryloxenium ions have little in common with the proposed reactive intermediates. They do not provide enough information about the intermediacy of 1 in term of its generation, reactivity and selectivity.

Reliable experimental information regarding any reactive intermediate requires a method for generating the species in question. The major hindrance to detailed mechanistic study of 1 is the lack of available precursors that can be used to generate these intermediates under mild solvolysis or photolysis conditions. Abramovitch and co-workers demonstrated that N-(aryloxy)pyridinium tetrafluoroborates decompose at 180-200 °C in anisole and benzonitrile by apparent nucleophilic attack of solvent on O or C of the aryloxy portion of the pyridinium salt (Scheme 1.8).37-41 If Y is electron withdrawing (p-NO₂, p-CN) phenols and diphenyl ethers predominate;37 if Y is electron donating biphenyl products predominates.40 The authors concluded that these reactions occurred through 1 because product distributions are independent of the substituents R on the pyridinium moiety and aryloxy radicals made by other methods did not generate these products.38,40 The phenol was attributed to hydrogen scavenging by a possible ground-state triplet ion.37

**SCHEME 1.8.** Thermolysis of aryloxypyrindinium salts.

However, Okamoto et al. have shown that N-tosyl-O-arylhydroxylamines react with benzene at room temperature in the presence of trifluoroacetic acid/trifluoromethanesulfonic acid mixtures to yield biphenyl derivatives.42-45 Even the p-NO₂ compound yielded no phenol or diphenyl ether (Scheme 1.9).44,45 The reactions were attributed to 1 generated by acid catalyzed loss of tosylamide.44
SCHEME 1.9. Acid-catalyzed reaction of \( N \)-acyl-\( O \)-aryloxyhydroxylamines with benzene.\(^{44}\)

The differences in the products of aryloxypyridinium salts in Scheme 1.8 and \( O \)-arylhydroxylamines in Scheme 1.9 were attributed to different reaction conditions.\(^{44}\) Subsequent low level \textit{ab initio} calculations suggested that the singlet is the ground state for unsubstituted aryloxenium ion (\( Y = H \)) by \textit{ca.} 30 kcal/mol, bringing into doubt the proposal of a ground-state triplet ion.\(^{41}\) In another investigation into the reactions of \( N \)-phenoxyphthalimide derivatives in benzene with \( \mathrm{AlCl}_3 \) catalyst, Miyazawa \textit{et al.} reported results similar to those observed by Okamoto for \( N \)-aryloxyhydroxylamines in benzene in the presence of acid.\(^{46}\) A curious result of these studies is the low yield of products of attack on the \textit{para}-carbon of the apparent \( 1 \), while attack on the \textit{para}-carbon dominates for the same or similar apparent intermediates derived from phenol oxidation.\(^{11,12,14-16,23}\)

Hegarty and Keogh have demonstrated the generation of a 2,4,6-trialkyl-substituted \( 1 \) from the bromo derivative (Scheme 1.10) in aqueous solution by common ion rate depression and \( \mathrm{N}_3^- \) trapping results.\(^{47}\) The addition of \( \mathrm{Br}^- \) decreases the solvolysis rate while the addition of \( \mathrm{N}_3^- \) changes product distribution but does not affect the reaction rate. Cation \( \text{O} \) has an estimated lifetime in water of 0.55 \( \mu \text{s} \) at 20 °C and the ratio of \( k_{\text{az}}/k_s \) which represents the azide/solvent selectivity of \( \text{O} \), is 2800 M\(^{-1}\), indicating the high selectivity and low reactivity of \( \text{O} \). Our data (in Chapter 2) suggest that the lifetime of this ion is influenced by steric hindrance to nucleophilic attack. In contrast to the findings of Abramovitch and Okamoto, the predominant reaction of both the trimethyl and tri-\textit{tert-}Bu oxenium ion is the attack by nucleophiles at the \textit{para}-position as observed during phenol oxidation.\(^{47}\)
Except for Hegarty’s ions and the stabilized species mentioned above, it is entirely possible that \(1\) has not been generated in any of the cited cases. Insufficient information exists to determine which examples are genuine and how substituents affect the chemistry of \(1\).

There was only one example of the possible photochemical generation of an aryloxenium ion during the photolysis of 1,2-benzisoxazoles in 96% sulfuric acid. The intermediacy of the ion was inferred from reaction product structures. Photochemical generation of \(1\) was largely unexplored before our recent work.

The chemistry of carbenium ion \(A\) and nitrenium ion \(B\) that are isoelectronic with \(1\) is well understood. There are differences in the effects of substituents on stability of these ions, and on the regio-selectivity of reactions with nucleophiles. For example, \(\pi\)-donors are far more effective at stabilizing \(B\) than \(A\), and hard base nucleophiles react with \(B\) at the \textit{ortho}-position and \textit{para}-position of the ring, rather than at the exocyclic position common to \(A\). Unlike the arylcarbenium ion \(A\), the species \(B\), \(C\), and \(D\) have low-lying triplet states because of the possible promotion of a nonbonded electron into the empty \(p\)-orbital. Experiments and calculations have shown that the triplet state of \(B\) (\(^3B\)) is likely not accessible in thermal reactions since for all but the most electron-withdrawing substituents it is at least 20 kcal/mol above the ground state singlet. \(^3B\) has not been directly observed but there is evidence for its formation during triplet sensitized photolysis experiments. It apparently gives rise to the \(H\) atom abstraction product, the corresponding amine, although nucleophilic aromatic substitution products are also formed in these experiments. The yield of amine is reduced by triplet quenchers, and increased by \(H\) atom donors. It appears that in all but one case with multiple
electron withdrawing substituents the singlet is the ground state for B.\(^6\) \(^3\)C and \(^3\)D are more accessible because the unsubstituted species (Y = H, R = H) have triplet ground states, although triplet and singlet phenylcarbene are spin equilibrated (high-level calculations predicted \(\Delta E_{ST} = 4\) kcal/mol).\(^6\) For phenylcarbene the chemistry of the less reactive triplet is only dominant at –196 °C.\(^6\)\(^2\)\(^4\)\(^4\) There were insufficient data available for 1 to illustrate its ground spin state and make meaningful comparisons to the species discussed above before our recent investigations.

A desire to develop reliable methodologies to generate aryloxenium ions 1, that are not highly stabilized by extensive delocalization or by steric hindrance, from promising precursors under mild conditions (ca. room temperature in organic/aqueous mixed solvents in the presence or absence of UV light) grew out of our own interest in reactive intermediate chemistry. With all the evidence at hand, particularly the inspiration from the precursor of Hegarty’s cation O\(^4\)\(^7\) and from the precursors of arylnitrenium ions,\(^6\)\(^5\)\(^6\)\(^6\) we narrowed down the choice of potential precursors to two types of compounds (Scheme 1.11), 2,5-cyclohexadienone derivatives 2 and \(O\)-arylhydroxylamine derivatives 13, and initiated a mechanistic study of the intermediacy of aryloxenium ions that may be generated via solvolysis or photolysis reactions.\(^6\)\(^7\)\(^6\)\(^9\)

**SCHEME 1.11.** Potential precursors for aryloxenium ions.

![Scheme 1.11](image)

The preliminary results were quite encouraging.\(^6\)\(^7\)\(^6\)\(^9\) Biphenyloxenium ion 1a was our first indirectly detected aryloxenium ion generated from hydrolysis of quinol ester 2a (Scheme 1.11).\(^6\)\(^7\) The assignment of 1a was made based on common ion rate depression \((k_{OAc}/k_s = (3.3 \pm 0.2) \text{ M}^{-1} \text{ for } 1a)\), azide trapping experiments, and \(^1^8\)O-labeling studies. The estimated lifetime of 1a \((1/k_s)\) is ca. 12 ns, considerably shorter than that of the related nitrenium ion 8a \((0.6 \mu\text{s at } 20\)
°C) but much longer than those of carbenium ions A1 and A2 (ca. 0.1 ns and 0.5 ns, respectively, in 1/1 THF/H2O at 20-25 °C) (Figure 1.6).49, 70-72

Figure 1.6 Nitrenium ion 8a, carbenium ions A1 and A2

SCHEME 1.12. Indirect detection of 1a from hydrolysis of 2a.

An examination of the decomposition of 2c also indicates the generation of oxenium ion 1c does occur but only partially governs the product distribution in the presence of N3⁻.73 There is a bimolecular substitution process competing with oxenium ion formation in this compound probably due to the more strongly inductively electron withdraving 4-(4'-bromophenyl) substituent of 2c.73

4-Acetoxy-4-methyl-2,5-cyclohexadien-1-one 2d was also synthesized and subjected to decomposition studies, but the expected ion 1d was not detected by those methods employed in the detection of 1a.67,68 Kinetic results show that 1d must be ca. 10⁴-fold less stable than 1a relative to their acetoxy precursors.67 As is the case of nitrenium ion 8 (8d is much less stable than 8a with a lifetime in H₂O that is 750-fold shorter at ca. 0.8 ns at 20 °C), 74,75 1 is significantly stabilized by π-donors. The results also show that substituent effects on oxenium ion stability can be quite different from those of carbenium ions. The difference in the lifetime of
1a and Hegarty’s species O (0.5 μs) suggest that steric effects play a dominant role in stabilizing the latter ion.

Calculations at the HF/6-31G* and pBP/DN*/HF/6-31G* levels show that 1a is planar while 8a has a dihedral of 21.9° about the two aryl rings. The greater co-planarity of the two rings for the oxenium ion 1a allows more positive charge delocalization into the distal ring and 1a is ca. 12 kcal/mol less stable than 8a relative to their respective hydration products (eq 1.1, Y = Ph).67 These results are consistent with N3⁻ attack on the distal ring of 1a (Scheme 1.12, 4a’, a similar product is not observed for 8a70), and with the observed relative kinetic lability of the two ions. The calculated geometry of 1a is consistent with the canonical structure of 1a in eq 1.1. For 1a and 1d the calculated ΔE for the isodesmic reaction of eq 1.2, X = O, is ca. 18 kcal/mol suggesting that p-phenyl group is far more effective at stabilizing 1 than is a p-alkyl group.68 For 8a and 8d (eq 1.2, X = NH) ΔE is ca. 11 kcal/mol so 1 may be more sensitive to π-donor stabilization than is 8.68

\[
\begin{align*}
\text{NH} & \quad + \quad \text{Y} \quad \rightarrow \quad \text{Y} \quad + \quad \text{Y} \\
1a & = \text{Ph} \quad 1d & = \text{CH}_3 \\
8a & = \text{Ph} \quad 8d & = \text{CH}_3
\end{align*}
\]

\[(1.1)\]

\[
\begin{align*}
\text{H}_3\text{C} & \quad + \quad \text{Ph} \quad \rightarrow \quad \text{Ph} \quad + \quad \text{CH}_3 \\
1a & = \text{O} \quad 8a & = \text{NH} \\
1d & = \text{O} \quad 8d & = \text{NH}
\end{align*}
\]

\[(1.2)\]

Supported by the knowledge of 1a, further investigations into the chemistry of 1 are demonstrated in this dissertation in Chapter 2 and 3, with the emphasis on detection of aryloxenium ion 1b generated via hydrolysis or photolysis from different sources 2b and 13b (Scheme 1.11) and on the studies of its properties as a reactive intermediate. For the first time, an aryloxenium ion (1b) that is not unusually stabilized was directly detected during laser flash photolysis of its corresponding precursor 2b in this work.76,77 In addition to the detection and characterization of 1b, mechanistic rationale of other interesting chemistry occurring during the decomposition of those two target compounds in the absence or presence of UV light is...
demonstrated as well. Phenoxy radical 5b is found to be generated along with 1b during the photolysis of 2b and is responsible for the formation of photoproducts 6b and 7b (Scheme 1.13). Different mechanisms for the decomposition of 13b in an aqueous environment are demonstrated. Based on systematic kinetic and product studies, the possible involvement of methanesulfonylnitrene 15 is discussed (Figure 1.7).

**SCHEME 1.13.** Photolysis of 2b in aqueous solution.

![Scheme 1.13](image)

**Figure 1.7** Decomposition products of 13b in aqueous solution.

During the last decade, a series of benzothiazole derivatives based on two lead compounds: 4-(benzothiazol-2-yl)-4-hydroxy-2,5-cyclohexadien-1-one 20 (Figure 1.8), and 2-(4-aminophenyl)benzothiazole 25 (Figure 1.9) have received intensive research attention because of their remarkable biological properties.78-85,86-98 They have been under rapid development as antitumor,93-95 antimicrobial, and antifungal agents99,100 and as radiopharmaceuticals for binding and in vivo imaging of Aβ-plaques, one of the earliest pathological processes in the development of Alzheimer’s disease.101,102 For example, a derivative of 25, Phortress 27 has been developed as an antitumor prodrug and entered Phase I clinical trial in Britain (Figure 1.10).94 However, research on the mechanism of the action of these compounds has lagged, and the reasons for their biological activity are not well understood.83-85, 96-98 A SciFinder Scholar search of compounds related to 20 and 25 shows that since 2000, 42 patents have been issued for
biological applications of these two classes of compounds (27 since 2004). Continued
development of these compounds as drug candidates for treatment or detection of various
diseases is certain. For that reason knowledge of the chemistry of metabolites of these
compounds, and reactive intermediates derived from them, will become increasingly important.
Based on our experience with the chemistry of carcinogenic metabolites of aromatic amines and
our knowledge of nitrenium and oxenium ion chemistry, it is our hypothesis that the anti-tumor
activity of these compounds is due to their conversion, by a series of metabolic and chemical
reactions, into selective, electrophilic oxenium and nitrenium ions of general structure 21 (Figure
1.8), and 26 (Figure 1.9). To test this hypothesis, we initiated a project meant to investigate if the
cationic species 21 and 26 can be formed from the decomposition of likely metabolic products of
20 and 25 such as 19 and 24, and ultimately, if these reactive intermediates are responsible for
the biological activities of these compounds.

*Figure 1.8* Structures of quinol ester 19, quinol 20, and proposed intermediate aryloxenium ion
21

![Figure 1.8](image)

*Figure 1.9* Structures of aminophenylbenzothiazole 25, its putative metabolite 24, and proposed
intermediate nitrenium ion 26.

![Figure 1.9](image)
As an extension of the research interest in the intermediacy of oxenium ions, compounds that are studied in this dissertation are 20 and its putative metabolite acetic acid ester 19. It was shown that 19 and 20 possess \textit{in vitro} activity in HCT 116, HT 29 colon and MCF-7, MDA 468 breast cancer cell lines at the 40-800 nM level.\textsuperscript{79} Selective activity against renal and colon cancer cell lines was discovered on the NCI Developmental Therapeutics Screening Program \textit{in vitro} screen against 60 human cancer cell lines.\textsuperscript{79} 20 also exhibits \textit{in vivo} activity against human renal cancer xenografts in mice.\textsuperscript{79} Structurally related quinols, including some indol-2-yl and benzimidazol-2-yl derivatives, have also shown activity against breast, colon, and renal cancer cell lines.\textsuperscript{80-82} Some of these are more potent than 20.\textsuperscript{80-82} Fluorinated analogues of 20 retain anti-tumor activity, but no candidate for clinical trials has been put forth to date.\textsuperscript{82} In previous mechanistic studies thioredoxin has been identified as one target of 20 and related quinols.\textsuperscript{83,84} Irreversible binding of 20 to the protein via Michael addition has been proposed as the basis of the biological activity of 20, but the chemical nature of the reaction has not been studied in detail.\textsuperscript{83} Other possible protein targets of 20 have been identified, but non-protein targets have not been elucidated.\textsuperscript{84} Mechanistic studies of the chemical basis for the action of 19 is even more limited.

In Chapter 3, evidence that supports our hypothesis about the generation of aryloxenium ion 21 during the hydrolysis reaction of 19 are provided. A comprehensive study of the decomposition chemistry of 19 and 20 in the absence and presence of N\textsubscript{3}\textsuperscript{-} in aqueous solutions over a wide pH range is reported, a comparison of 21 with other aryloxenium ions generated from 2a, 2b and 13b is made. Azide trapping results, including the kinetic behavior of the reaction of 19 and the product formation (azide adduct 23 is shown in Figure 1.11) in the absence and presence of N\textsubscript{3}\textsuperscript{-} have proven the generation of 21 in an aqueous environment. The attempted photogeneration of 21 from 19 was also performed in our group by other members and the results are briefly discussed here.
Figure 1.11 Azide adduct 23 generated via oxenium ion 21

![Chemical structure](image)
CHAPTER 2

Decomposition of 4-Acetoxy-4-(4’-methylphenyl)-2,5-cyclohexadien-1-one, 2b
2.1 Introduction

Until recently, mechanistic studies of aryloxenium ions 1 (Figure 2.1) were limited since the generation and detection of these species always remained ambiguous. Although this type of intermediate has been invoked to explain a variety of reactions such as phenol oxidations and biomimetic oxidative coupling reactions, unequivocal evidence for the existence of this type of cation was not presented in most cases. Prior to our investigations a few highly stabilized examples of 1, such as species K, L, and M (see Figure 1.4), were observed or isolated. More recently, a stable oxenium ion (α-TO+, see Figure 1.5) that can survive for several hours in solution was generated from chemical and electrochemical oxidation of α-tocopherol. Unfortunately, these unusually stabilized species do not provide sufficient information to help us understand the chemistry of the short-lived aryloxenium ion as a reactive intermediate.

Figure 2.1 Aryloxenium ions 1, and potential oxenium ion precursors 2,5-cyclohexadienone derivatives 2.

It was our intention to initiate a study of aryloxenium ions 1 that are not highly stabilized by extensive delocalization or by steric hindrance. To generate the species of interest, 2,5-cyclohexadienone derivatives 2 (Figure 2.1), as one type of potential precursor, were subjected to our study. In part of this work accomplished earlier, our group was able to indirectly detect the generation of biphenylyloxenium ion 1a and 1c from catalyzed or uncatalyzed solvolysis of 2a and 2c through N₃⁻ trapping experiments, common ion rate depression, and ¹⁸O-labeling studies in ¹⁸O-H₂O. The study subject of the research work presented in this chapter is another compound in this series, quinol ester 2b. In addition to the indirect detection of 1b during hydrolysis of 2b by azide trapping experiments, the direct detection and further characterization
of 1b during laser flash photolysis (LFP) of 2b is presented as well (Figure 2.2). However, 1b is not the only transient species generated during the photolysis. A longer lived intermediate that shows different reaction patterns and properties and is associated with a different UV absorbance band is generated along with 1b (Figure 2.2). Since their UV spectra do not overlap significantly, these species can be separately characterized. This additional transient species is assigned to an aryloxy radical 5b. The mechanisms for the formation of a variety of photoproducts through the intermediacy of 1b and 5b and specific kinetic behaviors of these species are demonstrated.

Figure 2.2 Transient absorption bands observed after laser flash photolysis of 2b in 5 vol% CH₃CN-H₂O. Bands associated with 1b and 5b are labeled.

2.2 Results and Discussion

2.2.1 Kinetic studies, product analyses, and azide trapping studies of the decomposition of 2b

Compound 2b was synthesized by a standard method established in our laboratory. Kinetics of the decomposition of 2b were measured over the pH range 1-8 at 30 °C by monitoring UV absorbance change as a function of time. Absorbance vs. time data fit a first-order rate equation well. It was found previously that buffer effects are minimal with the exception that 2b exhibited common ion rate depression in acetate buffers similar to that previously observed for 2a and 2c. Most rate data in buffer solutions were obtained at total buffer concentrations of 0.02 M and
was not corrected by extrapolation to 0 M buffer. Rate constants taken at a minimum of two wavelengths were averaged at each pH. The pH dependence of the decomposition of 2b compared to that of 2a and 2c is summarized in Figure 2.3. Rate constants vs. pH data for 2a-c were fitted to eq 2.1.

\[ k_{\text{obs}} = k_o + k_{\text{H}}[H^+] \]  \hspace{1cm} (2.1)

**Figure 2.3** pH Profiles for the decomposition reactions of 2a-c.

Quinol ester 2b exhibits pH dependence of decomposition qualitatively identical to that previously reported for 2a and 2c with two observable rate constants \( k_o \) and \( k_{\text{H}} \).\(^{67,73} \) The rate constants \( k_{\text{H}} \) describes \( \text{H}_2\text{O}^+ \)-dependent decomposition, while \( k_o \) describes a pH-independent decomposition that is significant over a wide pH range. Derived rate constants for hydrolysis of 2b are reported in Table 2.1.

**Table 2.1** Derived rate parameters for the decomposition of 2b

<table>
<thead>
<tr>
<th>Compound</th>
<th>( k_o ) (s(^{-1}))</th>
<th>( k_{\text{H}} ) (M(^{-1})s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>((1.02 \pm 0.01) \times 10^{-3})</td>
<td>((1.95 \pm 0.08) \times 10^{-2})</td>
</tr>
</tbody>
</table>

The decomposition product observed by HPLC for 2b in the absence of non-solvent nucleophiles at pH 2.5, 4.6, and 7.0 is the 4-hydroxy-4-(4'-methylphenyl)-2,5-cyclohexadien-1-one, 3b (Figure 2.4). Identity was confirmed by comparison to an authentic sample, and yields determined by HPLC were 90-100%. Previously, quinol 3a, which has a structure similar to 3b,
was observed as the exclusive decomposition product of \(2a\).\(^{67,68}\) It has been proved that quinol \(3a\) is derived by solvent (water) trapping of \(1a\) instead of ester hydrolysis based on \(^{18}\)O-H\(_2\)O labeling studies that have been accomplished by other members in our group.\(^{68}\)

**Figure 2.4** Major hydrolysis product of 2: quinol 3, and azide adduct 4

![Structures of quinol 3 and azide adduct 4](image)

Results of azide trapping experiments performed on \(2b\) are summarized in Figure 2.5. Only one azide adduct \(4b\) (Figure 2.4) is generated at the expense of the quinol \(3b\) as \([\text{N}_3^-]\) increases. Trapping by \(\text{N}_3^-\) occurs with no acceleration of the rate of decomposition of \(2b\) (Figure 2.5, Insert). These observations are consistent with what we reported for azide trapping experiments performed on \(2a\), which has been proved to be the precursor for oxenium ion \(1a\).\(^{68}\) Here, all of \(4b\) can be attributed to trapping of the cation \(1b\). Standard “azide clock” equations, eq 2.2 and eq 2.3, were used to fit the peak area vs. time data for \(3b\) and \(4b\), respectively.\(^{49,50,105}\) In eq 2.2 \([3b]_o\) represents the yield of \(3b\) from the hydrolysis of \(2b\) in the absence of \(\text{N}_3^-\); \([4b]_o\) in eq 2.3 corresponds to the maximum yield of \(4b\) from the hydrolysis of \(2b\) in the presence of \(\text{N}_3^-\). \(k_{\text{az}}/k_s\) is the ratio of the second-order rate constant for trapping of the cation by \(\text{N}_3^-\) to the first-order rate constant for trapping by solvent. This ratio represents the azide/solvent selectivity of the cationic intermediate that leads to \(3b\) or \(4b\) through nucleophilic attack by water or by \(\text{N}_3^-\). By fitting the data in Figure 2.5 to “azide clock” equations, \(k_{\text{az}}/k_s\) can be obtained. For \(1b\) this ratio is \((1.0 \pm 0.2) \times 10^3 \text{ M}^{-1}\). Compared to the ratio of \(k_{\text{az}}/k_s\) previously obtained for \(1a\) \((77 \pm 5) \text{ M}^{-1}\), it is concluded that \(1b\) reacts with \(\text{N}_3^-\) considerably more selectively than does \(1a\).
**Figure 2.5** Azide trapping experiments for 2b performed in pH 7.0, 0.02 M phosphate buffer. Data for quinol 3b and azide adduct 4b were fitted by least-squares procedures to eq 2.2 and eq 2.3, respectively.

\[
[3b] = [3b]_0/(1 + (k_{zw}/k_3)[N_3^-]) \tag{2.2}
\]

\[
[4b] = [4b]_\infty[N_3^-](k_{zw}/k_3)/(1 + k_{zw}/k_3[N_3^-]) \tag{2.3}
\]

The situation for 2c is more complicated. N_3^- accelerates the decomposition reaction probably due to a bimolecular substitution process on the quinoid ring that competes with the oxenium ion formation. However, the cationic intermediate 1c still accounts for, in part, the generation of azide adduct 4c: the common ion rate depression observed for 2c indicates that a dissociative process does occur for this ester. The ester hydrolysis is not an option since the yield of quinol 3c reaches an asymptote of 0 at high [N_3^-].

**Figure 2.6** The dependence of the decomposition of 2b on temperature in pH 4.6, 0.02 M acetate buffer.
Temperature dependence of the decomposition of \(2b\) was studied in 0.02 M acetate buffer, pH 4.6, at 20, 30, and 40 °C (Figure 2.6). Based on this relationship between \(k_{\text{obs}}\) for the decomposition of \(2b\) and temperature, the activation parameters for hydrolysis of \(2b\) can be obtained. \(\Delta H^\ddagger\) and \(\Delta S^\ddagger\) derived from this relationship are \((79.4 \pm 2.2)\) kJ/mol and \((-42.3 \pm 14.4)\) J/K mol. Negative entropy of activation apparently reflects the order imposed by aqueous solvation on the transition state that leads to the free ion 1b.

In conclusion, biphenylyloxenium ions 1a, 1b, and 1c were indirectly detected from acid-catalyzed and uncatalyzed hydrolysis of the corresponding quinol esters 2 in the dark (Scheme 2.1). Based on the assumption that the reaction between oxenium ion 1 and \(N_3^-\) is diffusion limited, as observed for the nitrenium ions with similar structure,54-56 lifetimes of 1a-c can be estimated as shown in Scheme 2.1. This study concludes that 1b has substantially longer lifetime compared to 1a and 1c. Oxenium ion 1b is readily observable if it can be generated by laser flash photolysis.

**SCHEME 2.1.** Mechanism for the hydrolysis of 2a-c in the absence and presence of \(N_3^-\)

### 2.2.2 Absorption spectra observed after laser flash photolysis of 2b in aqueous solution

In an attempted direct observation of the generation of 1b, laser flash photolysis (LFP) of 2b (2.5 \(\times\) 10\(^{-4}\) M) at 266 nm was performed in Ar or O\(_2\)-saturated 0.02 M phosphate, pH 7.1, (5 vol% CH\(_3\)CN/H\(_2\)O, \(\mu = 0.5\) (NaClO\(_4\)), 22 °C). Two transient absorption bands that can be detected within 20 ns after the flash were observed. Figure 2.7 (A) shows two strong transient absorbance bands at \(\lambda_{\text{max}}\ ca. 360\) nm (A-360), and \(\lambda_{\text{max}}\ ca. 460\) nm (A-460). A-460 decays more rapidly than A-360 after excitation. Figure 2.7 (B) shows that in the presence of 1 mM \(N_3^-\) the
decay rate of A-460 increases, while the decay rate of A-360 appears to be unaffected. Neither of these two bands appears to be strongly affected by the presence or absence of O₂.

**Figure 2.7** Transient absorbance spectra obtained after 266 nm excitation of 2b in O₂-saturated 0.02 M phosphate buffer, pH 7.1, (A) in the absence and (B) in the presence of 1 mM of N₃⁻. **Key for A:** red: 20 ns after flash, green: 120 ns, blue: 220 ns. **Key for B:** red: 20 ns after flash, green: 120 ns, blue: 220 ns. All spectra recorded over a 20 ns window.

These two bands decay at significantly different rates and therefore must be associated with two different species. It is concluded that two major intermediates are generated during the photolysis of 2b in aqueous solution: one is associated with A-460 and the other one associated with A-360. The N₃⁻-dependent decay of A-460 suggests that this band is due to a cationic intermediate.
2.2.3 Identification of the intermediate with $\lambda_{\text{max}}$ 460 nm

The intermediate associated with the absorbance band at 460 nm is assigned to aryloxenium ion \textbf{1b}, based on the direct measurements of its decay kinetics in the absence and presence of $\text{N}_3^-$, the nanosecond time-resolved resonance Raman (ns-TR\textsuperscript{3}) spectrum recorded immediately after LFP and its comparison with vibrational transitions calculated for \textbf{1b} by DFT methods (B3LYP/6-31G(d)). These results strongly indicate that the properties of \textbf{1b} are predominately those expected for its 1-oxo-2,5-cyclohexadienyl carbenium ion resonance structure as previously indicated by the experimental properties and calculated structures of \textbf{1a} and related ions.\textsuperscript{67-69,73}

2.2.3.1 Decay kinetics

Kinetics of the decay of the transient species associated with A-460 was monitored at 460 nm (22 °C) immediately after LFP irradiation. Figure 2.8 shows that, in the absence of $\text{N}_3^-$ the intermediate decays in a first-order manner (green curve). The lifetime of this species can be directly measured as $(170 \pm 10)$ ns ($1/k_{\text{obs}}$ at 0 mM $[\text{N}_3^-]$). Since an identical lifetime was measured in Ar-saturated 0.02 M phosphate buffer, pH 7.1, this intermediate appears to be insensitive to the presence or absence of $\text{O}_2$. Quenching of A-460 in the presence of $\text{N}_3^-$ exhibits pseudo-first-order kinetics (blue curve). Rate constants for the decay of the intermediate associated with A-460 obtained at different $[\text{N}_3^-]$ are shown in Table 2.2.

\textit{Figure 2.8} Decay of A-460 in $\text{O}_2$-saturated 0.02 M phosphate buffer, pH 7.1, containing 1 mM $\text{N}_3^-$. Data were fitted to a standard first-order rate equation (blue curve). The green curve shows the time course of A-460 decay in the absence of $\text{N}_3^-$.\textsuperscript{26}
A linear dependence of the observed rate constant for the decay of the species associated with A-460 on [N$_3^-$] can be observed (Figure 2.9). Kinetic data were fitted to eq 2.4, where $k_s$ is the first-order rate constant for decay of A-460 in the buffer alone, and $k_{az}$ is the second-order rate constant for the N$_3^-$-dependent reaction. Derived rate parameters for the decay of this intermediate are shown in Figure 2.9.

$$k_{obs} = k_s + k_{az}[N_3^-]$$  \hspace{1cm} (2.4)

### Table 2.2 Rate constants for quenching of absorbance band A-460$^a$

<table>
<thead>
<tr>
<th>[N$_3^-$] (mM)</th>
<th>$10^{-6}k_{obs}$ (s$^{-1}$)</th>
<th>[N$_3^-$] (mM)</th>
<th>$10^{-6}k_{obs}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.44 ± 0.02</td>
<td>2.0</td>
<td>20.22 ± 0.08</td>
</tr>
<tr>
<td>0</td>
<td>5.75 ± 0.03</td>
<td>2.0</td>
<td>20.74 ± 0.06</td>
</tr>
<tr>
<td>0</td>
<td>5.93 ± 0.03</td>
<td>2.0</td>
<td>20.99 ± 0.10</td>
</tr>
<tr>
<td>0.5</td>
<td>9.09 ± 0.03</td>
<td>3.0</td>
<td>24.84 ± 0.10</td>
</tr>
<tr>
<td>0.5</td>
<td>8.66 ± 0.02</td>
<td>3.0</td>
<td>27.17 ± 0.18</td>
</tr>
<tr>
<td>0.5</td>
<td>8.44 ± 0.02</td>
<td>3.0</td>
<td>25.13 ± 0.13</td>
</tr>
<tr>
<td>1.0</td>
<td>11.49 ± 0.04</td>
<td>4.0</td>
<td>31.39 ± 0.17</td>
</tr>
<tr>
<td>1.0</td>
<td>11.87 ± 0.05</td>
<td>4.0</td>
<td>31.36 ± 0.17</td>
</tr>
<tr>
<td>1.0</td>
<td>11.73 ± 0.04</td>
<td>4.0</td>
<td>31.84 ± 0.21</td>
</tr>
</tbody>
</table>

$^a$Conditions: 5 vol% CH$_3$CN-H$_2$O, 22°C, 0.02 M phosphate, $\mu = 0.5$ (NaClO$_4$), pH 7.1, saturated with O$_2$. 

27
**Figure 2.9** Plot of $k_{obs}$ for the decay of the transient species associated with A-460 in pH 7.1 phosphate buffer vs. [N$_3^-$]. Data were fit by a linear least-squares procedure to obtain $k_s$ and $k_{az}$.

Adjusted $r^2 = 0.9895$

$\begin{align*}
    k_{az} &= (6.6 \pm 0.2) \times 10^9 \text{ M}^{-1}\text{s}^{-1} \\
    k_s &= (5.8 \pm 0.4) \times 10^6 \text{ s}^{-1}
\end{align*}$

Based on these results, the transient species associated with A-460 can be identified as oxonium ion 1b, which reacts rapidly with N$_3^-$ with an apparently diffusion-limited, second-order rate constant, $k_{az}$, of $(6.6 \pm 0.2) \times 10^9$ M$^{-1}$s$^{-1}$. A diffusion limit of ca. $5-7 \times 10^9$ M$^{-1}$s$^{-1}$ has previously been observed for the reaction of N$_3^-$ with transient carbenium and nitrenium ions under similar conditions. The equivalence of the $k_{az}/k_s$ ratio measured from LFP of 2b ((1.14 ± 0.09) × 10$^3$ M$^{-1}$) with the same ratio measured from the N$_3^-$-trapping product study of 2b in identical aqueous solutions at 30 °C of (1.0 ± 0.2) × 10$^3$ M$^{-1}$ provides further confirmation of this assignment.

### 2.2.3.2 Steady state photolysis of 2b: product studies

The aqueous solution, steady state photolysis of 2b was performed with an initial ester concentration of $5 \times 10^{-5}$ M in pH 7.1, 0.02 M phosphate buffer (5 vol% CH$_3$CN-H$_2$O, $\mu = 0.5$) at 15 °C. Irradiation of 2b for 45 s led to ca. 95% conversion. Quinol 3b was detected by HPLC as a major product, but its yield was only 9%. The control experiment on the stability of authentic 3b under the same condition was carried out. It shows that 3b decays rapidly during photolysis: after excitation for 45 s, only 27% of 3b remained. In addition, 2b does spontaneously undergo a hydrolysis reaction under this condition with a rate constant of $(1.80 \pm 0.02) \times 10^{-4}$ s$^{-1}$. A negligible amount of 2b decomposes via hydrolysis during the photolysis experiments (0.8% for
Therefore, after the correction for decomposition of 3b itself and for background hydrolysis of 2b, the calculated yield of 3b from photolysis of 2b is ca. 30-35%. Irradiation of 2b in the presence of 40 mM N₃⁻ led to complete suppression of the HPLC peak for 3b. However the corresponding azide adduct 4b was not detected since authentic 4b does not survive these photolysis conditions. Similar results were obtained from irradiation of 2b with UVB at 281-315 nm for 90 s. Compared to this, the hydrolysis of 2b in the dark leads to quantitative formation of 3b arising from oxenium ion 1b. It is completely replaced by 4b in the presence of 40 mM N₃⁻. Steady state photolysis confirms, from the perspective of product formation, that photolysis of 2b in aqueous medium does generate the oxenium ion of interest.

Quinol 3b, however, is not the exclusive photoproduct of 2b in aqueous solution. Other products were generated since 1b is not the only intermediate generated under this condition. Further discussion of photolysis products will be presented in Section 2.2.4.5.

### 2.2.3.3 Time-resolved resonance Raman characterization of 1b

Nanosecond time-resolved resonance Raman (ns-TR³) spectra were obtained at room temperature in phosphate buffered 20 vol% CH₃CN/H₂O and in CH₃CN on freshly-prepared 2 mM solutions of 2b.⁷⁷ A pump laser pulse of 266 nm, identical to that used for the LFP studies was used to generate the transient species. Laser pulses of 354.7 nm and 435.7 nm were used to probe the transients. These two probe pulses are within the absorption bands for the 360 nm and 460 nm species observed by LFP. TR³ spectra were recorded on freshly-prepared, buffered aqueous solutions of 2b, but no signal was observed 10 minutes after mixing 2b with buffered water. This is consistent with the known rapid decomposition of 2b in water. Figure 2.10 shows the 435.7 nm TR³ spectra obtained in 20 vol% CH₃CN/H₂O (A) and in CH₃CN (B) 10 ns after flash photolysis of 2b. The scaled difference spectrum (diff = (A-B)) was generated to remove the band υ₁₁ contribution of (B) from (A). The vibrational frequencies obtained from the difference spectrum are tabulated in Table 2.3 with the calculated frequencies obtained from the fully optimized structure of 1b at the B3LYP/6-31G(d) level of theory.
Figure 2.10 435.7 nm Resonance Raman spectra obtained 10 ns after 266 nm photolysis of \(2b\) in mixed aqueous solution (A), and pure CH\(_3\)CN (B). The bottom curve (\(\text{diff} = \text{A} - \text{B}\)) is obtained by subtracting the scaled (B) from (A), removing the band \(\nu11\) contribution of (B) from (A). Star symbols mark solvent-subtraction artifacts, stray-light and ambient-light artifacts.

![Resonance Raman spectra](image)

Figure 2.11 Observed and simulated vibrational spectrum of \(1b\). The simulated spectrum was obtained by independently scaling the calculated intensities of the IR active bands (blue) and the Raman active bands (red).

![Vibrational spectrum](image)
**Table 2.3.** Comparison of the experimental and calculated vibrational frequencies for 1b.

<table>
<thead>
<tr>
<th>Vibrational mode</th>
<th>B3LYP/6-31G(d) calcd value (cm⁻¹)</th>
<th>transient resonance Raman frequency shift (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R7</td>
<td></td>
<td>817</td>
</tr>
<tr>
<td>R7 ArCH bend</td>
<td>1167</td>
<td>1164</td>
</tr>
<tr>
<td>IR4</td>
<td>IR4 ArCH bend, C-CH₃ stretch</td>
<td>1184</td>
</tr>
<tr>
<td>R6</td>
<td>R6 ArCH bend, C-CH₃ stretch</td>
<td>1226</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1272</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1308</td>
</tr>
<tr>
<td>IR3</td>
<td>IR3 Ar-Ar’ stretch</td>
<td>1328</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1340</td>
</tr>
<tr>
<td>R5</td>
<td>R5 CH₃ bend</td>
<td>1373</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1391</td>
</tr>
<tr>
<td>IR2</td>
<td>IR2 ArCH bend, Ar-Ar’stretch</td>
<td>1411</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1426</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1438</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1452</td>
</tr>
<tr>
<td>R4</td>
<td>R4 Ar’ angle deformation</td>
<td>1495</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1500</td>
</tr>
</tbody>
</table>
The assigned vibrational modes in the 1100-1700 cm\(^{-1}\) range include all of the most intense predicted IR (IR1-IR4) and Raman (R1-R7) active modes from the frequency calculations. Agreement between the calculated and observed frequencies is generally good (< ± 25 cm\(^{-1}\) for 8 of 11 assigned bands), but some modes, notably R1 and IR3, have discrepancies between calculated and observed frequencies of ca. 35 cm\(^{-1}\). Figure 2.11 shows a simulation of the observed Raman spectrum obtained by scaling the calculated IR and Raman intensities independently of each other to match the intensities of the observed spectrum. TR\(^3\) spectra taken in mixed aqueous solvent and in CH\(_3\)CN with the 354.7 nm probe pulse (Figure 2.12) are different from those taken with the 435.7 nm probe (for comparison, see Figure 2.13).
Figure 2.12 354.7 nm Resonance Raman spectra obtained at 10 ns after 266 nm photolysis of 2b in mixed aqueous solution (top), and pure CH$_3$CN (bottom). Star symbols mark solvent-subtraction artifacts, stray-light and ambient-light artifacts.

Figure 2.13 Comparison of 10 ns transient Raman spectra obtained using 354.7 nm and 435.7 nm probe lasers, in mixed aqueous solvent (20 vol% CH$_3$CN-buffered water) and CH$_3$CN. Star symbols mark solvent-subtraction artifacts, stray-light and ambient-light artifacts.
The spectra taken in the predominately aqueous solution at the two wavelengths show some similarities to each other, as do those taken in CH$_3$CN. Frequencies of transitions in each solvent are similar at both probe wavelengths, though relative peak intensities change considerably with probe wavelength. Since we know that the absorbance at 360 nm observed in the LFP experiments is predominately not due to $1b$, and $1b$ is not generated by LFP in CH$_3$CN (see below in Figure 2.2.16), The 435.7 nm probe should specifically cause electronic excitation of $1b$, while the 354.7 nm probe should predominately excite the other species associated with A-360. So these results are not surprising. There does appear to be some absorbance due to $1b$ at 360 nm, so it is possible that the aqueous solution TR$^3$ spectrum taken with the 354.7 nm probe contains some contributions from $1b$.

The optimized geometry of $1b$ at B3LYP/6-31G(d) level of theory is depicted in Figure 2.14. There is a small inter-ring dihedral angle of 14° at this level of theory. At the HF/6-31G* level of theory the cation is planar. There is good evidence for strong bond alternation throughout the biphenyl moiety and the C-O bond length of 1.222 Å is typical of a carbonyl. This suggests the oxenium ion has significant cyclohexadienyl character in the phenyl ring and carbonyl character in the carbon-oxygen bond. This is similar to the significant cyclohexadienyl character in the phenyl rings and imine character in the carbon-nitrogen bond of the analogous 4-biphenylynitrenium ions previously studied by TR$^3$ spectroscopy and DFT calculations. The highest frequency Raman band in the gas phase, corresponding to a C-O stretch, is also typical of a carbonyl (1672 cm$^{-1}$ after scaling). The observed Raman shift is somewhat lower at 1635 cm$^{-1}$, but still within the range of a carbonyl with significant $\pi$-delocalization. We note that hydrogen bonding of water at the carbonyl bond has been previously observed to noticeably downshift the C=O stretching Raman band for aromatic carbonyls like para-methoxyacetophenone from about 1695 cm$^{-1}$ in cyclohexane to about 1672 cm$^{-1}$ in a 50 vol% CH$_3$CN-H$_2$O solvent. This is quite similar to the downshift in the vibrational frequency observed for the analogous C=O Raman band in the spectrum of the oxenium ion (from 1672 cm$^{-1}$ for the DFT gas phase calculation to the experimental 1635 cm$^{-1}$ seen in the aqueous solution where hydrogen bonding of the carbonyl is very likely significant). Thus, the hydrogen bonding of water to the C-O bond most likely accounts for the difference in the Raman vibrational frequencies between the gas phase DFT predicted frequency for the C=O stretch Raman band and that actually observed in the experimental TR$^3$ spectrum for the oxenium ion. Mulliken atomic charges confirm delocalization
of the positive charge into the 4-\textit{para}-tolyl substituent. Group charges on the substituent ring account for 0.52 of the total charge and charge is concentrated upon both C-4 (+0.12) and C-4' (+0.2). The carbonyl bears a charge of only +0.07. The dipole moment of 4.45 D is directed along the longitudinal axis of the molecule, as expected. In valence bond terms, resonance structures \textbf{II} and \textbf{III}, rather than \textbf{I} (Figure 2.14), are dominant. We have found similar results for 1a from calculations at the HF/6-31G* and pBP/DN*/HF/6-31G* levels of theory.\textsuperscript{69} The agreement between the calculated and observed vibrational spectrum for 1b indicates that the calculated properties of the cation do reproduce those of the actual cation.

\textbf{Figure 2.14} Calculated (B3LYP/6-31G(d)) bond lengths (Å), Mulliken charges (charges on H summed into heavy atoms), and dominant resonance structures for 1b and the corresponding nitrenium ion, 8b.

The computed properties of the analogous nitrenium ion 8b at the B3LYP/6-31G(d) level are similar to 1b.\textsuperscript{77} Less charge is localized into the 4-\textit{para}-tolyl substituent (+0.45) though Mulliken charges at the C-4 and C-4' positions are similar. There is a slightly larger inter-ring dihedral angle of 16.7° in 8b. This, and the longer inter-ring bond indicate less resonance through to the 4-\textit{para}-tolyl substituent. Bond alternation is also somewhat reduced throughout the structure and nearly twice as much positive charge resides on the CNH of 8b (+0.11) than on the CO of 1b.
The dipole moment of 1.479 D is considerably modified by the NH bond. The component of the dipole moment along the C-N bond, corrected for the N-H bond contribution, is estimated to be 1.22 D, considerably less than the dipole moment of 1b. Similar differences in calculated properties have been noted for other aryloxenium ions, including 1a, and their analogous arylnitrenium ions at the HF/6-31G* and BP/DN*/HF/6-31G* levels of theory.69

It is initially surprising that the IR active bands (IR1-4) appear as significant bands in the TR³ spectrum of 1b. Figure 2.11 shows that the strong IR bands are also weakly allowed in the calculated Raman spectrum due to the low symmetry of 1b. However, the observed intensities of the TR³ spectrum are quite different from the calculated Raman intensities. The intensities of resonance Raman spectra can be very different from those observed or calculated Raman spectra obtained under non-resonant conditions.108 The probe Raman excitation wavelength is in resonance with an electronic transition of the species being probed. The bands in the resonance Raman spectrum associated with vibrational modes of molecular components that undergo a significant change in structure in the excited state relative to the ground state will be enhanced.108

For example, selective probe wavelength-dependent resonance Raman enhancement of bands assigned to vibrational modes of the benzoin chromophore in benzoin diethyl phosphate has been demonstrated.108a In the present example, the Raman bands R1 and R2 and the R band IR1 are C=O, ArC=C and Ar´C=C stretch modes and are fairly intense bands in the TR³ spectrum. The HOMO⁻¹ (π), non-bonding (πY) and LUMO (π*) orbitals are depicted in Figure 2.15. The π-π* and n-π* transitions lead to changes in bond order of the ArC=C and Ar´C=C as well as the C=O bonds and hence the lengths of these bonds in the excited state. This change in excited state structure would be expected, as observed, to enhance vibrational modes associated with changes in these bond lengths.

**Figure 2.15** The HOMO (non-bonding) (πY, middle), HOMO⁻¹ (π, left) and LUMO (π*, right) orbitals for 1b calculated at the B3LYP/6-31G(d) level.
2.2.4 Identification of the intermediate with $\lambda_{\text{max}}$ 360 nm in aqueous solution

Assignment of the 360 nm absorbance band to a radical intermediate 5b (Figure 2.16) was based on the LFP generation of the same intermediate in CH$_3$CN, comparison of the observed UV-vis spectra attributed to 5a and 5b with previously published spectra for 5a (Figure 2.16),$^{109,110}$ isolated photolysis reaction products of 2a and 2b that are attributable to 5a and 5b, and modeling of the decay kinetics of 5a and 5b.

**Figure 2.16** aryloxy radical 5

![Aryloxy radical 5](image)

a Ar = Ph  
b Ar = 4'-MePh

2.2.4.1 Decay kinetics of A-360 observed in aqueous solution

The decay of the transient absorbance at 360 nm observed in 5 vol% CH$_3$CN-H$_2$O in the absence or presence of N$_3^-$ in Figure 2.17 occurs in a biphasic manner. The absorbance vs. time data at $t \geq 1 \mu$s (to avoid complications from absorbance of 1b at that wavelength) can be fit to an equation containing two first-order rate constants ($k_{1AQ}^{O_2}$ and $k_{2AQ}^{O_2}$) that are not dependent on [N$_3^-$]. All rate constants are reported in Table 2.4. The lifetimes of these decay processes (12 $\mu$s and 75 $\mu$s) are significantly longer than that of 1b (170 ns).
**Figure 2.17** Quenching of A-360 in 0.02 M phosphate buffer, pH 7.1, at 20 °C in the absence of N$_3^-$ (A) and in the presence of 6 mM N$_3^-$ (B). Data were fitted to an equation with a double exponential. All data taken from 1 μs to 250 μs were included in the fit.

2.2.4.2 Absorption spectra observed after laser flash photolysis of 2b in CH$_3$CN

It was observed that LFP of 2b in O$_2$-saturated CH$_3$CN (Figure 2.18) apparently generates only one transient. The absorbance observed at 460 nm in aqueous solution that was assigned to 1b disappeared, so that 1b was not formed in CH$_3$CN from photolysis. The strong transient absorbance band at shorter wavelengths remained, but $\lambda_{\text{max}}$ shifted to ca. 350 nm (A-350). A much weaker band at longer wavelengths (> 460 nm) was also observed (A-575, since the decay kinetics for this weaker band was monitored at 575 nm). In Ar-saturated CH$_3$CN the band at 350 nm and the weaker long wavelength band were still observed. In addition, a prominent shoulder at 400 nm that disappeared within 10 μs was detected (Figure 2.19). This rapidly decaying transient absorbance did not interfere with the decay of the two major absorbance bands.
Figure 2.18 Transient absorbance spectra obtained after 266 nm excitation of 2b in O₂-saturated CH₃CN. **Key:** red, 20 ns after flash; blue, 1 µs; green, 100 µs; magenta, 200 µs. All spectra were recorded over a 20 ns window.

Figure 2.19 Transient absorbance spectra obtained after 266 nm excitation of 2b in Ar-saturated CH₃CN **Key:** red: 20 ns after flash, blue: 3 µs, green 100 µs, magenta 200 µs, brown 400 µs. All spectra recorded over a 20 ns window.

Previously, Das et al. reported a very similar absorbance spectrum attributed to aryloxy radical 5a (for the structure of 5a, see Figure 2.16) observed in 1/2 benzene/di-tert-butyl peroxide.¹¹⁰ For comparison purposes, LFP of 2a in O₂-saturated 0.02 M phosphate buffer, pH 7.1, or in O₂-saturated CH₃CN was performed. Results are shown in Figure 2.20.
No transient that can be assigned to oxenium ion 1a was detected in either aqueous solution or CH$_3$CN. Although steady state photolysis product studies indicate that some 1a was formed in water (below in Section 2.2.4.5), it is not surprising that it was not detected in the ns-LFP experiments because the lifetime of 1a estimated from an N$_3^-$-trapping product study performed during hydrolysis of 2a under the same aqueous conditions was only 12 ns.$^{67,68}$ Monitoring absorbance vs. time data at 450 nm (near $\lambda_{max}$ for 1b) at early reaction times revealed an apparent fluorescence that decayed within 15 ns after the flash. After that, slow decay of the signal occurred on a longer 10-100 µs time scale. The fluorescence signal obscured any absorbance due to 1a at short reaction times within the estimated lifetime of 1a. The LFP results confirm our previous conclusions based on N$_3^-$-trapping of hydrolysis reactions of oxenium ion precursors that the aqueous solution lifetimes of 4´-substituted-4-biphenylyloxenium ions are highly dependent on the nature of the 4´-substituent. These results are also in agreement with the calculations that show significant delocalization of the positive charge into the distal rings of these cations.$^{69,73}$

Although 1a was not detected, another transient with $\lambda_{max}$ 350 nm was detected in aqueous solution. In CH$_3$CN a transient was generated with $\lambda_{max}$ 340 nm. This solvent shift is equivalent to that observed for the transient derived from 2b with $\lambda_{max}$ 360 nm in aqueous solution but $\lambda_{max}$ 350 nm in CH$_3$CN. In both solvents a weaker absorbance band, apparently associated with the same transient, was observed at $\lambda > 460$ nm. The spectrum observed in aqueous solution was
indistinguishable from that previously observed during pulse radiolysis of N₂O-saturated aqueous solutions of 6a that was attributed to 5a.¹⁰⁹

It is concluded that the transient spectra in Figure 2.20 are due to 5a, and the similar transient absorbance observed in Figure 2.7, 2.18 and 2.19 is due to 5b. The kinetics of decay of 5a was examined in less detail than that of 5b, but the transient absorbance at 340 nm in O₂-saturated CH₃CN decayed in a biphasic manner very similar to that observed for 5b. Rate constants are shown in Table 2.4.

2.2.4.3 Decay kinetics of A-350 and A-575 observed in CH₃CN

Both of these bands disappear in a biphasic manner. Absorbances vs. time data fit a consecutive first-order equation well, and equivalent rate constants were obtained for the decay of absorbance at both wavelengths (Table 2.4). This indicates that both absorbance bands are associated with the same intermediate. The magnitudes of these rate constants (k₁ACN⁰² and k₂ACN⁰² for decay of A-350) are similar to those for the decay of band A-360 observed in O₂-saturated aqueous solution (k₁AQ⁰² and k₂AQ⁰²), indicating that this absorbance band at 350 nm is due to a neutral intermediate not strongly affected by solvation that is equivalent to the intermediate with λ_max 360 nm detected in water. The lack of generation of 1b in the CH₃CN solutions is consistent with solvation-based destabilization of the transition state leading to the cation in CH₃CN under conditions in which a competing homolytic photolysis to generate radical 5b is not strongly affected by the solvent. In Ar-saturated CH₃CN the band at 350 nm and the weaker absorbance at longer wavelength were still observed (Figure 2.19). Monitoring of the kinetics at 350 nm showed that the intermediate disappears in a biphasic manner with rate constants k₁ACN⁰² and k₂ACN⁰² in Ar-saturated CH₃CN. The directly observed decay of the UV absorption at 350 nm is shown in Figure 2.21. The magnitudes of these rate constants are somewhat smaller than those observed in the presence of O₂ (Table 2.4).
Figure 2.21 Kinetic fits for absorbance band at 350 nm vs. time in (A) O₂-saturated CH₃CN and (B) Ar-saturated CH₃CN. Data fit to a biphasic first-order rate equation the derived rate constants are shown in Table 2.4.

![Image of Figure 2.21](image)

Table 2.4 Rate constants obtained from LFP experiments for 2a and 2b.⁺⁺

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Reaction Conditions</th>
<th>Rate Constant (units), Wavelength Monitored</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>5 vol% CH₃CN/H₂O, O₂ sat</td>
<td>$k_{az}$ (M⁻¹s⁻¹), 460 nm</td>
<td>$(6.6 \pm 0.2) \times 10^9$</td>
</tr>
<tr>
<td>1b</td>
<td>5 vol% CH₃CN/H₂O, O₂ sat</td>
<td>$k_{s}$ (s⁻¹), 460 nm</td>
<td>$(5.8 \pm 0.4) \times 10^6$</td>
</tr>
<tr>
<td>5b</td>
<td>5 vol% CH₃CN/H₂O, O₂ sat</td>
<td>$k_{1AQ}^{O₂}$ (s⁻¹), 360 nm</td>
<td>$(8.06 \pm 0.08) \times 10^4$</td>
</tr>
<tr>
<td>5b</td>
<td>5 vol% CH₃CN/H₂O, O₂ sat</td>
<td>$k_{2AQ}^{O₂}$ (s⁻¹), 360 nm</td>
<td>$(1.29 \pm 0.02) \times 10^4$</td>
</tr>
<tr>
<td></td>
<td>CH₃CN, O₂ sat</td>
<td>$k_{1ACN}^{O₂}$ (s⁻¹), 350 nm</td>
<td>(11.0 ± 0.7) × 10⁴</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>5b</td>
<td>CH₃CN, O₂ sat</td>
<td>$k_{2ACN}^{O₂}$ (s⁻¹), 350 nm</td>
<td>(2.35 ± 0.07) × 10⁴</td>
</tr>
<tr>
<td>5b</td>
<td>CH₃CN, O₂ sat</td>
<td>$k_{1ACN}^{O₂}$ (s⁻¹), 575 nm</td>
<td>(13.2 ± 0.6) × 10⁴</td>
</tr>
<tr>
<td>5b</td>
<td>CH₃CN, O₂ sat</td>
<td>$k_{2ACN}^{O₂}$ (s⁻¹), 575 nm</td>
<td>(2.82 ± 0.32) × 10⁴</td>
</tr>
<tr>
<td>5b</td>
<td>CH₃CN, Ar sat</td>
<td>$k_{1ACN}^{Ar}$ (s⁻¹), 350 nm</td>
<td>(7.18 ± 0.57) × 10⁴</td>
</tr>
<tr>
<td>5b</td>
<td>CH₃CN, Ar sat</td>
<td>$k_{2ACN}^{Ar}$ (s⁻¹), 350 nm</td>
<td>(1.18 ± 0.09) × 10⁴</td>
</tr>
<tr>
<td>5b</td>
<td>CH₃CN, Ar sat</td>
<td>$k_{1ACN}^{Ar}$ (s⁻¹), 575 nm</td>
<td>(7.83 ± 0.30) × 10⁴</td>
</tr>
<tr>
<td>5b</td>
<td>CH₃CN, Ar sat</td>
<td>$k_{2ACN}^{Ar}$ (s⁻¹), 575 nm</td>
<td>(1.19 ± 0.11) × 10⁴</td>
</tr>
<tr>
<td>5a</td>
<td>CH₃CN, O₂ sat</td>
<td>$k_{1ACN}^{O₂}$ (s⁻¹), 340 nm</td>
<td>(5.56 ± 0.48) × 10⁴</td>
</tr>
<tr>
<td>5a</td>
<td>CH₃CN, O₂ sat</td>
<td>$k_{2ACN}^{O₂}$ (s⁻¹), 340 nm</td>
<td>(6.85 ± 1.70) × 10⁵</td>
</tr>
</tbody>
</table>

All rate constants were collected at 22 °C under the conditions described in the Table. Rate constants and error limits for 5a and 5b are averages, and standard deviations that were determined from three to five independent measurements. Rate constants for 1b were determined as described in Section 2.2.3. Determined from the slope ($k_{az}$) or intercept ($k_s$) of a plot of $k_{obs}$ vs. $[N_3^-]$ at six $[N_3^-]$ between 0 – 4 mM (see Section 2.2.3.1)

### 2.2.4.4 Steady state photolysis of 2b: product studies (completed)

All major products generated by steady-state photolysis of 2b in both aqueous solution and CH₃CN are summarized in Scheme 1.3 and compared with that of 2a. The quinols (3) and the phenols (6) are known compounds. The new perox compounds (7) were isolated and fully characterized. The yields were obtained based on HPLC response factors. Unlike the aqueous solution photolysis of 2b, photolysis of 2b in CH₃CN was performed with an initial ester concentration of 2.5 mM. Both 3 and 7 are significantly photoreactive under our conditions. To minimize this effect, product yields were obtained at early reaction times corresponding to ca. 15-30% photoreaction for the reactions run at 2.5 mM. The aqueous solution photolysis of 2b and the discussion of the yield of 3b have been stated above in Section 2.2.3.2. The yield of 3a
shown in Scheme 2.2 was obtained under conditions in which the hydrolysis is too slow to compete with the photolysis.

**SCHEME 2.2.** Photolysis products of 2 and their yields under different conditions.

The data leaves little doubt that quinol 3a and 3b are generated through the intermediacy of oxenium ion 1a and 1b. The lack of generation of 3b in CH₃CN is consistent with the observation made during LFP studies of 2b that 1b is not detected in CH₃CN but is detected in aqueous solution. Although 1a was not directly detected by LFP, the generation of 3a in the aqueous solution photolysis experiments indicates that this short-lived intermediate is generated by photolysis. The greater yield of 3b compared to 3a in the aqueous photolysis experiments may be due to transition state stabilization for photolytic generation of the more stable cation. The peroxo compound 7a is not produced in N₂-saturated CH₃CN, and experiments in CD₃CN demonstrate that the methyl group in 7a is derived from the acyl methyl of 2a, not from the solvent.⁷⁷ The products 6 and 7 are not formed during hydrolysis of 2a or 2b, but they are detected during photolysis of 2a and 2b in both aqueous solution and CH₃CN. This is consistent with the generation of 5a and 5b during LFP of 2a and 2b under both conditions. Clearly they are the products arising from aryloxy radical, 5. The phenols 6 are the expected products of
hydrogen abstraction of 5. A mechanism for generation of the peroxy compounds 7 that is consistent with the available data is shown in Scheme 2.3.

**SCHEME 2.3. Proposed mechanism for the formation of 7**

Simple alkyl radicals, including methyl radical, react with O₂ to form alkyl peroxy radicals with rate constants of \( \text{ca.} \ 10^9 \ M^{-1}s^{-1} \), while aryloxy radicals are unreactive with O₂.\(^{111-113} \) Primary alkyl peroxy radicals are relatively unreactive to hydrogen abstraction, double bond addition, and electron transfer.\(^{111,112} \) Self reaction occurs near the diffusion limit, but at low peroxy radical concentration, trapping by other radicals, such as 5, should be competitive.\(^{113} \)

Most minor products detected by HPLC were not characterized, but one minor product of 2a observed in both aqueous solution and CH₃CN with a long HPLC retention time has an m/e of 337 by negative ion mass spectrometry. This mass corresponds to (M-1)⁻ for a dimer of 5a. Since this material can be detected by negative ion mass spectrometry, it is likely to be a phenol, but it was not isolated since it is \(<\ 1\%\) of the photolysis product mixture of 2a in CH₃CN.

**2.2.4.5 Kinetic modeling and possible mechanism for the decay of 5b**

As mentioned in Section 2.2.4.4, the biphasic decay kinetics observed for 5a and 5b can be fitted by a double exponential rate equation very well. But this fit does not provide a mechanistic understanding of the decay processes for these radicals. It is known that aryloxy radicals are relatively long-lived species in solution that decay primarily by dimerization in the absence of radical traps.\(^{114-120} \) In many cases in which there is a 4-alkyl or 4-aryl substituent, including 5a, the dimerization is reversible and biphasic decay kinetics can be observed.\(^{114,117,119} \) A mechanism similar to that shown in Scheme 2.4 has been used to analyze these cases.\(^{114,119} \)
SCHEME 2.4. Kinetic scheme for the decay of 5.

The dimer 9 was not isolated, but its structure is assumed to be analogous to the isolatable, but highly reactive dimer obtained from DDQ oxidation of 2,6-di-tert-butyl-4-methylphenol. This scheme was applied to the decay of the absorbance of 5b at 360 nm in O₂-saturated 5 vol% CH₃CN/H₂O or at 350 nm in both O₂-saturated and Ar-saturated CH₃CN, and to the decay of the absorbance of 5a at 340 nm in O₂-saturated CH₃CN. The scheme was utilized because of the biphasic nature of the decay of the absorbance under these conditions, and because the negligible yields of dimeric products observed in these photolyses suggest that 9 does not have an efficient pathway to lead directly to stable dimeric products. The monomeric products 6 and 7 identified as photoproducts of 2 (Section 2.2.4.5) are clearly obtained from 5 in processes that are not kinetically first-order, but a pseudo-first-order rate constant, k₃, can be used to describe these processes under reaction conditions in which species other than 5 are held at constant concentration. Since the initial concentrations of 5a and 5b in the LFP experiments are ≤ 3 × 10⁻⁵ M (see below), this may be the case.

Absorbance vs. time data were fitted to the mechanism shown in Scheme 2.4 using a Powell fitting algorithm implemented in the KINTECUS kinetics simulation program. The three rate constants, k₁, k₂, k₃, and the initial (t = 0) absorbance were used as variable parameters to optimize the fit. Examples of fits are shown in Figure 2.22, and fitted rate constants are shown in Table 2.5.
Figure 2.22 Kinetic fits for absorbance of 5b at 350 nm vs. time in (A) O₂-saturated CH₃CN and (B) Ar-saturated CH₃CN. Blue lines: the fit to a biphasic first-order rate equation (Table 2.4). Green lines: the fit to the kinetic mechanism of Scheme 2.4 (Table 2.5). About 90% of the data points were removed for clarity, but all data points were used for the fits.

Table 2.5. Rate constants derived from kinetic modeling to Scheme 2.4.

<table>
<thead>
<tr>
<th>Intermediate, Reaction Conditions</th>
<th>$k_1/\varepsilon$ (cm s⁻¹)</th>
<th>$k_1$ (M⁻¹s⁻¹)</th>
<th>$k_2$ (s⁻¹)</th>
<th>$k_3$ (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b, 5% CH₃CN/H₂O, O₂ sat</td>
<td>$(9.9 \pm 0.5) \times 10^4$</td>
<td>$(1.9 \pm 0.9) \times 10^9$</td>
<td>$(1.7 \pm 0.1) \times 10^4$</td>
<td>$(2.8 \pm 0.2) \times 10^4$</td>
</tr>
</tbody>
</table>
Evaluation of the rate constant $k_1$ requires knowledge of the extinction coefficient, $\varepsilon$, for 5a or 5b at its short wavelength $\lambda_{\text{max}}$ in the 340-360 nm range. The previously measured extinction coefficient for 5a at the long wavelength absorbance band (502 nm) in 1/2 benzene/di-tert-butyl peroxide of 2580 M$^{-1}$cm$^{-1}$ provides an estimate of $\varepsilon$ at 340 nm for 5a of $1.9 \times 10^4$ M$^{-1}$cm$^{-1}$ based on the observed absorbance ratio at $\lambda_{\text{max}}$ of the two bands for 5a in CH$_3$CN.$^{110}$ The same extinction coefficient was assumed for 5b at its short wavelength $\lambda_{\text{max}}$ in both CH$_3$CN and in the aqueous solution. The error limit for $\varepsilon$ may exceed $\pm$ 50%, but it provides a reasonable estimate of the initial concentration of 5a or 5b of ca. 1-3 $\times$ 10$^{-5}$ M in all the LFP experiments. This is 3%-10% of the initial concentrations of 2a or 2b present in solution. Estimates for $k_1$ are provided in Table 2.5. The values are 5-10 fold less than the expected diffusion limit. Previously measured dimerization rate constants of aryloxy radicals near room temperature have varied from ca. $10^7$ M$^{-1}$s$^{-1}$ to the approximate diffusion controlled limit of $5-6 \times 10^9$ M$^{-1}$ s$^{-1}$ in solvents as diverse as benzene, CCl$_4$ and water.$^{114-118,120}$ The dimerization rate constant of 5a in benzene at 30 $^\circ$C is reported to be $3.4 \times 10^7$ M$^{-1}$s$^{-1}$.$^{116}$ Dimerization rate constants for several other aryloxy radicals in benzene are about an order of magnitude smaller than the same radicals in water, so our values for $k_1$ appear to be in reasonable agreement with the limited available data.$^{116}$

The difference between $k_1$ in aqueous solution and in CH$_3$CN for 5b should not be over interpreted considering our assumptions concerning the magnitude of $\varepsilon$. Comparisons of the rate constants for 5b in O$_2$-saturated CH$_3$CN with those in Ar-saturated CH$_3$CN show that the most significant difference is in $k_3$. The two rate constants that describe the dimerization equilibrium
(\(k_1\) and \(k_2\)) are quite similar under the two reaction conditions, and the dimerization equilibrium constant, \(K_d = k_1/k_2\), is invariant at \(3.1 \times 10^4\) M\(^{-1}\) under both reaction conditions, but \(k_3\) in O\(_2\)-saturated CH\(_3\)CN is 2.4-fold larger than in Ar-saturated CH\(_3\)CN. The relatively small effect of O\(_2\) on the decay kinetics of 5b is consistent with the reported lack of reactivity of aryloxy radicals with O\(_2\).\(^{35}\) The observed increase in \(k_3\) in O\(_2\)-saturated CH\(_3\)CN is consistent with the proposed role of O\(_2\) in the formation of 7b (Scheme 2.2). The dimerization equilibrium for 5a in O\(_2\)-saturated CH\(_3\)CN appears to be very similar to that of 5b with \(K_d = 2.4 \times 10^4\) M\(^{-1}\), but \(k_3\) is somewhat smaller for 5a in O\(_2\)-saturated CH\(_3\)CN than \(k_3\) for 5b under the same reaction conditions. We do not understand the reasons for the substituent effect on \(k_3\). Speculation on the nature of the effect would not be warranted at this time since the decay processes represented by \(k_3\) are quite complicated, and we have not identified all of the products generated from the decay of 5a and 5b. The dimerization equilibrium constants measured here for 5a and 5b appear to be in the range of \(K_d\) measured for other aryloxy radicals.\(^{114,119,120}\) For example, \(K_d\) for 2,6-di-tert-butyl-4-methylphenoxyl has been measured at room temperature as \(6 \times 10^4\) M\(^{-1}\) in benzene and \(1 \times 10^5\) M\(^{-1}\) in CCl\(_4\).\(^ {114,119}\) For a more closely related radical, 2,4-dicyclohexyl-4-phenylphenoxyl, \(K_d\) is \(2.5 \times 10^4\) M\(^{-1}\) at 20 °C in propanol.\(^ {120}\)

**SCHEME 2.5** Proposed mechanism for photolysis of 2 in aqueous solution and in CH\(_3\)CN
2.3 Conclusions

While hydrolysis of the quinol esters 2 with electron-donating substituents on the distal ring generates the biphenylyloxenium ions 1 exclusively based on the quantitative yield of the quinols 3 and results of N$_3^-$-trapping, common ion effects, and $^{18}$O-labeling studies,$^{67,68,73}$ photolysis of these esters in aqueous solution generates not only 1, but also aryloxy radicals 5 that leads to potoproducts 6 and 7 as shown in Scheme 2.5. Product yields from photolysis of 2a and 2b suggest that photolytic generation of 1 is more favorable for the ester with the more electron-donating substituent, 2b. Only 1b was detected directly after nanosecond LFP at 266 nm because the lifetime of 1a is too short for detection. The ion 1b with $\lambda_{\text{max}}$ 460 nm was characterized by the N$_3^-$-dependence of its decomposition kinetics, by comparison of $k_{\text{az}}/k_{s}$ measured directly with the same ratio measured by N$_3^-$-trapping of the hydrolysis reaction, and by the comparison of the TR$^3$ spectrum of the intermediate with calculated vibrational transitions at the B3LYP/6-31G(d) level of theory. The agreement between calculated and observed transitions strongly suggests that the calculated structure is an accurate representation of the cation. That structure indicates that 1b should largely be considered as a 4-(4'-methylphenyl)-1-oxo-2,5-cyclohexadienylcarbenium ion (see the resonance structure II in Figure 2.14) with significant charge delocalization into the substituent ring. The strong dependence of cation lifetimes on the substituent in the distal ring and the nature of the hydrolysis reaction products, 3, are consistent with this interpretation. Nonetheless, the oxenium center does impart unique reactivity patterns to these ions that, in our opinion, justifies the continued use of the term “oxenium ion” to describe these species.

The excellent agreement of the direct measurement of the lifetime of 1b with the indirect measurements made by N$_3^-$-trapping of the hydrolysis reaction of 2b provides confidence in the indirect lifetime estimates we have made for several other 4'-substituted biphenylyloxenium ions (MeO, H, Br).$^{73,76}$ Ren and McClelland have measured the lifetimes of the corresponding nitrenium ions under similar conditions (20 vol% CH$_3$CN/H$_2$O, 20 °C).$^{57}$ A plot of log $k_{s}$ for the biphenylyloxenium ions vs. log $k_{s}$ for the corresponding biphenyllylnitrenium ions (Figure 2.23) shows that relative substituent effects on the stabilities of these ions are nearly identical (slope ≈ 1.0), although the nitrenium ions are ca. 30-fold more stable than the corresponding oxenium ions within the three orders of magnitude range of cation stabilities that can be compared.
This is surprising given the results of the DFT calculations that show somewhat more charge delocalization into the distal rings of the biphenylyloxygenium ions. This suggests that the oxenium ions would be more sensitive to substituent effects in the distal ring, which would be manifested by a slope > 1.0. The calculated differences are not large though, and compensating factors such as differential solvation of the more polar oxenium ions could mask the expected effect.

Although 1b is only generated during photolysis of 2b in water, the aryloxy radical 5b can be detected after LFP in both aqueous solution and CH$_3$CN. The unsubstituted radical 5a can also be detected after LFP of 2a in both solvents. The radicals appear to be the exclusive initial photolysis products in CH$_3$CN, based on UV-vis spectra taken after LFP, and on isolated product yields (Scheme 2.6). These radicals were characterized by their reaction products, by comparison with the published UV-vis spectrum of 5a, and by modeling of their decay kinetics. The kinetics of the decomposition of 5a and 5b have been successfully modeled by a kinetic scheme applied to describe the decay of other aryloxy radicals.\textsuperscript{114-120}
2.4 Experimental

2.4.1 In general

Nanosecond time-resolved resonance Raman (ns-TR³) experiments was accomplished by our collaborator Dr. David Lee Phillips’s group at University of Hong Kong. Nanosecond laser flash photolysis (LFP) experiments described in Chapter 2 and 3 were accomplished with the assistance of Jin Wang and Peng, Huo-Lei from Dr. Platz’s group at the Ohio State University. Density functional calculations involved in all projects were carried out by Dr. Stephen A. Glover at the University of New England in Australia. Detailed descriptions can be found elsewhere. 77, 123-126

All kinetic studies were performed in 5 vol% CH₂CN-H₂O μ = 0.5 (NaClO₄) solutions. The pH was maintained by a variety of solutions or buffers as mentioned in individual chapters. All pH values were measured at ambient (20-23 °C) temperature and are uncorrected. All water used in the kinetic and product studies was distilled, deionized, and then distilled again in an all-glass apparatus. Reagent grade CH₂CN was purified as previously described. 127 For kinetic studies, an initial concentration with magnitude of ca. 1-5 × 10⁻⁵ M was obtained by injection of 15 μL of pre-prepared stock solution of the compound of interest into 3 mL of reaction solution. The standard rate equations typically used for kinetic data fitting are eq 2.5, a standard first-order rate equation; eq 2.6, a double exponential rate equation; and eq 2.7, a triple exponential rate equation.

\[ A_t = A_\infty + A_1 \exp(-kt) \]  
\[ A_t = A_\infty + A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t) \]  
\[ A_t = A_\infty + A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t) + A_3 \exp(-k_3 t) \]

First-order and pseudo-first-order rate constants were calculated using a nonlinear least-square program (eq 2.5). \( A_\infty \), \( A_1 \), and the first-order rate constant \( k \) are treated as variable parameters which are adjusted to optimize the fit of the absorbance vs. time data, or the HPLC peak area vs. time data to the first-order rate equation. In all cases good agreement was obtained between observed and calculated \( A_\infty \) and \( A_1 \) values. Consecutive first order rate constants for biphasic kinetics were calculated by fitting the data to the double-exponential rate equation eq 2.6 in which \( A_\infty \), \( A_1 \), \( A_2 \), and two first-order rate constants \( k_1 \) and \( k_2 \) are subjected to adjustment. Observed rate constants were obtained as the average of those taken at different wavelengths, or
of those taken for reactant and products if utilizing HPLC to monitor the reaction process. The application of eq 2.7 will be described in Chapter 3. In all cases at least 5 half-lives of data (usually 8-10 half-lives) were used in the calculations.

2.4.2 Synthesis

The ester 2b was synthesized by oxidation of 4'-methyl-biphenyl-4-ol 6b with PIDA in acetic acid. Quinol 3b was synthesized in our group by a similar oxidation in 50/50 CH3CN-H2O as previously described for 3a.67 The 4'-methyl-biphenyl-4-ol 6b was made by a microwave assistant Suzuki coupling procedure.128,129 An authentic sample of azide adduct 4b was isolated by other group members from reaction mixtures by a method similar to that described for 5a.67

4-Acetoxy-4-(4'-methylphenyl)-2,5-cyclohexadien-1-one (2b): The phenol 6b (0.92 g, 5 mmol) was dissolved in 40 mL of acetic acid, and the resulting solution was stirred vigorously as 1.77 g (5.5 mmol) PIDA (phenyliodonium diacetate) in 40 mL of acetic acid was added in a dropwise fashion over a period of 6 hrs. After the completion of the addition the AcOH solution was evaporated under vacuum (bath temperature ca. 35 °C) to a volume of ca. 5 mL. Approximately 100 mL of saturated aqueous NaHCO3 solution was quickly pooled into the same flask and the resulting solution was extracted with CH2Cl2 (4 × 25 mL). Combined extract was dried over anhydrous Na2SO4, filtered, and evaporated to dryness under vacuum. The crude product was purified by multiple application of radial chromatography on silica gel (50/50-75/25 Hexanes/EtOAc) and recrystallization from the mixture of Hexanes and EtOAc (5:1).m.p.138-138.5 ºC; IR 1729, 1661, 1231, 1037, 983 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 2.20 (3H, s), 2.37 (3H, s), 6.34 (2H, d, J = 10.2 Hz) 6.98 (2H, d, J = 10.2 Hz), 7.21 (2H, d, J = 8.4 Hz) 7.32 (2H, d, J = 8.4 Hz); ¹³C NMR (125.8 MHz, CD2Cl2) δ 20.7, 21.3, 77.2, 125.2, 127.8, 129.6, 133.7, 138.8, 147.7, 169.1, 185.3.

4'-Methyl-biphenyl-4-ol (6b): A mixture of 4-iodophenol (1.10 g, 5 mmol), 4-methylphenylboronic acid (0.68 g, 5 mmol), K2CO3 (2.075 g, 15 mmol), and 5% Pd/C (30-33 mg) in 50-55 mL of H2O was placed in a sealable Teflon microwave reaction vessel and subjected to microwave heating at 40 psi at a maximum power of 410 watts, with a ramp time of 10 min and a hold time of 6 min. The reaction mixture was allowed to cool in an ice-water bath, neutralized with 7.5 mL of 2 M HCl, and allowed to stand for about 15 min. The off white precipitate was collected
by vacuum filtration, and dissolved in about 15 mL of EtOAc. The mixture was dried over Na₂SO₄, and filtered to remove the drying agent and Pd/C. The resulting solution was then subjected to rotary evaporation to yield a yellow-white solid that was sufficiently pure for synthetic purposes. A cleaner product could be obtained by column chromatography on silica gel using CH₂Cl₂ as eluent (yield: 55%) m.p.153-154.5 °C, lit.¹²⁸ m.p.153-154 °C; ¹H NMR (300 MHz, CDCl₃) δ 2.37 (3H, s), 4.77 (1H, s, br), 6.87 (2H, dd, J = 9.0 Hz), 7.20 (2H, d, J = 9.0 Hz), 7.43 (4H, dd, J = 3.0 Hz).

**4-Hydroxy-4-´(methylphenyl)-2,5-cyclohexadien-1-one (3b):** m.p.134-137 °C; IR 3352, 3174, 1659, 1611, 1047, 941 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.37 (3H, s), 6.24 (2H, d J = 10.0 Hz) 6.91 (2H, d, J = 10.0 Hz), 7.21 (2H, d J = 8.3 Hz) 7.38 (2H, d J = 8.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 21.5, 71.3, 125.6, 127.1, 130.0, 136.2, 138.7, 151.5, 186.3.

**3-Azido-4´-methyl-biphenyl-4-ol (4b):** mp 97-98 °C; IR 3397, 2101, 1596, 1497, 1211, 802 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) δ 2.42 (3H, s), 5.41 (1H, s(br)), 7.00 (1H, d, J = 8.3 Hz), 7.28 (2H d, J = 8.0 Hz) 7.32 (1H, dd, J = 2.1, 8.3 Hz), 7.34 (1H, d, J = 2.1 Hz), 7.48 (2H, d, J = 8.0 Hz); ¹³C NMR (75 MHz, CD₂Cl₂) δ 21.1(Me), 116.5(C-5), 117.2(C-2), 124.9(C-6), 126.7(C-1), 126.8(C-2′,C-6′), 129.9(C-3′,C-5′), 135.0(C-1′), 137.4(C-3), 137.5(C-4′), 147.0(C-4)

### 2.4.3 Kinetic studies of the decomposition of 2b

Reactions were performed in 5 vol% CH₃CN-H₂O, μ = 0.5 (NaClO₄) at 20, 30, and 40 °C for 2b. The pH was maintained with HClO₄ solutions (pH < 3.0), or in HCO₂H/NaHCO₂, AcOH/AcONa, and NaH₂PO₄/Na₂HPO₄ buffers. A stock solution of 2b was prepared at ca. 0.01 M in CH₃CN to obtain initial concentrations of 5 × 10⁻⁵ M in the reaction solutions after injection of 15 μL of the stock solution into 3 mL of the aqueous reaction solution incubated at the appropriate temperature for 15-20 min prior to the injection. All reactions were followed by UV spectroscopy monitoring the changes in UV absorbance at a minimum of two wavelengths, and rate constants obtained at each wavelength were averaged. Product yields were monitored by HPLC on the same solutions used for kinetics after 10 half-lives of the hydrolysis reaction. HPLC conditions were: 20 μL injections on a 4.7 mm × 250 mm C-8 column, 65/35 MeOH/H₂O eluent, 1.0 mL/min flow rate, UV detection at 245 nm and 255 nm. Product yield data were fit to the standard “azide clock” equations described in section 2.2.1.
2.4.4 Laser flash photolysis and kinetics

Laser flash photolysis (LFP) was carried out using a Nd:YAG laser (266 nm, ca. 5 ns pulse) with a 1 cm light path. All reactions were performed at ambient temperature (22 °C). Solutions of 2b were prepared in O2 or Ar saturated pH 7.1, 0.02 M phosphate buffer (5 vol% CH3CN-H2O, µ=0.5(NaClO4)) or in O2 or Ar saturated CH3CN by injecting 15 µL of a ca. 0.04 M stock solution of 2b into 3 mL of solution, so that the initial concentrations were ca. 2.5 × 10⁻⁴ M. LFP of 2a was only performed in O2-saturated solutions. These solutions had an absorbance of ca. 0.50 to 0.85 at 266 nm with a 1 cm light path. Since 2a and 2b undergo slow hydrolysis reactions in aqueous buffers, all solutions were used promptly after mixing, and experiments were completed within 5 minutes after mixing. Concentrations of N3⁻ were in the range from 0-6 mM.

Transient absorbance spectra were monitored in the range from 280-540 nm. Initial spectra were obtained with a delay of 20 ns after the laser pulse. Subsequent spectra were obtained at times dictated by the quenching of transient bands generated by LFP of 2a at 350 nm in aqueous buffer and 340 nm in CH3CN, and by LFP of 2b at 360 nm and 460 nm in aqueous solution, and at 350 nm and 575 nm in CH3CN. All transient spectra were collected over a 20 ns time window. Kinetics measurements for 2a were made at 350 nm in aqueous solution and at 340 nm in CH3CN, for 2b at 360 nm and 460 nm in aqueous solutions, and at 350 nm and 575 nm in CH3CN, for time spans that ranged from 1.25 µs to 250 µs depending on quenching rates of individual intermediates. Kinetics measurements at all wavelengths were averaged three to five times. Between each measurement, the sample was re-mixed to avoid depletion of reactants within the volume of the cuvette exposed to the flash. Kinetics traces were fit to either a standard first-order rate equation containing a single exponential (460 nm) or to a rate equation containing a double exponential (350 nm, 360 nm, 575 nm). All data at t ≥ 10 ns were used for the first-order fits at 460 nm, delays of 1 µs to 7 µs were used for the data taken at the other wavelengths. The delays were necessitated by fast decaying transients that disappeared at early reaction times.

2.4.5 Steady state photolysis experiments and photoproduct studies

Generally the steady state photolysis was performed in a Rayonet photochemical reactor in a jacketed quartz reactor that connects to a circulated temperature control water bath. Two types of lamps were used: Luzchem LZC-UVC that has emission (ca. 90% of total lamp energy) in the range of 235-280 nm with a sharp maximum at 254 nm, and Luzchem LZC-UVB that has
emission in the range of 281-315 nm. A bank of 4 lamps arranged at 0 °, 90 °, 180 °, and 270 ° within the reactor were turned on 20 min before initiating the reaction. For the photolysis of 2b the reaction was initiated by injection of 500 µL of a 0.01 M stock solution of 2b in CH₃CN into 100 mL of N₂ or O₂ saturated pH 7.1, 0.02 M phosphate buffer (5 vol% CH₃CN-H₂O, µ = 0.5 (NaClO₄)). This generated solutions with initial concentrations of 2b of 5 × 10⁻⁵ M. Slow O₂ or N₂ bubbling was continued throughout the photolysis. Buffers either contained no N₃⁻ or 40 mM N₃⁻. Irradiation times were 90 sec. for UVB and 45 sec. for UVC. The photolysis process and subsequent decomposition of unreacted 2b were analyzed by HPLC (C-8 reverse phase column, 65/35 MeOH/H₂O eluent, 1mL/min, monitored by UV absorbance at 225 nm and 245 nm).

Control experiments regarding the stability of quinol 3b and peroxo compound 7b under UV irradiation were carried out under identical photolysis conditions for 2b with same initial concentration. The reaction mixture was subjected to HPLC examination before and after the UV irradiation in order to determine the amount of 3b or 7b that decomposed. In another control experiment the hydrolysis reaction of 2b in the same phosphate buffer in the dark was monitored.

The following modifications were made for photolysis in CH₃CN. UVC lamps were used as the UV source. The desired amount of 2b was dissolved in ca. 1 mL of CH₃CN. This solution was transferred into 100 mL of O₂ or N₂ saturated CH₃CN in the photolysis reactor by disposable pipette. Reaction solutions were generated with initial concentrations of 2.5 × 10⁻³ M. The photolysis was initiated after the addition of 2b was complete and the reaction solution was fully mixed. Irradiation times were variable, ranging from 3 to 15 minutes. The progress of photolysis as a function of irradiation time was monitored by HPLC. The HPLC conditions for monitoring the photolysis of 2b were: C-8 reverse phase column, 65/35 MeOH/H₂O eluent, 1mL/min, monitored by UV absorbance at 225 nm and 245 nm.

In photoproduct studies, quinols 3a and 3b, phenols 6a and 6b were identified by direct comparison to authentic samples. Isolation and characterization of 7a and 7b were performed by undergraduate student Kyoung Joo Jin. Quantification of all products was obtained by calibration of HPLC peak areas with those of known concentrations of the photolysis products.

4-(Methylperoxy)-4-phenyl-2,5-cyclohexadinen-1-one (7a): Clear oil at room temperature. IR (thin film) 3060 (w), 2965 (w), 1668, 1630, 1449, 1390, 1165, 1063, 1000, 855, 752, 696 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) δ 3.91 (3H, s), 6.31(2H, d, J = 10.5 Hz), 7.03 (2H, d, J = 10 Hz), 7.38 (5H, m); ¹³C NMR (125.8 MHz, CD₂Cl₂) δ 64.44, 81.35, 126.27, 129.26, 129.33, 129.73,
137.13, 148.50, 185.60; LC/MS (ESI, positive) m/e 192 (M + Na – CH₃O₂)+, 217 (M + H)+, 239 (M + Na)+; High-resolution MS (ES, positive), C₁₃H₁₂O₃Na (M + Na) requires 239.0684, found 239.0694.

4-(Methylperoxy)-4-(4’-methylphenyl)-2,5-cyclohexadien-1-one (7b): Clear oil at room temperature. IR (thin film) 3030 (w), 2963 (w), 1668, 1630, 1390, 1165, 1065, 1005, 958, 856, 815 cm⁻¹; ¹H NMR (500 MHz, CD₂Cl₂) δ 2.34 (3H, s), 3.90 (3H, s), 6.30 (2H, d, J =10 Hz), 7.03 (2H, d, J =10.5 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.5 Hz); ¹³C NMR (125.8 MHz, CD₂Cl₂) δ 21.19, 64.41, 81.25, 126.18, 129.57, 129.90, 134.02, 139.56, 148.73, 185.63; LC/MS (ESI, positive) m/e 206 (M + Na – CH₃O₂)+, 253 (M + Na)+, 269 (M + K)+; High-resolution MS (ES, positive), C₁₄H₁₄O₃Na (M + Na) requires 253.0841, found 253.0817.
CHAPTER 3

Decomposition of $O$-(4-(4’-methylphenyl)phenyl)-$N$-
methanesulfonylhydroxylamine, 13b
3.1 Introduction

In order to expand the study of the 4′-methyl-biphenyloxyenium ion 1b, the possible generation of the same intermediate from different precursors other than the quinol ester 2b (Chapter 2) needs to be taken into consideration.\textsuperscript{37-40,42-46} Previously, \(O\)-aryl-\(N\)-sulfonyldroxyamines were utilized as possible precursors that yield aryloxenium ions in organic solvents in the presence of acid.\textsuperscript{42,44,45} Compounds that have similar structures were shown to generate arylnitrilium ions under solvolytic conditions.\textsuperscript{65,66} For instance, Novak et al. reported the generation of arylnitrilium ions from sulfate esters of \(N\)-hydroxy-\(N\)-arylacacetamides via N-O bond heterolysis in aqueous and alcohol solutions (Figure 3.1).\textsuperscript{65} The original motivation for studying the solution chemistry of \(O\)-(4-(4′-methylphenyl)phenyl)-\(N\)-methanesulfonylhydroxylamine 13b (Figure 3.2), was to determine if it is a potential source of oxenium ion 1b. We verified that sulfonylhydroxylamine 13b, in part, does generate oxenium ion 1b in aqueous solution through heterolytic O-N bond dissociation.\textsuperscript{73} We also noticed that more than one reaction pathway is involved in the decomposition process of this compound based on several lines of evidence, including the pH-dependence of reaction kinetics, the identities of different products, and the pH-dependent distribution of these products. Since 13b can be ionized to its conjugate base, 13b\(^{-}\) near neutral pH, the pH of the reaction solution may play an important role in determining the chemistry of 13b.

Photochemical generation of 1b from 13b was also attempted but was not successful. It appears that photolysis of sulfonylhydroxylamine 13b predominantly generates the phenoxy radical 5b. Biphenyloxyenium ion 1b was not generated at all since the featured UV absorbance of 1b at 460 nm was not observed.

Figure 3.1 Sulfate esters of \(N\)-arylacacetamide and corresponding nitrenium ion

![Figure 3.1](image)

| \(X = \text{SO}_3^-\) |
| \(Y = \text{Ph, 2-fluoro-phenyl}\) |
Figure 3.2 Methanesulfonylhydroxylamine 13b, oxenium ion 1b, and phenoxy radical 5b.

3.2 Results and Discussion

3.2.1 Decomposition kinetics of 13b in aqueous solution

Sulfonamide 13b was synthesized, according to Scheme 3.1, by amination of hydroxylamine 12 using the aminating agent 11, which was freshly made from 10. Compound 13b was then subjected to a series of decomposition kinetic studies at 30 °C in aqueous media throughout the pH range of 1-13. The effects of buffer concentration and temperature on the reaction kinetics were studied as well.

Scheme 3.1. Synthesis of O-(4-(4’-methylphenyl)phenyl)-N-methanesulfonylhydroxylamine 13b
In part of this work that appeared earlier, a preliminary kinetic study was performed on the decomposition of 13b in aqueous solution within the pH range 1-9. It was discovered that decomposition of 13b remains pH-independent from pH 1 to 7 and exhibits a decrease in the reaction rate from pH 7 to 9 associated with an apparent ionization of 13b. The rate law used in data fitting over the pH range of 1-9 was the first term of eq 3.1.

Focusing on the same reaction but in basic aqueous solution, reaction kinetics were measured at 30 °C in pH 5-8 NaH2PO4/Na2HPO4 buffers, pH 7-9 TrisH+/Tris buffers, pH 9.8 HCO3-/CO3^{2-} buffer, and pH 11-13 NaOH solutions (5 vol % CH3CN-H2O, \( \mu = 0.5 \) (NaClO4)) by UV spectroscopy: 227 and 260 nm were used for monitoring the reactions in buffers while 232 and 269 nm were used for the reactions in NaOH solutions due to a shift in the maximum UV absorbance change. All four wavelengths were applied for monitoring the reaction in HCO3-/CO3^{2-} buffer. Because of the low solubility of 13b in water, all reactions were performed with an initial concentration of sulfonamide 13b of ca. \( 1 \times 10^{-5} \) M to prevent precipitation. Rate constants taken at two wavelengths were averaged at each pH to obtain the observed rate constant \( k_{obs} \). The pH dependence of the decomposition of 13b is summarized in Figure 3.3. The \( k_{obs} \) were fitted to the rate law of eq 3.1. The derived rate constants are presented in Table 3.1, and all observed rate constants are shown in Table 3.2.

**Figure 3.3** pH dependence of the decomposition of 13b in aqueous solution at 30 °C. Red circles correspond to the rate constants for decomposition of 13b determined by UV spectroscopy. Blue circles correspond to the rate constants obtained by HPLC (described below). Data were fitted by eq 3.1 as described in the text. Insert: Spectrophotometric titration curve of 13b at 227 and 259 nm.
\[ k_{\text{obs}} = k_o([H^+]/(K_a + [H^+])) + k_-(K_a/(K_a + [H^+])) \] (3.1)

Table 3.1 Derived rate parameters for the decomposition of 13b

<table>
<thead>
<tr>
<th>T (°C)</th>
<th>( k_o ) (s(^{-1}))</th>
<th>( k_- ) (s(^{-1}))</th>
<th>pK(_a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13b</td>
<td>30</td>
<td>(1.62 ± 0.03) (\times) 10(^{-4})</td>
<td>(2.17 ± 0.07) (\times) 10(^{-5})</td>
</tr>
</tbody>
</table>

The first term of eq 3.1 corresponds to a pH-independent decomposition of neutral 13b. The second term of eq 3.1 corresponds to the uncatalyzed decomposition pathway of the conjugate base of 13b, 13b\(^-\) (Figure 3.4). This term becomes important at pH > pK\(_a\) of 13b. Therefore the dominant process under basic conditions is the pH-independent decomposition of 13b\(^-\). The rate constant for decomposition of 13b\(^-\), \( k_- \), is ca. 7.5 fold smaller than the rate constant for decomposition of its conjugate acid, \( k_o \). Previously ionization of 13b to form its conjugate base 13b\(^-\) near neutral pH was demonstrated by spectrophotometric tritration (pK\(_a\) = 7.8 ± 0.1) (Figure 3.3, insert). This confirmed that the kinetic pK\(_a\) of 13b, 7.77 ± 0.04, is in a good agreement with the observed spectrophotometric pK\(_a\).

Table 3.2 Rate constants for the decomposition of 13b at different pH obtained by UV spectroscopy (\( k_{\text{obs}}^U \)) or HPLC (\( k_{\text{obs}}^H \))

<table>
<thead>
<tr>
<th>pH</th>
<th>( k_{\text{obs}}^U \times 10^4 ) (s(^{-1}))</th>
<th>( k_{\text{obs}}^H \times 10^4 ) (s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.01</td>
<td>1.77 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>1.51</td>
<td>1.63 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>2.01</td>
<td>1.61 ± 0.37 (\times) 10(^{-2})</td>
<td></td>
</tr>
<tr>
<td>2.53</td>
<td>1.58 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>3.12</td>
<td>1.60 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>3.57</td>
<td>1.56 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>4.03</td>
<td>1.56 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>4.66</td>
<td>1.64 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>5.56</td>
<td>1.66 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>5.57</td>
<td>1.67 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>6.03</td>
<td>1.66 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>6.54</td>
<td>1.60 ± 0.05</td>
<td></td>
</tr>
</tbody>
</table>
6.96 | 1.38 ± 0.03
---|---
7 | 1.44 ± 0.01
7.36 | 1.06 ± 0.08
7.42 | 1.14 ± 0.01
7.43 | 1.12 ± 0.01
7.66 | 1.04 ± 0.06
7.92 | 0.74 ± 0.05
8.39 | 0.51 ± 0.11
8.7 | 0.43 ± 0.03
8.87 | 0.34 ± 0.07
9.16 | 0.32 ± 0.05
9.76 | 0.23 ± 0.03
11.5 | 0.16 ± 0.01
11.6 | 0.21 ± 0.49 × 10^{-3}
12.1 | 0.21 ± 0.49 × 10^{-3}
13 | 0.19 ± 0.02

Conditions: 5 vol% CH₃CN-H₂O, \( \mu = 0.5 \) (NaClO₄), 30 °C

**Figure 3.4** Neutral 13b and its conjugate base 13b⁻

For reactions carried out in 0.02 M tris buffers, pH 8.7 and 9.2, and in 0.005 M NaOH solution, pH 11.5, kinetic data were also gathered by monitoring the changes in HPLC peak area for sulfonamide 13b and its three major decomposition products: 3b, 14, and 6b, as provided in Figure 3.5. The detailed product study will be described in Section 3.2.2. HPLC analysis results for hydrolysis of 13b at three different pH are summarized in Figure 3.6.
**Figure 3.5** Three major decomposition products of 13b in an aqueous environment.

![Three major decomposition products of 13b in an aqueous environment.](image)

**Figure 3.6** HPLC peak area measurements as a function of time for the decomposition of 13b at 30 °C in 0.02 M tris buffer, pH 8.7(A), 0.02 M tris buffer, pH 9.2(B), and in 0.005 M NaOH solution, pH 11.5 (C) at 269 nm. In A and B, peak area data for quinol 3b (blue triangle) are obtained at 227 nm while 14 and 6b were obtained at 260 nm. Red circles correspond to sulfonamide 13b; green diamonds correspond to product 14; magenta inverted triangles correspond to product 6b.

![HPLC peak area measurements as a function of time for the decomposition of 13b at 30 °C in 0.02 M tris buffer, pH 8.7(A), 0.02 M tris buffer, pH 9.2(B), and in 0.005 M NaOH solution, pH 11.5 (C) at 269 nm. In A and B, peak area data for quinol 3b (blue triangle) are obtained at 227 nm while 14 and 6b were obtained at 260 nm. Red circles correspond to sulfonamide 13b; green diamonds correspond to product 14; magenta inverted triangles correspond to product 6b.](image)
Data for 13b and the two products 3b and 6b were fitted by a standard first-order rate equation at all three pH. A double exponential rate equation was used for data fitting for product 14. The rate constants obtained for the reaction of 13b based on HPLC analysis are shown in Table 3.3. They are comparable to those determined by UV spectroscopy under the same conditions. The two products 3b and 14 were still formed in tris buffers at pH up to ca. 9.0, but they were no longer produced when the pH of the solution reached 10. 3b was stable in tris buffers at pH 8.7 and 9.2 whereas 14 decomposed at a rate smaller than its rate of formation. In more basic NaOH solution, no observation of the peaks corresponding to 3b and 14 or their decomposition products was made. Phenol 6b was the only observable product.

The stabilities of 3b and 14 in basic aqueous media incubated at 30 °C were studied by HPLC examination as well. A fast decomposition of ca. $1 \times 10^{-5}$ M of 3b in 0.1 M NaOH solution, pH 12.8 was observed. No HPLC peak corresponding to 3b can be detected within the detection limit after 1 h. Instead a new peak which has a similar HPLC retention time as 3b was found. It is likely that 3b undergoes a base-catalyzed acyloin rearrangement. This product was not observed during the reaction of 13b in NaOH solution. On the other hand, consistent with what we observed during the decomposition of 13b in 0.02 M tris buffer, pH 9.2 at 30 °C, 14 with an initial concentration of ca. $1 \times 10^{-5}$ M did slowly decompose with a first-order rate constant of $(5.26 \pm 0.04) \times 10^{-6}$ s$^{-1}$. The decomposition products of 3b and 14 were not further identified. In the other control experiment regarding the stability of 14 in 0.02 M phosphate buffer, pH 7.1, at 30 °C, no change in the HPLC peak area for 14 was observed over a time period of 10 half-lives for the decomposition of 13b at this pH. Compound 14 remains stable in phosphate buffers.
Table 3.3 Rate constants obtained by HPLC analysis of decomposition of 13b at pH 8.7, 9.2, and 11.5

<table>
<thead>
<tr>
<th>pH 8.7</th>
<th>4.24 ± 0.66</th>
<th>3.53 ± 0.29</th>
<th>3.75 ± 3.80</th>
<th>2.68 ± 1.40</th>
<th>4.08 ± 0.06</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 9.2</td>
<td>3.87 ± 0.07</td>
<td>3.66 ± 0.20</td>
<td>4.85 ± 1.30</td>
<td>2.74 ± 0.68</td>
<td>3.65 ± 0.15</td>
</tr>
<tr>
<td>pH 11.5</td>
<td>1.73 ± 0.04</td>
<td></td>
<td></td>
<td></td>
<td>1.56 ± 0.16</td>
</tr>
</tbody>
</table>

Kinetic results obtained in 0.02 M phosphate buffer, pH 7.4 (Figure 3.7(A)), and in 0.02 M tris buffer, pH 7.6(Figure 3.7(B)) show that the decomposition kinetics of 13b is independent of buffer concentration in the range of 0.01-0.04 M.

Figure 3.7 Rate constants for the decomposition of 13b in 0.02 M phosphate buffer, pH 7.4(A) and in 0.0.2 M tris buffer, pH 7.6(B) at different buffer concentrations.
3.2.2 Product, buffer effects and temperature dependence studies of the decomposition of 13b

Three major products observed by HPLC for the decomposition of 13b in the absence of strong nonsolvent nucleophiles in aqueous solutions were generated in consistent pH-independent yields at pH 4-7. These products were isolated from a large scale hydrolysis reaction of 13b in 0.02 M acetate buffer, pH 4.6, at 30 °C. Two products were identified as 4-(4’-methylphenyl)-4-hydroxy-2,5-cyclohexadien-1-one 3b, and 4’-methylbiphenyl-4-ol 6b by comparison to authentic samples. Quinol 3b is the most significant product at pH < 7. As presented in Chapter 2, it is the expected product of the attack of water on biphenyloxenium ion 1b at C-4. The identity of the third product was confirmed as N-(4-hydroxy-4’-methylbiphenyl-3-yl)methanesulfonamide 14 by analysis of NMR and LC-MS data. The individual yields of 3b, 14, and 6b determined by HPLC quantification after 10 half-lives (ca. 12 h) of the hydrolysis of 13b were (37.4 ± 1.1)%, (34.3 ± 1.5)%, and (9.1 ± 1.1)% in 0.02 M acetate buffer, pH 4.6, and were (34.5 ± 3.5)%, (28.6 ± 0.5)%, and (12.1 ± 1.1)% in 0.02 M phosphate buffer, pH 7.1. In basic solutions at pH > 7, the yield of phenol 6b increases whereas the yields of 3b and 14 decrease with increasing pH. In NaOH solutions, 6b becomes the most significant product while 3b and 14 are no longer observable. Based on HPLC quantification 6b accounted for (70.6 ± 2.8)% of the decomposition products of 13b in 0.005 M NaOH solution, pH 11.5. Yields of the three major decomposition products of 13b in aqueous solutions at pH 4-13 obtained by HPLC quantification are summarized in Figure 3.8. Data for 3b and 14 were fitted to eq 3.2 and eq 3.3 respectively. Terms [3b]o and [14]o are the maximum concentrations of 3b and 14 formed under acidic conditions. A titration curve (eq. 3.4) was used to fit the concentration vs. pH data for 6b. Parameters [6b]o and [6b] represent, respectively, the limiting concentration of 6b produced from the decomposition of 13b under acidic conditions, and from 13b- under basic conditions.
Figure 3.8 pH dependence of the yields of decomposition products generated from 13b. Data for 3b (blue triangles) and 14 (green diamonds) were obtained at 227 nm while data for 6b (magenta inverted triangles) were obtained at 260 nm. Initial concentration of 13b is ca. 1 × 10^{-5} M.

\[ [3b] = [3b]_o ([H^+] / (K_a' + [H^+])) \]  
\[ [14] = [14]_o ([H^+] / (K_a' + [H^+])) \]  
\[ [6b] = [6b]_o ([H^+] / (K_a' + [H^+])) + [6b]_o (K_a' / (K_a' + [H^+])) \]  

Table 3.4 pK_{a'} obtained from yields vs. pH data for 3b, 14 and 6b

<table>
<thead>
<tr>
<th>Data fitting</th>
<th>3b</th>
<th>14</th>
<th>6b</th>
<th>Average pK_{a'}</th>
</tr>
</thead>
<tbody>
<tr>
<td>pK_{a'}</td>
<td>8.76 ± 0.07</td>
<td>8.71 ± 0.09</td>
<td>9.15 ± 0.15</td>
<td>8.84 ± 0.19</td>
</tr>
</tbody>
</table>

Based on the average of all three fittings (Table 3.4), the apparent pK_a, pK_{a'}, can be obtained as (8.84 ± 0.19). This pK_{a'} differs in magnitude from the thermodynamic pK_a of 13b (7.77 ± 0.04). Since k_o is 7.5-fold larger than k_s, the products generated from 13b have a kinetic advantage over those from 13b, and that results in the difference between pK_{a'} and pK_a. This deviation can be derived by modifying the original pK_a with a kinetic factor: k_o/k_s as shown in eq 3.5. The calculated pK_{a'} (8.64 ± 0.05), obtained by eq 3.5 and the kinetic parameters of Table 3.1, is in good agreement with the one derived from product yields vs. pH data fitting.

\[ pK_{a'} = pK_a + \log(k_o/k_s) \]  

Results of the buffer effects on product yields in two different buffers over the concentration range from 0.01 to 0.04 M in buffer are summarized in Figure 3.9. Yields of all three products in both phosphate and tris buffer show little sensitivity to buffer concentration. Studies of temperature dependence of the rate constants for the hydrolysis of 13b in 0.02 M acetate buffer, pH 4.6, were performed at 30, 40, and 50 °C (Figure 3.10). Derived ΔH^\ddagger and ΔS^\ddagger are (95.4 ± 3.0)
kJ/mol and (-1.5 ± 9.6) J/K mol, respectively. Positive entropy of activation is usually expected for an ionization process in the gas phase. It is more complicated to analyze a reaction mechanism based on activation parameters in solvent environment. Moreover the activation parameters of the decomposition of 13b are not derived from a single pathway but a combination of three different pathways. It cannot be simply related to any individual path. Product studies focusing on the proportion of decomposition products at different temperatures (30 and 50 °C) also show that there is no significant change in the proportion of 3b, 14, and 6b. Yields of each individual product at the two temperatures are summarized in Table 3.5. This suggests that the energy barriers for pathways involved in the decomposition chemistry of 13b at pH < 7 are only slightly different from each other. It is difficult to estimate the activation parameters for all three paths because of the small dependence of the yield of products on temperature.

**Figure 3.9** Concentrations of decomposition products of 13b determined by HPLC quantification in 0.02 M phosphate buffer, pH 7.5(A) and in 0.02 M tris buffer, pH 7.8(B). Buffer concentration ranges from 0.01 M to 0.04 M. Blue triangles: quinol 3b; green diamonds: rearrangement product 14; magenta inverted triangles: phenol 6b.
Figure 3.10 Temperature dependence of the decomposition rate constant (ln($k_{obs}/T$)) of 13b. Reactions were performed in 0.02 M acetate buffer, pH 4.6, at 30, 40, and 50 °C.

Table 3.5 Product yields at 30 and 50 °C in pH 4.6 acetate buffer.

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Yield of 3b</th>
<th>Yield of 14</th>
<th>Yield of 6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 °C</td>
<td>(37.4 ± 1.1) %</td>
<td>(34.3 ± 1.5) %</td>
<td>(9.1 ± 1.2) %</td>
</tr>
<tr>
<td>50 °C</td>
<td>(33.3 ± 2.1) %</td>
<td>(34.7 ± 2.5) %</td>
<td>(7.3 ± 0.3) %</td>
</tr>
</tbody>
</table>

3.2.3 Azide trapping studies

As a result of the azide trapping experiments performed on 13b in 0.02 M phosphate buffer, pH 7.0, as shown in Figure 3.11, azide adduct 4b is generated at the expense of the quinol 3b.\textsuperscript{73} As [N\textsubscript{3}\textsuperscript{-}] increases this trapping occurs without overall rate acceleration (Figure 3.11, insert).
Figure 3.11 Azide trapping results for 13b in 0.02 M phosphate buffer, pH 7.0. HPLC peak area vs. [N$_3^-$] data for 3b (blue triangle) and azide adduct 4b (rose cross) were fitted by least-squares procedures to the standard “azide-clock” equations eq 2.2 and eq 2.3, respectively. Insert: rate constants for decomposition of 13b in the presence of N$_3^-$ remain consistent.

Yields of water and N$_3^-$ derived products 3b and 4b vary with increasing [N$_3^-$] in a manner consistent with that observed for quinol esters 2a and 2b, precursors for oxenium ions 1a and 1b. The selectivity ratio for 1b, $k_{az}/k_s$, measured previously is $(1.2 \pm 0.1) \times 10^3$ M$^{-1}$. This ratio is experimentally indistinguishable from $k_{az}/k_s$ of $(1.0 \pm 0.2) \times 10^3$ M$^{-1}$ measured from azide trapping experiments performed on 2b (Chapter 2, Section 2.2.1). The equivalence of the measured selectivity ratio and of the two reaction products 3b and 4b generated from the two different precursors 2b and 13b indicates that they both generate the same cation, 1b, during hydrolysis. However, unlike for the hydrolysis of 2b, ionization of 13b leading to the cationic intermediate 1b is not the only pathway for the decomposition of 13b in water since it is not responsible for the formation of the other two products simultaneously formed with 3b in the same reaction. The effect of [N$_3^-$] (0-0.03 M) on the yield of 14 and of 6b was examined in 0.02 M phosphate buffer, pH 7, by HPLC under reaction conditions identical to those used previously. The peak area data for quinol 3b and azide adduct 4b were collected as well. Results of that study are summarized in Figure 3.12. Data for quinol 3b and azide adduct 4b were fitted by least-squares procedures to “azide-clock” equations eq 1.2 and eq 1.3, respectively. The observed value of $k_{az}/k_s$ of $(1.3 \pm 0.2) \times 10^3$ M$^{-1}$ is experimentally equivalent to the value obtained by azide trapping experiments performed on 13b (see above) and 2b (Chapter 2, Section 2.2.1). Neither 14 nor 6b responds significantly to the changes in N$_3^-$ concentration under the reaction.
conditions. This indicates that the pathways leading to 14 and 6b do not involve the cationic intermediate 1b that is trapped by N3\(^-\). Other pathways should be considered.

**Figure 3.12** Yield of 3b (blue triangle), 14 (green diamond), 6b (magenta inverted triangle), and 4b (orange plus) at pH 7 in 0.02 M phosphate buffer at different [N\(_3\)]\(^-\). Data for 4b, 14, and 6b shown in this figure were obtained at 260 nm, data for 3b were obtained at 227 nm.

3.2.4. **Proposed reaction mechanism for the decomposition of 13b in aqueous solution**

The dependence of decomposition kinetics and product yields on pH, and the lack of effect of N3\(^-\) on the formation of 14 and 6b at neutral pH indicate that there are several competing pathways for the decomposition of 13b over the pH range examined. A mechanism that is consistent with all the kinetic data and azide trapping results for the decomposition of 13b in aqueous solutions over a wide range of pH (1-14) is presented in Scheme 3.2.

3.2.4.1. **Different pathways for the decomposition of 13b under different conditions**

The scheme proposed that the three major decomposition products are generated by four different pathways. Paths I through III are proposed to account for the products generated from 13b via \(k_\alpha\), while path IV is proposed to account for the generation of 6b from 13b\(^-\) via \(k_\beta\).
SCHEME 3.2 Proposed mechanism for the decomposition of 13b in aqueous solution

Since the quinol 3b is the most abundant product at pH < pK_a’, path I is a major pathway for the decomposition of 13b under these conditions. It was confirmed that quinol 3b is produced through the intermediacy of an oxenium ion 1b by azide trapping experiments performed on 13b and previous 18O-labeling studies.68,73 It is, however, not the exclusive pathway under these conditions since the production of the other major products 14 and 6 do not require going through 1b.

The rearrangement product 14 is reminiscent of similar rearrangement products generated during the decomposition of N-arylhydroxylamine derivatives in aqueous solution.74,75 The insensitivity of the yield of 14 toward [N_3^-] could be used to support a mechanism involving a completely separate pathway, a concerted 1,3-rearrangement accompanying O-N bond cleavage shown as Path II,132 or alternatively, an ion-pair rearrangement proceeding through a very short-lived tight ion-pair.133 It is not possible to decide between these alternatives at this time, but the concerted pathway is preferred. In aqueous solution free ion 1b is a relatively stable cation (lifetime = 170 ns) with a high azide/solvent selectivity ratio, k_{az}/k_s, of 1.0 × 10^3 M^{-1}. Novak et al
systematically studied the effect of aryl nitrenium ion stability on the involvement of ion pairs in the hydrolysis of corresponding esters of N-arylhydroxylamines. They found that if the nitrenium ion is highly selective with \( k_{ax}/k_s \) in the range of that observed for 1b, the yield of the rearrangement product arising from the ion-pair is typically very low (less than 5 %). This is due to the fact that the ion pair has a very short lifetime in water (ca. \( 10^{-10} \) s), and if the ion is selective, the ion-pair does not react significantly at that stage. In this case, the yield of rearrangement product 14 is almost equal to that of quinol 3b, and the cation 1b is highly selective. These observations suggest that 14 is less likely to result from the ion-pair. In order for the rearrangement product 14 to be generated through the ion-pair, \( k_r \) (Scheme 3.3) will need to be nearly equivalent to \( k_{-d} \), the diffusion-limited rate constant for the ion pair separation, based on the relative yield of 3b and 14 (ca. 1:1). However, a \( k_r \) of \( 10^{10} \) s\(^{-1}\) is ca. 100 fold larger than that observed in the similar reactions for aryl nitrenium ions.

**Scheme 3.3 Ion-pair mediated pathway**

At pH \( \leq 7.0 \), the detection of 6b reveals that a third pathway for reaction of 13b (Path III) under acidic conditions must occur. The phenoxy radical 5b, derived from a homolytic cleavage of the N-O bond accompanied with the generation of another species 18, may be responsible for the formation of 6b in ca. 10% yield at pH \( \leq 7 \).

Under basic conditions the yield of phenol 6b increases dramatically up to ca. 70%. Compounds 3b and 14 were simultaneously suppressed and finally not detectable in NaOH solutions. The dominant form of 13b in basic solution is the ionized species, 13b\(^{-} \); path I, II, and III are no longer viable at pH > pK\(_a\). A stepwise base-catalyzed \( \alpha \)-elimination (path IV)
proceeding via $13b^-$ can explain the increased generation of $6b$ at $pH > pK_a^-$, although path III may still contribute to $6b$ up to ca. $pH$ 9.0. A $pK_a$ of 10 makes $6b^-$ a relatively good leaving group. There can be little doubt from these results that the rate-limiting step is the N-O bond dissociation, due to the fact that $13b^-$ is detected spectrophotometrically at basic $pH$.

3.2.4.2. Attempted detection of methansulfonylnitrene 15

According to the mechanism described above (Scheme 3.2), methanesulfonylnitrene 15, is required to be formed along with $6b^-$ under basic conditions. Sulfonyle nitrenes, $RSO_2N$, are known reactive intermediates that can be generated from sulfonyl azides and other precursors by thermolysis in aprotic solvents or photolysis in protic solvents.135,136 Methanesulfonylnitrene, 15, has a triplet ground state based on a triplet EPR signal observed at very low temperature.137,138 Nitrene 15 can react as a diradical (triplet) undergoing H-abstraction or as an electrophile (singlet) inserting into aromatic or aliphatic hydrocarbons.135,136 It was reported that 15, generated from photolysis of methanesulfonyl azide in EtOH, underwent both H-abstraction and O-H insertion leading to methanesulfonamide 16 (yield: 43%) and N-ethoxymethanesulfonamide 17 (yield: 48%) respectively.139 Methanesulfonamide 16 can be easily detected by GC,140 but the characterization for N-ethoxymethanesulfonamide was not reported in the literature.139 To investigate the possible generation of 15, MeOH solutions containing 1 mM and 10 mM NaOMe were employed as reaction media for the decomposition of $13b$ at 30 °C in the dark to replace the aqueous NaOH solutions. Standard $N$-methoxymethanesulfonamide 17 (Figure 3.13) was synthesized for comparison purposes.141

*Figure 3.13* $N$-methoxymethanesulfonamide 17.141

![17]

The reaction process was periodically followed by HPLC and GC-MS. The decomposition rate of 13b is [MeO-] dependent. Compound 13b decomposed faster in MeOH solution with lower base concentration. Compared to the reaction of 13b in basic aqueous solutions, the decomposition in basic MeOH at the same temperature was much slower. It required ca. 1 month for 13b with an initial concentration of 0.01 M to disappear in 10 mM NaOMe/MeOH solution
incubated at 30 °C. HPLC analysis of the reaction mixture shows that 6b is the most significant decomposition product of 13b in basic MeOH solution. Methanesulfonamide 16 was found with an increasing yield during the course of the reaction by GC-MS. It is the expected product arising from triplet 15 through H-abstraction. However, the expected O-H bond insertion product MeSO₂NH-OMe attributed to singlet 15 was not detected. This result is consistent with that recently reported by Desikan et al. ¹⁴² They reported a nearly quantitative yield of methanesulfonamide 16 for direct photolysis of methanesulfonyl nitrene precursor in MeOH but no observation of 17. They were not able to directly detect 15 by nanosecond time-resolved IR spectroscopy (ns-TRIR) suggesting that singlet 15 must have a lifetime shorter than 50 ns, which is the time resolution of ns-TRIR spectrometer. ¹⁴² It is likely, therefore, in MeOH the singlet-triplet intersystem crossing is dominant over the reaction of singlet nitrene.

3.2.5 Attempted photogeneration of 1b from 13b

Previously the direct detection of the generation of oxenion ion 1b and phenoxy radical 5b from nano-second laser flash photolysis (ns-LFP) of quinol ester 2b in aqueous solution and exclusive generation of 5b from LFP of 2b in CH₃CN were described (Chapter 2, Scheme 2.5). ⁷⁶,⁷⁷ As another type of precursor for cation 1b under hydrolysis conditions, sulfonamide 13b was subjected to the investigation of its photochemistry as well. Steady state photolysis of 13b was carried out at initial concentrations of 13b of ca. 1 × 10⁻⁵ M in N₂-saturated 5 vol% CH₃CN-H₂O buffered with 0.02 M phosphate buffer, pH 7.1, and in N₂ or O₂-saturated CH₃CN with an initial concentration of 13b of 5 × 10⁻⁵ M. The aqueous reaction solution was examined by HPLC immediately after irradiation. As the initial concentration of 13b for the reactions in CH₃CN was relatively higher, photolysis of 13b was monitored by HPLC as the irradiation time was increased and the reaction proceeded.

HPLC analyses showed that there was little difference in terms of the photoproducts between the reactions in aqueous buffers and in CH₃CN or between the reactions carried out in N₂ saturated and O₂ saturated reaction media. In all cases rearrangement product 14 and phenol 6b were both formed. The initial relative yield of 6b and 14 is ca. 3:1 in aqueous solutions and in CH₃CN. Both 14 and 6b started decomposing with long irradiation time, but 14 was more photosensitive than 6b. Utilizing the UVC lamp as the UV source, in N₂-saturated aqueous buffer 14 was detected after irradiation for 15 s but not detectable after irradiation for 45 s while
6b still remained; in CH3CN with the initial concentration of 13b 5 fold larger than that in aqueous solution, the concentration of 14 decreased after 300 s irradiation while the concentration of 6b did not decrease until exposure to the UV light for 360 s. Quinol 3b was not identified as a photoproduct of 13b in any case. Compound 13b was also subjected to ns-LFP in Ar or O2 saturated 50 vol% CH3CN-H2O buffered by pH 7.1 phosphate buffer, and in CH3CN. The UV spectra for the reaction in O2-saturated aqueous solutions taken immediately after the laser flash are shown in Figure 3.14 (A). They are identical to the UV spectra for reactions in CH3CN under the same condition. Two transient absorbance bands at λmax 300 nm (A-300) and λmax 360 nm (A-360) were observed and no absorbance was observed at longer wavelength. Figure 3.14 (B) shows the UV spectra taken after the LFP of 2b in 5 vol% CH3CN-H2O buffered by pH 7.1 phosphate buffer. It has been proven that the absorbance band at 360 nm resulted from the phenoxy radical 5b generated from photolysis of 2b.76,77 The transient with λmax 360 nm generated from photolysis of 13b shows identical UV absorption feature as the phenoxy radical 5b generated from photolysis of 2b.

Figure 3.14 Transient absorbance spectra obtained after 266 nm excitation of 13b in O2-saturated 50 vol% CH3CN-H2O at pH 7.1(A) and the spectra taken after 266 nm excitation of 2b in O2-saturated 5 vol% CH3CN-H2O at pH 7.1(B). Key for A: red, 20 ns after flash; green, 100 ns. Key for B: red, 20 ns after flash; green, 120 ns; blue, 220 ns.
Kinetics of the decay of A-300 and A-360 monitored at 300 nm and 360 nm, respectively, at room temperature are summarized in Figure 3.15.

**Figure 3.15** Decay of UV absorbance bands A-360 (A) and A-300 (B) in O₂-saturated phosphate buffer, pH 7.1 (50 vol% CH₃-H₂O, μ = 0.5 (NaClO₄)). Data were fitted to a double exponential rate equation for (A) and a triple exponential rate equation (eq 2.5, in text) for (B) (blue curves).
The transient associated with A-360 decays in a biphasic manner. Data in Figure 3.15 (A) were fitted by a double exponential rate equation. Two derived rate constants for the decay of A-360 in 50 vol% CH$_3$CN-H$_2$O are similar in the magnitude to those for the decay of 5b in 5 vol% CH$_3$CN-H$_2$O (Table 3.6). Based on the UV spectra and the decay kinetics, the transient species with $\lambda_{\text{max}} = 360$ nm generated from LFP of 13b is identified as phenoxy radical 5b. Cation 1b is not generated in the same reaction since its characteristic UV absorbance at 460 nm was not observed. Therefore, the homolytic dissociation of 13b to generate the phenoxy radical 5b is the dominant process for the photolysis reaction of 13b. This conclusion is supported by the product study results obtained for steady state photolysis of 13b: quinol 3b, produced through the intermediacy of 1b, was not observed under photolysis conditions. Instead, phenol 6b becomes the major photoproduct as a result of the intermediacy of 5b.

Modeling of the decay kinetics of the other transient species associated with A-300, on the other hand, is difficult because of the scattered data. Fitting the data by a triple exponential rate equation (Chapter 2, eq 2.7) (Figure 3.15 (B)) shows that an additional process with a large rate constant of $k_1 = (3.22 \pm 0.46) \times 10^5$ s$^{-1}$ that only can be observed at 300 nm occurs in the first few microseconds after photolysis. This rate constant is one order of magnitude larger than any of those observed for the decay of 5b. In fact the other two rate constants derived from the same fitting, shown in Table 3.6 as $k_2$ and $k_3$ for decay of A-300, appears to be more comparable with the decay rate constants of 5b. This indicates that, the absorption at 300 nm is attributed, in part, to 5b and to another shorter lived species. The identity of this species still remains unclear. It is not likely to be either singlet or triplet nitrene 15 since 15 cannot be detected by ns-TRIR method. Given the fact that the rearrangement product 14 was also generated photochemically, this rapidly decayed species might be an excited state leading to 14. Further investigation will be pursued in the future work.
Table 3.6 Decay rate constants for phenoxy radical $5b$ in O$_2$-saturated 5 vol% CH$_3$CN-H$_2$O and for two absorbance bands A-360$^b$ and A-300$^c$ observed after LFP of $13b$ in O$_2$-saturated 50 vol% CH$_3$CN-H$_2$O.$^d$

<table>
<thead>
<tr>
<th></th>
<th>$k_1 \times 10^{-4}$ (s$^{-1}$)</th>
<th>$k_2 \times 10^{-4}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decay of $5b$ in 5 vol% CH$_3$CN-H$_2$O, O$_2$ sat.$^a$</td>
<td>8.06 ± 0.08</td>
<td>1.29 ± 0.02</td>
</tr>
<tr>
<td>Decay of A-360 in 1/1 CH$_3$CN-H$_2$O, O$_2$ sat.$^b$</td>
<td>3.44 ± 0.48</td>
<td>0.68 ± 0.09</td>
</tr>
<tr>
<td>Decay of A-300 in 1/1 CH$_3$CN-H$_2$O, O$_2$ sat.$^c$</td>
<td>$k_2 = 1.45 \pm 0.13$</td>
<td>$k_3 = 0.24 \pm 0.13$</td>
</tr>
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</table>

$^a$Rate constants were obtained from a single measurement. $^b$Rate constants and error limits are averages and standard deviations of four independent measurements. $^c$Derived from a single measurement has the least scattered data. Three rate constants $k_1$, $k_2$, and $k_3$ were derived from the data fitting. Only $k_2$ and $k_3$ are shown in the table, $k_1$ is described in the text separately. $^d$All the absorbance data for A-300 and A-360 except the data collected within the first 1 μs were used in data fitting.

3.4 Conclusion

Originally methanesulfonylhydroxylamine $13b$ was considered to be the potential precursor of 4’-methyl-4-biphenylyloxenium ion $1b$. Kinetically, first-order azide trapping without overall rate acceleration demonstrates that $13b$ does generate biphenylyloxenium ion $1b$ like quinol ester $2b$ under solvolytic conditions. Unlike the hydrolysis of $2b$, however, ionization that leads to the cation $1b$ is not the only pathway for the decomposition of $13b$ in aqueous solution since three major products including quinol $3b$, rearrangement product $14$ and phenol $6b$ were identified. The formation of these products is pH-dependent. The insensitivity of $14$ and $6b$ to azide also indicates that they result from mechanisms not going through the intermediacy of a cationic intermediate. The rearrangement product $14$ is more likely to be produced directly from $13b$ through concerted intramolecular rearrangement, than from the ion-pair. This argument is reinforced by the relatively high selectivity of oxenium ion $1b$, the high yield of $14$, and the short lifetime of the ion-pair in water. Formation of phenol $6b$ under acidic conditions may require homolytic dissociation of the O-N bond in $13b$. Formation of $6b$ under basic conditions, on the other hand, is mainly due to a base-catalyzed $\alpha$-elimination of $13b$ via its conjugate base $13b^\cdot$. The pH dependence of the decomposition kinetics of $13b$, and the good agreement of the kinetically observed $pK_a$ with the spectrophotometrically observed $pK_a$ for $13b$ both confirm that $13b^\cdot$ is generated at pH $> pK_a$ with a lifetime of ca. $3.20 \times 10^4$ s. Cation $1b$ only forms at the pH
when neutral $13b$ still dominates in the solution. Accompanying the generation of $6b^-$, the conjugate base of $6b$, methanesulfonylnitrene $15$ can be produced from $13b^-$. An attempted detection of nitrene $15$ under basic solvolytic condition at the same temperature was performed on $13b$ in basic MeOH solution. Methanesulfonamide $16$, the expected product arising from H-abstraction of triplet nitrene $15$ was observed, although methoxymethanesulfonamide $17$, the expected product of the O-H bond insertion of singlet nitrene $15$ was not observed. This is probably because the singlet-triplet intersystem crossing is kinetically dominant over the reaction of the singlet nitrene in MeOH.

It has been demonstrated that LFP of $2b$ generates two transient species, oxenium ion $1b$ and phenoxy radical $5b$, that are responsible for the formation of a variety of photoproducts in aqueous solution. In comparison with this, LFP of $13b$ does not generate oxenium ion $1b$ but the phenoxy radical $5b$. This conclusion is supported by the direct observation of the UV spectra taken after LFP, and by the fact that quinol $3b$ is not detected as the photoproduct at all. There is another fast decay process observed at 300 nm. This process was not detected at 360 nm so that it is not related to $5b$. Since both phenol $6b$ and rearrangement product $14$ were generated from steady state photolysis of $13b$, it is possible that the fast decay process observed at 300 nm is due to an excited state leading to the rearrangement product. Identify of this species will be subjected to further investigation.

### 3.5 Experimental

#### 3.5.1 Synthesis:

Compound 4'-methylbiphenyl-4-ol $6b$ was made by a Suzuki coupling procedure provided in Chapter 2. $^{128,129,143}$ Sulfonamide $13b$ was synthesized by treatment of $O$-(4'-methylbiphenyl-4-yl)hydroxylamine $12$ with methanesulfonyl chloride in pyridine. $^{67}$ The hydroxylamine was generated by amination of $6b$ using aminating agent $11$ through a previously published procedure. $^{144}$

$t$-Butyl-$N$-mesitylenesulfonyloxycarbamate (10). $^{144}$ Mesitylenesulfonyl chloride (5.46 g, 0.025 mol) and $t$-butyl-$N$-hydroxycarbamate (3.32 g, 0.025 mol) were dissolved in 100 mL of ether. 3.5 mL of triethylamine was added in a dropwise fashion into the reaction mixture while stirring in
an ice-water bath. After the completion of the addition, the reaction mixture was stirred in the
ice-water bath for another 30 min. It was then filtered, the precipitate was washed with cold ether
(2 × 15 mL). Combined filtrates were subjected to rotary evaporation to remove ether. The
remained residue was immediately dissolved in 8 mL of warm benzene following the addition of
30 mL of warm petroleum ether to precipitate the product. The mixture was then filtered to
collect the precipitate. (yield: 96%) m.p.104-106 °C. lit\textsuperscript{144}. m.p. 102-104 °C. \textsuperscript{1}H NMR (300 MHz,
CDCl\textsubscript{3}) δ 1.33 (9H, s), 2.34 (3H, s), 2.69 (6H, s), 7.01 (2H, s), 7.01 (2H, s), 7.71 (1H, s).

\textbf{O-Mesitylenesulfonylhydroxylamine (11).}\textsuperscript{144} \textbf{10} (4g, 12.7 mmol) was added to 15 mL of
trifluoroacetic acid kept in an ice-water bath. The reaction solution was stirred for 5 min then
poured in to 100 mL of ice water. White solid was filtered out of the mixture, dissolved in
minimum amount of ether, and then precipitated again by the addition of three to two times the
volume of petroleum ether. The mixture was cooled in ice for 15 min and filtered to obtain the
product. (yield: 34%) \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 2.31 (3H, s), 2.62 (6H, s), 4.39 (3H, s, br),
6.98 (2H, s)

\textbf{O-(4'-Methylbiphenyl-4-yl)hydroxylamine (12).} \textbf{6b} (1.27 g, 6.9 mmol) was dissolved in 14 mL of MeOH. Potassium t-butoxide (0.774 g, 6.9 mmol) was added quickly. The resulting solution was allowed to cool to room temperature before removing the solvent by rotary evaporation. The
solid residue was kept under a vacuum for 24 h. The solid was then suspended in 8 mL of dry DMF,
stirring under N\textsubscript{2} while it was cooled in an ice-water bath. A solution of freshly prepared \textbf{11} (1.32
g, 6.1 mmol) in 6 mL of dry DMF was added all at once from an additional funnel, and the
mixture was stirred in the ice-water bath for 30 min. The reaction mixture was then diluted with
100 mL of water and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 50 mL). The combined extracts were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated to dryness. Residual DMF was removed by subjecting
the sample to a vacuum of ca. 0.1 torr overnight. The crude product was purified by column
cchromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2} eluent).yield: 50%. m.p.117-118.5 °C; IR 3318, 1606,
1494, 1244, 1136, 1120 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}) δ 2.32 (3H, s), 6.94 (2H, s), 7.13
(2H, d, J = 8.7 Hz), 7.22 (2H, d, J = 7.8 Hz), 7.47-7.54 (4H, m); \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) δ
20.6, 113.4, 125.9, 127.1, 129.4, 132.1, 135.7, 161.1.

\textbf{O-(4-(4'-Methylphenyl)phenyl)-N-methanesulfonylhydroxylamine (13b).} \textbf{12} (0.11g, 0.5
mmol) was dissolved in 1 mL of dry pyridine, and the resulting solution was stirred under N\textsubscript{2}
while methanesulfonyl chloride (54 µL, 0.7 mmol) was added via syringe. The mixture was
stirred overnight at room temperature, then diluted with 10 mL of CH₂Cl₂, and washed with water (2 × 4mL) and brine (2 × 4mL). The organic solution was dried over anhydrous Na₂SO₄, filtered, and evaporated by rotary evaporation. The residue was subjected to vacuum overnight. The solid remained was purified by recrystallization from CH₂Cl₂. (yield: 51%) m.p.114-116 °C; IR 3144, 1601, 1489, 1312, 1146 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 2.33 (3H, s), 3.18 (3H, s), 7.21-7.26 (4H, m), 7.51 (2H, d, J = 8.0 Hz), 7.61 (2H, d, J = 8.6 Hz), 10.82 (1H, s); ¹³C NMR (75 MHz, DMSO-d₆) δ 21.5, 37.9, 115.4, 127.1, 128.3, 130.4, 135.7, 137.1, 137.5, 159.8.

N-(Methoxy)methanesulfonamide (17). Methanesulfonyl chloride (0.93 mL, 12 mmol) was added to a stirred solution of methoxyamine hydrochloride (1.02 g, 12 mmol) in 10 mL of MeOH/H₂O mixture (3:1) that was cooled in an ice-water bath. K₂CO₃ (1.665 g, 12 mmol) in 4 mL of H₂O was added to the reaction mixture in a dropwise fashion. After 15 min the ice-water bath was removed and the reaction mixture was stirred at room temperature for another 20 min. The precipitate was removed by filtration and washed with MeOH (2 × 1 mL). The combined filtrates were cooled in an ice-water bath for 15 min then refiltered. The filtrate was collected and the solvent was removed by rotary evaporation. The crude product that remained as a white solid was purified by recrystallization from MeOH (yield: 99%) m.p.97.5-99.0 °C, lit m.p.94.5-98 °C; IR 3219, 3033, 2984, 2948, 1399, 1315, 1203, 1149, 1049 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 2.97 (s, 3H), 3.66 (s, 3H), 9.99 (s, 1H).

3.5.2 Kinetic studies:
Kinetic studies of the decomposition reactions of 13b were performed in 5 vol % CH₃CN-H₂O, μ = 0.5 (NaClO₄) over a wide range of pH at 30 °C in the dark. The pH was maintained with HClO₄ solutions (pH < 3.0), NaOH solutions (pH > 10.0), or with HCO₂H/NaHCO₂, AcOH/AcONa, NaH₂PO₄/Na₂HPO₄, TisH⁺/Tris base, and HCO₃⁻/CO₃²⁻ buffers. Owing to the low solubility of 13b in water, a 0.002 M stock solution of 13 in CH₃CN was prepared and injected (15 µL) into 3 mL of reaction solution to obtain a low initial concentration of 1 × 10⁻⁵ M to prevent precipitation of 13b. Reactions were monitored by measuring the changes in UV absorbance as a function of time using UV spectroscopy at all examined pH, and by measuring the changes in the peak area for 13 and its decomposition products as a function of time using HPLC in 0.02 M tris buffers at pH 8.7 and 9.2, and 0.005 M NaOH solution, pH 11.5, at dual wavelength. (HPLC condition: 20 µL injections on a 4.7 mm × 250 mm C-8 reverse phase column, 65/35 MeOH/H₂O
elution solvent, flow rate 1.0 mL/min). The wavelength chosen for monitoring the decomposition process varied slightly for different reaction media due to a slight shift of the maximum absorbance changes observed during a repetitive scan of the reaction solution: 227 and 260 nm used for reactions in all buffers, 232 and 269 nm for reactions in aqueous NaOH solutions. For the reactions monitored by UV spectroscopy, the observed rate constants were obtained as an average of two rate constants taken at each wavelength. For the reactions analyzed by HPLC, rate constants were obtained for each compound as an average of two taken at two wavelengths. The buffer effect on both reaction kinetics and product formation of 13b was investigated in 0.01, 0.02, 0.04 M 1/9 NaH$_2$PO$_4$/Na$_2$HPO$_4$ buffers and in 0.01, 0.02, 0.03, 0.04 M 3/1 TrisH$^+$/Tris base buffers. Three control experiments regarding the stability of rearranged product 14 in 0.02 M phosphate buffer, pH 7.1, and in 0.02 M tris buffer, pH 9.1, and the stability of quinol 3b in 0.1 M NaOH solution, pH 12.8, at 30 °C were performed. Reactions were initiated by injection of 15 μL of ca. 2 mM stock solution of 3b or 14 in CH$_3$CN into 3 mL of reaction solution incubated at 30 °C and subjected to HPLC examination periodically. Decomposition kinetics of 14 in tris buffer was determined by fitting the peak area vs. time data to a double exponential rate equation. Rate constants for the decomposition of 13 at different temperatures were obtained in 0.02 M 1/1 AcOH/AcONa buffers, pH 4.6, at 30, 40, and 50 °C.

3.5.3 Product analyses and azide trapping studies

The same reaction solutions of 13b used for kinetic studies were subjected to HPLC analyses after the completion of the hydrolysis reaction. Individual yields of three major products were determined by HPLC quantification and studied as a function of pH over the pH range 4-13. The product proportion was determined in pH 4.6 acetate buffer at 30 and 50 °C for comparison purpose. HPLC conditions were: 20 μL injections on a 4.7 mm × 250 mm C-8 reverse phase column, 65/35 MeOH/H$_2$O elution solvent, flow rate 1.0 mL/min, monitoring wavelengths: 227, 260 nm for reactions in buffers, 232, 269 nm for reactions in NaOH solutions. Three major products were isolated from large scale hydrolysis reaction of 13b in 0.02 M acetate buffer at pH 4.6. A general procedure is as following: 13b (0.104g, 0.376mmol) was dissolved in 5 mL of CH$_3$CN and the resulting solution was slowly added to 1 L of 0.02 M acetate buffer, pH 4.6, incubated at 40 °C by syringe pump. The steady-state concentration of 13b in the reaction medium was maintained as ca. 1 × 10$^{-5}$ M to avoid precipitation of 13b during the reaction. After the
completion of the addition the mixture was incubated in the dark at 40 °C for another 10 half-lives (ca. 160 min. at 40 °C \( t_{1/2} \) is ca. 16 min). The reaction was quenched by neutralization with saturated aqueous NaHCO₃ solution and was extracted with CH₂Cl₂ (3 × 250 mL) until HPLC examination indicated no products remained in the aqueous layer. The combined extract was dried over anhydrous Na₂SO₄, filtered, and evaporated to dryness under vacuum. The residue was subjected to separation and purification by multiple application of radial chromatography on silica gel using 20/1 CH₂Cl₂/EtOAc as eluent. Two products are known compounds identified by comparison to authentic samples. The third product 14 was characterized by NMR, IR, and LC-MS.

\[ \text{N-(4-Hydroxy-4'-methylbiphenyl-3-yl)methanesulfonamide (14).} \]

IR 3377, 3255, 3020, 2919, 1614, 1502, 1385, 1298, 1135, 1111, 983 cm⁻¹; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \( \delta \) 2.32 (3H, s), 2.97 (3H, s), 6.96 (1H, d, \( J = 9.0 \) Hz), 7.23 (2H, d, \( J = 9.0 \) Hz), 7.33 (1H, dd, \( J = 10.4 \) Hz, 2.1 Hz), 7.46 (3H, m), 8.80 (1H, s(br)), 9.98 (1H, s(br)); \(^{13}\)C NMR (75.5 MHz, DMSO-\(d_6\)) \( \delta \) 20.55, 116.16, 124.30, 124.63, 124.74, 125.83, 129.41, 131.35, 135.81, 136.83, 150.30; LC-MS (ESI, positive) m/e 300 (M + Na)⁺, 199 (M – SO₂Me + H)⁺; (ESI, negative) m/e 276 (M - H)⁻, 183 (M – NHSO₂Me)⁻.

Azide trapping experiments were performed on the hydrolysis reaction of 13b in 0.02 M phosphate buffer, pH 7.0 (5 vol% CH₃-H₂O, \( \mu = 0.5 \) (NaClO₄)) containing different amount of N₃⁻ (0.0005-0.03 M). HPLC examinations were performed on the reaction solutions after 10 half-lives (ca. 12 h). HPLC peak area for 14 and 6b, the decomposition products of 13b, and for azide adduct 4b were plotted as a function of [N₃⁻], respectively. Compound 4b was identified by comparison to the authentic sample. HPLC conditions were the same as those used for product studies but only the data obtained at 260 nm were considered to be used.

3.5.4 Detection of methanesulfonylnitrene 15:

The decomposition of 13b in 0.01 M NaOMe/MeOH solution was monitored periodically by GC-MS to observe the generation of 16 and by HPLC until the HPLC peak for 13b was no longer observable. 13b (13.8 mg, 0.05 mmol) was directly added into 5 mL of basic MeOH solution (0.01 M NaOMe in MeOH) incubated at 30 °C to gain an initial concentration of 13b of 0.01 M. Simultaneously 0.01 M of 17 in the same basic MeOH solution was incubated at 30 °C as a control experiment. The sample used for HPLC analysis was prepared by diluting 100 µL of
the reaction mixture with 1 mL of HPLC eluent. Another 100 µL of reaction mixture or the solution of control experiment was dried by exposing to N₂ flow, re-dissolved in 100 µL of EtOAc, and then subjected to GC-MS examination. HPLC conditions were: 20 µL injections on a 4.7 mm × 250 mm C-8 reverse phase column, 65/35 MeOH/H₂O elution solvent, flow rate 1.0 mL/min, monitoring wavelengths: 227, 262 nm. GC-MS conditions were: 30 m × 0.25 mm × 0.25 µm UF-35 ms column, column temperature 50 °C for 3 min and 250 °C for 32 min, column pressure 0.1 psi. Identities of the major products generated under this reaction condition were qualitatively determined by comparison to the authentic samples of 16 and 17 using GC-MS and to 14 and 6b using HPLC.

3.5.5 Steady state photolysis experiments:

Steady state photolyses of 13b in 0.02 M phosphate buffer, pH 7.1(5 vol% CH₃CN-H₂O, µ = 0.5 (NaClO₄)), and in CH₃CN were performed in a Rayonet photochemical reactor in a jacketed quartz vessel kept at 30 °C. Luzchem LZC-UVC lamps that have emission in the range of 235-280 nm and LZC-UVB lamps with emission range of 281-315 nm were used as the UV source. A brief description of the apparatus has been provided in Chapter 2. For reactions proceeded in the aqueous buffer, an initial concentration of ca. 1 × 10⁻⁵ M of 13b was obtained by adding 0.5 mL of 0.002 M stock solution of 13b in CH₃CN to 100 mL of N₂-saturated phosphate buffer. Reaction mixture was subjected to either 15 s or 45 s irradiation using UVC lamps, and 90 s irradiation using UVB lamps. For reactions in CH₃CN, 5 mL of 0.01 M stock solution of 13b in CH₃CN was injected into 100 mL of N₂ or O₂-saturated CH₃CN to get the initial concentration of 13b of 5 × 10⁻⁵ M. Reactions performed in aqueous solutions were examined by HPLC immediately after the irradiation (C-8 reverse phase column, 65/35 MeOH/H₂O elution solvent, 1mL/min, monitored by UV absorbance at 227 nm and 260 nm). In the reactions carried out in CH₃CN, 13b was exposed to the UV irradiation for intervals that when combined reached 270 s in N₂-saturated CH₃CN and 360 s in O₂-saturated CH₃CN. The reaction mixture was examined by HPLC after the irradiation at each time in order to monitor the process of the photoreaction.

3.5.6 Laser flash photolysis experiments:

The standard procedure provided in Chapter 2 was employed for LFP of 13b. Solutions of 13b were made in O₂ or Ar saturated 0.02 M phosphate buffer, pH 7.1(50 vol% CH₃CN-H₂O, µ = 0.5
(NaClO₄)) by injecting 15 μL of ca. 0.02 M stock solution of 13b into 3 mL of the buffer, so that the initial concentration of 13b was ca. 2.5 × 10⁻⁴ M. Since 13b undergoes slow hydrolysis under this condition, all solutions were used promptly after mixing. Transient absorbance spectra were monitored in the range 280-540 nm.
CHAPTER 4

Decomposition of 4-Acetoxy-4-(benzothiazol-2-yl)-2,5-cyclohexadien-1-one, 19
4.1 Introduction

The 4-(benzothiazol-2-yl)-substituted quinol ester 19 and the parent quinol 20 (Figure 4.1) have been shown to have remarkable activity against the human colon cancer cell lines HCT 116 and HT 29 as well as against the breast cancer cell lines MCF-7 and MDA 468 with IC₅₀ values at the 40-800 nM level. Selective activity for both compounds against renal and colon cancer cell lines was discovered on the NCI Developmental Therapeutics Screening Program in vitro screen against 60 human cancer cell lines. In vivo activity against the human renal tumor xenograft RXF 944LX in mice was also demonstrated. Structurally related quinol derivatives, including some indol-2-yl and benzimidazol-2-yl derivatives, have also shown activity against breast, colon, and renal cancer cell lines. Thioredoxin has been identified as one target of 20 and related quinols. Irreversible binding of 20 to the protein has been demonstrated, but the chemical nature of the reaction has not been studied in detail. Other possible protein targets of 19 and 20 have been identified, but non-protein targets have not be elucidated.

Figure 4.1 Quinol ester 19 and parent metabolite quinol 20

The irreversible inhibition of thioredoxin is thought to occur by a double conjugate addition of two cysteine residues in the active site of the protein directly on 20. However, our experience with quinols closely related to 20 shows that they are not very reactive with nucleophiles. Quinol esters similar to 19, including quinol esters 2a-c, have been shown to generate biphenylyloxenium ions 1a-c in aqueous solution (Chapter 2 and 3). These cations are reactive with water but still react very selectively with strong nucleophiles in an aqueous environment. An alternative hypothesis to the direct reaction of 20 with biological nucleophiles would be the reaction of the 4-(benzothiazol-2-yl)phenyloxenium ion 21 (Figure 4.2), generated by ionization of 19, a likely metabolite of 20 in biological systems, with these nucleophiles.
This hypothesis relies on the ability of the benzothiazol-2-yl group to stabilize 21 by delocalization of the positive charge. Qualitatively, this seems likely and calculations performed at the B3LYP/6-31G(d) level presented herein support that assumption. However, the benzothiazol-2-yl group is a known inductive electron withdrawing substituent with a $\sigma_p$ of 0.29 determined from its effect on the ionization constants of substituted benzoic acids.\textsuperscript{146,147} This substituent may cause a significant deceleration of the ionization process that has previously been shown to be sensitive to electron withdrawing substituents.\textsuperscript{73} It was not clear which effect of the benzothiazol-2-yl group would be dominant in the chemistry of 19. If the inductive electron withdrawing effect destabilizes the transition state leading to ionization sufficiently it is possible that the chemistry of 19 is dominated by reactions that do not generate 21. On the other hand, if the transition state for ionization is sufficiently cation-like, the ability of the 2-benzothiazolyl group to delocalize the positive charge via resonance may dominate. In this chapter, indirect detection of 21 from hydrolysis of 19 by kinetic and product studies is demonstrated. The evidence supporting that both of the expected electronic properties of the benzothiazol-2-yl group play are important in the chemistry of 19 is provided.

Previously in Chapter 2 it has been shown that oxenium ions 1a and 1b can be photochemically generated from 2a and 2b in aqueous solution, although this process occurs in competition with homolytic generation of corresponding radicals 5a and 5b (Scheme 2.5).\textsuperscript{76,77} The homolysis occurs exclusively in the less polar solvent CH$_3$CN.\textsuperscript{77} Photolysis products of 19 in aqueous solution and in CH$_3$CN can also be explained, in part, by a combination of heterolysis and homolysis, although some products appear to be generated by other processes.
4.2 Results and Discussion

4.2.1 Theoretical calculations

We have previously used calculated $\Delta E$ of isodesmic reactions such as eq 4.1 to successfully correlate the experimental lifetimes of 4'-substituted biphenylyloxenium ions. Similar calculations have been used to understand the properties of other aryloxenium and arylnitrenium ions. $\Delta E$ of eq 4.1 measures the thermodynamic stability of 1a and 1b relative to their respective hydration products 3a and 3b. At the pBP/DN*/HF/6-31G(d) and BP/6-31G(d)//HF/6-31G(d) levels $\Delta E$ for eq 4.1 without ZPE corrections is 3.41 kcal/mol and 5.46 kcal/mol, respectively. The calculated stabilization of 1b relative to 1a agrees well with the observed ca. 14 fold greater lifetime of 1b in aqueous solution at 30 °C (170 ns for 1b vs. 12 ns for 1a) in a correlation of log(lifetime) vs. $\Delta E$ for four 4'-substituted biphenylyloxenium ions. A similar correlation of log(lifetime) vs. $\Delta E$ was observed for a much larger series of arylnitrenium ions and their hydration products at the HF/6-31G(d)/3-21G level of theory.

The energetics of the isodesmic reactions of eq 4.1 and eq 4.2 were compared at the B3LYP/6-31G(d) level with and without ZPE corrections. The results are shown in the equations. $\Delta E$ calculated at this level for eq 4.1 is comparable to the results previously obtained at the pBP/DN*/HF/6-31G(d) and BP/6-31G(d)//HF/6-31G(d) levels. The results for the isodesmic
reaction of eq 4.2 suggest that the 4-(benzothiazol-2-yl) substituent is similar to the 4-Ph substituent in its ability to stabilize an aryloxenium ion. If \( \text{21} \) can be generated by ionization of \( \text{19} \), it should have a lifetime long enough for it to be detected by \( \text{N}_3^- \) trapping (Chapter 2 and 3).

This conclusion is supported by the computed properties of \( \text{21}, \text{1a}, \text{and 1b} \). B3LYP/6-31G(d) charges and bond lengths for \( \text{1b} \) have been discussed in Chapter 2, and have been reported along with its computed and experimental vibrational spectrum.\(^{77}\) Corresponding data for \( \text{21} \) and \( \text{1a} \) are given in Figure 4.3 (a) and (b). All three ions exhibit 2,5-cyclohexadien-1-one-4-yl cationic character. The carbonyl stretch frequency for \( \text{1b} \) has been calculated at 1672 cm\(^{-1}\) in the gas phase. This correlates with that observed by time-resolved resonance Raman spectroscopy (1635 cm\(^{-1}\) in aqueous solution).\(^ {77} \) \( \text{21} \) and \( \text{1a} \) are computed to have similar scaled carbonyl stretch vibrations at 1663 and 1672 cm\(^{-1}\).\(^ {149} \) In all three ions, the positive charge is essentially on the 4-position and on the 4-aryl substituent, rather than on the oxygen atom.

**Figure 4.3** Bond lengths and charges computed at the B3LYP/6-31G(d) level for (a) \( \text{21} \), (b) \( \text{1a} \), and (c) 2-methylbenzothiazole (charges on H summed into the heavy atoms); (d) resonance forms for \( \text{21} \). Data in red correspond to charge differences between atoms in \( \text{21} \) and those of the corresponding atoms in 2-methylbenzothiazole.
The dipole moments for 21, 1a, and 1b are 4.00, 4.29 and 4.45 Debye, respectively, and are aligned largely along the molecular axes toward the substituent ring. The total Mulliken charge on the substituent aryl groups in 21 and 1a are, respectively, +0.49 and +0.47 while the corresponding charge on the p-tolyl group in 1b is +0.52 (Chapter 2). Though slightly less efficient than 4-(p-tolyl), both 4-phenyl and 4-(benzothiazol-2-yl) have a similar capacity to delocalize the positive charge away from the 4-position of the aryloxenium ion. Interestingly, B3LYP/6-31G(d) computes 1a and 1b to be slightly twisted, with inter-ring dihedral angles of 19° and 14°, respectively, while 21 is completely planar. The inter-ring bond in 21 (1.414Å), is also shorter than that in 1a and 1b (1.432Å and 1.427Å, respectively). These differences probably reflect the reduced steric demand of the heteroatoms in 21 as opposed to CH at C-2' and C-6' in 1a and 1b, rather than an enhanced resonance interaction with the benzothiazole system.

Like 1b, delocalization into the 4-phenyl ring of 1a is evidenced by strong bond alternation (Figure 4.3 (b)). Positive charge is greatest at C-2, C-4, and C-4', the known sites of trapping by water and azide. Delocalization throughout 21 is also evident from a comparison of the ground state structures of 21 with 2-methylbenzthiazole computed at the same level. While the carbon-carbon bond lengths in 2-methylbenzthiazole are similar (Figure 4.3 (c)), in 21 they show a high degree of bond length alternation (Figure 4.3 (a)). Notably, the ring-junction carbon-carbon bond is 0.032Å longer in the oxenium ion. This, together with significant lengthening of the N-(C-2') bond, corresponding contraction in the N-(C-3a') and S-(C-7a') bonds, as well as a charge increase on S of +0.176, point to a strong contribution of resonance form III in Figure 4.3 (d). Substantial increases in charge at C-4' and C-6' relative to 2-methylbenzothiazole are also evident, pointing to resonance representations IV and V. By analogy to 1a, in which water attacks at C-4 and azide reacts at C-2 and C-4',67,68 nucleophilic attack on 21 should occur at C-2 and C-4 of the phenyl ring, and at C-4' and C-6' on the distal benzothiazole group.

### 4.2.2 Kinetic studies of the decomposition of 19

The target compound 19 was synthesized from the oxidation of the corresponding phenol 22 by phenyliodonium diacetate (PIDA) in AcOH in ca. 20% yield. This procedure has been applied to synthesize other quinol esters as demonstrated in Chapter 2 in low to moderate yields. 19 is stable enough in the dark to be purified by radial chromatography on silica gel. The synthesis route is shown in Scheme 4.1.
SCHEME 4.1. Synthesis of 4-acetoxy-4-(benzothiazol-2-y1)-2,5-cyclohexadien-1-one 19

All reactions were performed at 80 °C in 5 vol% CH3CN-H2O over the pH range 1-7.5 with an initial concentration of quinol ester 19 of ca. 5 × 10⁻⁵ M. Rate constants taken at three or four wavelengths were averaged at each pH to obtain the observed rate constant. Absorbances vs. time data for the decomposition of 19 were fit by a standard first-order or a consecutive first-order rate equation that have been presented in Chapter 2. Consecutive first-order kinetics was only found at pH < 3.0. The absorbance vs. time data for the decomposition of authentic 20 at pH < 3.0 fit a standard first-order rate equation well. The kobs for decomposition of 19 at pH 1.0-7.5 were fit to the rate law of eq 4.3, while the kobs for decomposition of 20 at pH 1.0-2.5 were fitted to the rate law of eq 4.4. Both 19 and 20 could be protonated at N-3' in sufficiently acidic solution, but neither the kinetic data nor UV spectra of these compounds indicate that protonation occurs at pH ≥ 1.0. All kobs for 19 and 20 are provided in Table 4.1. The pH dependence of the decomposition of 19 and 20 are summarized in Figure 4.4.

Figure 4.4 pH dependence of the decomposition of 19 and 20 in aqueous solution at 80 °C. Red circles: rate constants for decomposition of 19; blue triangles: one rate constant derived by consecutive first order fitting of data for the decomposition of 19 at pH < 3.0; magenta triangles directly measured rate constants for acid catalyzed decomposition of authentic 20. Data were fitted to eq 4.3 and 4.4 as described in the text.
\[ k_{\text{obs}}^{19} = k_0^{19} + k_{\text{H}^+}^{19}[\text{H}^+] + k_{\text{OH}^-}^{19}[\text{OH}^-] \quad (4.3) \]
\[ k_{\text{obs}}^{20} = k_{\text{H}^+}^{20}[\text{H}^+] \quad (4.4) \]

Table 4.1 Observed rate constants for the decomposition of 18 and 19.

<table>
<thead>
<tr>
<th>Conditions^a</th>
<th>pH</th>
<th>(10^4 k_{\text{obs}}^{16}) (s(^{-1})) for 19^b</th>
<th>(10^4 k_{\text{obs}}^{17}) (s(^{-1})) for 20^b</th>
<th>(10^4 k_{\text{obs}}^{17}) (s(^{-1})) for 20^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 M HClO(_4)</td>
<td>1.01</td>
<td>8.41 ± 0.53</td>
<td>1.85 ± 0.09</td>
<td>2.02 ± 0.13</td>
</tr>
<tr>
<td>0.03 M HClO(_4)</td>
<td>1.51</td>
<td>3.93 ± 0.30</td>
<td>0.65 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>0.01 M HClO(_4)</td>
<td>2.01</td>
<td>2.20 ± 0.38</td>
<td>0.23 ± 0.01</td>
<td>0.22 ± 0.14</td>
</tr>
<tr>
<td>0.003 M HClO(_4)</td>
<td>2.53</td>
<td>1.92 ± 0.68</td>
<td>0.11 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>3/1 formate, 0.02 M</td>
<td>3.01</td>
<td>1.97 ± 0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1 formate, 0.02 M</td>
<td>3.57</td>
<td>1.82 ± 0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/3 formate, 0.02 M</td>
<td>4.03</td>
<td>2.13 ± 0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1 acetate, 0.02 M</td>
<td>4.66</td>
<td>1.81 ± 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/1 phosphate, 0.02 M</td>
<td>5.56</td>
<td>2.01 ± 0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/1 phosphate, 0.02 M</td>
<td>6.03</td>
<td>2.32 ± 0.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/1 phosphate, 0.02 M</td>
<td>6.54</td>
<td>2.24 ± 0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/3 phosphate, 0.02 M</td>
<td>7.10</td>
<td>2.15 ± 0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/9 phosphate, 0.02 M</td>
<td>7.52</td>
<td>4.09 ± 0.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^aOther Conditions: 5 vol% CH\(_3\)CN/H\(_2\)O, \(\mu = 0.5\) (NaClO\(_4\)), \(T = 80\) °C. All rate constants measured by UV spectroscopy as described in the Experimental Section. ^bDetermined during the decomposition of 19 at pH < 3.0 as one of the rate constants obtained by fitting the data to a double exponential rate equation. ^cMeasured during the decomposition of authentic 20 by fitting the data to a first-order rate equation.
Figure 4.4 shows that 19 exhibits pH-independent decomposition kinetics from pH 2 to 7 and pH-dependent decomposition at pH < 2 and pH > 7. Quinol 20 exhibits an acid catalyzed decomposition with first order kinetics at pH < 3.0. Its decomposition rate constant is experimentally equivalent to one of the rate constants for the decomposition of 19 derived from consecutive first-order data fitting under the same condition. Three rate constants, $k_{o}^{19}$, $k_{H}^{19}$, and $k_{OH}^{19}$, were used to fit the rate data for 19: $k_{o}^{19}$ corresponds to the pH-independent decomposition pathway that is dominant over a wide pH range, while $k_{H}^{19}$ and $k_{OH}^{19}$ describe acid-catalyzed and base-catalyzed decomposition pathways, respectively. The first two rate terms of eq 4.3 are consistent with what we observed for the oxenium ion precursors 2a and 2b.67,73 For these two esters the processes governed by both $k_{o}$ and $k_{H}$ involve formation of the cations 1a and 1b.67,68,73 However, no rate term corresponding to $k_{OH}$ was observed for 2a and 2b in basic phosphate buffers at pH < 8.0 (Chapter 2).73 Quinol 20 decomposes slowly through an acid catalyzed pathway governed by $k_{H}^{20}$. This process became exceedingly slow at pH > 3.0, so the decomposition of 20 no longer interfered with the measurement of the kinetics of decomposition of 19 except at pH > 7.0. HPLC examination and repetitive wavelength scans showed that 20 slowly decomposes in basic phosphate buffers, its decomposition kinetics were not examined in detail under these conditions though. Negligible absorbance changes occurred for the decomposition of 20 in phosphate buffers in the range from 250 to 270 nm, so it was possible to monitor the decomposition kinetics of 19 in this wavelength range without interference from the much slower decomposition of 20. Rate constants derived from the fits to eq 4.3 and eq 4.4 for the decomposition of 19 and 20 are reported in Table 4.2 with some comparisons to 2a and 2b.

Table 4.2 Derived rate parameters for the decomposition of 19 and 20, and 2a and 2b.

<table>
<thead>
<tr>
<th></th>
<th>T (°C)</th>
<th>$k_{o}$ (s$^{-1}$)</th>
<th>$k_{H}$ (M$^{-1}$s$^{-1}$)</th>
<th>$k_{OH}$ (M$^{-1}$s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>80</td>
<td>$(1.91 \pm 0.08) \times 10^{-4}$</td>
<td>$(6.2 \pm 0.8) \times 10^{-3}$</td>
<td>$(5.5 \pm 1.2) \times 10^{-2}$</td>
</tr>
<tr>
<td>20</td>
<td>80</td>
<td></td>
<td>$(2.5 \pm 0.4) \times 10^{-3}$</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>30</td>
<td>$(2.50 \pm 0.05) \times 10^{-5}$</td>
<td>$(1.45 \pm 0.08) \times 10^{-3}$</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>30</td>
<td>$(1.02 \pm 0.01) \times 10^{-3}$</td>
<td>$(1.95 \pm 0.08) \times 10^{-2}$</td>
<td></td>
</tr>
</tbody>
</table>
Comparison of $k_o^{19}$ to the corresponding rate constants for 2a and 2b clearly shows that the rate of uncatalyzed decomposition of 19 is significantly depressed compared to other quinol esters that generate oxinium ions. At 80 °C the uncatalyzed decomposition of 19 occurs ca. 24 fold more slowly than the decomposition of 2a and ca. 520 fold more slowly than 2b, while the N$_3^-$ trapping data shown below in Section 4.2.3 indicate that 19 does generate the cationic intermediate 21. Therefore, the benzothiazol-2-yl group is clearly acting as an electron withdrawing group that destabilizes the transition state for ionization, and decreases the rate of ionization.

The base catalyzed term $k_{OH}$ was not observed for 2a or 2b at pH < 8.0 (Chapter 2), probably due to the suppression of $k_o^{19}$. This suppress occurs because the electron withdrawing effect of the benzothiazole group is larger than that of the tolyl and phenyl groups. Assuming that $k_{OH}$ is about the same magnitude for 2a and 2b at 80 °C as $k_{OH}^{19}$, it would not be possible to detect the base catalyzed reaction for 2a below ca. pH 9.2 or for 2b below pH 10.6 because of the larger magnitudes of $k_o$ for these compounds compared to 19. Since it is probable that the base catalyzed hydrolysis of 19 is accelerated by the electron withdrawing benzothiazol-2-yl group, it is likely that the actual $k_{OH}$ for 2a and 2b are smaller than that for 19. So the pH estimates for the onset of observable base catalyzed hydrolysis of 2a and 2b are lower limits.

### 4.2.3 Product studies of the decomposition of 19

The HPLC examination of the decomposition of 19 showed that, at pH > 3.0 in the absence of any nucleophile other than H$_2$O, only one significant product was detected. This product, identified as the quinol 20, was isolated from the hydrolysis of 19 in pH 4.61 acetate buffer at 80 °C in 71% yield (determined by the amount of 20 isolated from this reaction). At pH < 3.0, 20 decomposes into a new material that has nearly the same HPLC retention time as 20. The new material can be differentiated from 20 by its different absorbance characteristics from 20 at the

<table>
<thead>
<tr>
<th>2a$^d$</th>
<th>80</th>
<th>$(4.5 \pm 0.4) \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b$^e$</td>
<td>80</td>
<td>$(1.0 \pm 0.1) \times 10^{-1}$</td>
</tr>
</tbody>
</table>

$^d$Data from ref. 67. $^e$Data have been published in ref. 73. $^c$Reaction conditions, except temperature, identical to 19. $^d$Extrapolated to 80 °C from data taken in the 30 °C to 70 °C range. $^e$Extrapolated to 80 °C from data taken in the 20 °C to 40 °C range.
two wavelengths used to monitor the HPLC chromatogram (212 nm and 235 nm) The same material was also detected by HPLC as the final product of the hydrolysis of 19 at pH < 3.0. This material was not isolated, but quinols similar to 20 have previously been shown to undergo acid-catalyzed dienone-phenol rearrangements under these conditions.\textsuperscript{68,150} The yield of 20 determined by HPLC quantification in buffers from pH 3.5 to 6.5 after 8 half-lives (\textit{ca.} 8 h) of the hydrolysis of 19 is \textit{ca.} 85-90%. In more basic phosphate buffers authentic 20 slowly decomposes so its yield determined after the same reaction time is lower. For example, the yield of 20 from the hydrolysis reaction of 19 in pH 7.5 phosphate buffer determined after 8 h of reaction is somewhat lower at \textit{ca.} 60%. For this reason, the wavelengths used to monitor the decomposition kinetics of 19 in phosphate buffers at pH 7.1 and 7.5 were chosen from the wavelength range in which the decomposition of 20 did not show an absorbance change.

Both the product and the kinetic data of the hydration of 19 are consistent with what we have observed for other quinol esters that yield oxenium ion intermediates, but these data do not require the intermediacy of 21. The attack of water on 21 is not the only path for the formation of 20. 20 can also be the product of an ordinary ester hydrolysis of 19.

\subsection*{4.2.4 Azide trapping experiments for hydrolysis of 19}

The crucial evidence for the generation of 21 during hydrolysis of 19 is provided by azide trapping experiments performed on 19. Product studies of hydrolysis of 19 in the presence of different amount of N\textsubscript{3}\textsuperscript{-} in 0.02 M phosphate buffer at pH 6.5 are summarized in Figure 4.5. The structure of the isolated azide adduct 23 is shown in Figure 4.5. In the presence of N\textsubscript{3}\textsuperscript{-} the hydration product 19 was replaced by the azide trapping adduct 21 without an increase in the overall rate constant for decomposition of 19. Rate constants for the hydrolysis reaction of 19 at different [N\textsubscript{3}\textsuperscript{-}] are provided in Table 4.3.
Figure 4.5 Azide trapping experiments for 19 performed at pH 6.5 in 0.02 M phosphate buffer. Data were fit by least-squares procedures to standard “azid-clock” equations (eq 2.2 and 2.3).

Table 4.3 Rate constants for the decomposition of 19 at different [N₃⁻]

<table>
<thead>
<tr>
<th>Conditionsᵃ</th>
<th>pH</th>
<th>$10^4 k_{obs}$ (s⁻¹) for 19ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1 phos, 0.02 M, 0 mM N₃⁻</td>
<td>6.54</td>
<td>2.24 ± 0.36</td>
</tr>
<tr>
<td>1/1 phos, 0.02 M, 2 mM N₃⁻</td>
<td>&quot;</td>
<td>2.11 ± 0.06</td>
</tr>
<tr>
<td>1/1 phos, 0.02 M, 4 mM N₃⁻</td>
<td>&quot;</td>
<td>2.17 ± 0.07</td>
</tr>
<tr>
<td>1/1 phos, 0.02 M, 6 mM N₃⁻</td>
<td>&quot;</td>
<td>2.23 ± 0.06</td>
</tr>
<tr>
<td>1/1 phos, 0.02 M, 8 mM N₃⁻</td>
<td>&quot;</td>
<td>2.31 ± 0.04</td>
</tr>
<tr>
<td>1/1 phos, 0.02 M, 10 mM N₃⁻</td>
<td>&quot;</td>
<td>2.16 ± 0.08</td>
</tr>
</tbody>
</table>

ᵃOther Conditions: 5 vol% CH₃CN/H₂O, μ = 0.5 (NaClO₄), T = 80 °C. All rate constants measured by UV spectroscopy as described in Section 4.4.ᵇDetermined by fitting the data to a standard first-order rate equation and averaging all rate constants obtained at two wavelengths.

This azide trapping pattern, equivalent to what we have observed for other oxenium ion precursors (see Chapter 2 and 3), requires a stepwise mechanism in which N₃⁻ and water compete for the same electrophilic intermediate generated in a prior rate-limiting step. The intermediate most consistent with the generation of 20 and 23 is the oxenium ion 21 (Scheme 4.2). Control experiments with respect to the sensitivity of 20 to N₃⁻ showed that the reaction between N₃⁻ and
quinol 20 is negligible under our reaction conditions. All the loss of 20 can be attributed to the trapping of the cation 21 by N$_3^-$.

**SCHEME 4.2.** Proposed mechanism for the decomposition of 19 in aqueous solution

![Scheme 4.2](image)

There are two apparent azide trapping products detected by HPLC corresponding to two closely placed long retention time peaks, but only the major one 23 was successfully isolated by multiple application of radial chromatography. The structure of 23 indicates that the positive charge in 21 is significantly delocalized into the thiazole substituent, particularly at C-6' of the benzothiazole ring. The product data obtained at different [N$_3^-$] fit the standard “azide clock” equations to generate $k_{az}/k_s$ (see Chapter 2, eq 2.2 and eq 2.3) the azide/solvent selectivity of oxenium ion 21, is of (310 ± 25) M$^{-1}$.

The two oxenium ion 1a and 1b derived from 2a and 2b, have $k_{az}/k_s$ of 77 M$^{-1}$ and 1.0 × 10$^3$ M$^{-1}$, respectively, at 30 °C (Chapter 2). Provided that these ratios are not strongly affected by temperature, the ability of the benzothiazol-2-yl substituent to stabilize the cation appears to be between that of phenyl and p-tolyl substituents when they are placed at the 4-position in the aryl ring of the cation. If the reaction between the intermediate 21 and N$_3^-$ is diffusion-limited, as is the case for other reactive oxenium and nitrenium ions, $k_{az}$ will be ca. 6.5 × 10$^9$ M$^{-1}$s$^{-1}$ at 20 °C. Extrapolation of $k_{az}$ to 80 °C, based on the temperature dependence of other diffusion controlled reactions, gives an estimate for the rate constant of ca. 1.6 × 10$^{10}$ M$^{-1}$s$^{-1}$. Then the estimated lifetime (1/$k_s$) of 21 in aqueous solution at 80 °C is ca. 20 ns. That lifetime would be expected to be longer at 30 °C, so 21 would appear to be somewhat longer lived than 1a (ca. 12 ns) under the same conditions.
The combination of kinetic data and azide trapping results show that the 4-(benzothiazol-2-yl) substituent has two significantly different electronic effects. Inductive electron withdrawal dominates in destabilizing the transition state for ionization as C-4 of 19 transforms from a saturated tetrahedral carbon to the trigonal carbon of 21. Once the cation is fully formed, charge delocalization through the π-system of the 4-(benzothiazol-2-yl) substituent stabilizes the cation to a somewhat greater extent than does a 4-phenyl substituent.

4.2.5 Relationship of photolysis of 19 to hydrolysis reactions

Photolyses of 2a and 2b have previously been shown, in Chapter 2, to generate both the cations 1a and 1b and the phenoxy radicals 5a and 5b.76,77 Homolysis to form the radical is the exclusive reaction in CH3CN, while both heterolysis and homolysis occur in aqueous solution.77 The intermediates 1b, 5b, and 5a, were directly detectable by fast UV spectroscopy following ns-laser flash photolysis.76,77 The cation 1a was not directly detectable due to its short lifetime, estimated to be 12 ns from azide trapping data,67 but 3a, the hydration product of 1a, was readily detected after photolysis in aqueous solution.77

Photolysis of 19 and identifications of resulting products were performed in a separate part of this project in order to find out if oxenium ion 21 can be generated from 19 photochemically.145 It appears that photo-ionization of 19 leading to cation 21 is strongly suppressed compared to 2a and 2b, based on the significantly lower yield of the quinol from photolysis in aqueous solution under similar reaction conditions (7.8% of 20, 18% of 3a, and 33% of 3b), and the greater yields of products from photolysis of 19 that are not derived from cationic intermediates.77 Suppression of photo-ionization is probably due to the inductive electron withdrawing effect of the benzothiazol-2-yl group. This effect may be particularly important in the photo-ionization reaction since the expected vertical ionization process would initially lead to a cation with a trigonal pyramidal geometry at C-4 that would not be effectively stabilized by resonance interaction with the benzothiazol-2-yl group until it had undergone structural reorganization. Other competitive photolysis pathways do exist. Products are generated that clearly do not come from the cationic intermediate. They are still undergoing further investigation.
4.3 Conclusion

Azide trapping and kinetic results of the decomposition of quinol ester \( \text{19} \) in aqueous solution, and comparison to the behavior of other quinol esters \( \text{2a} \) and \( \text{2b} \) that yield oxenium ions \( \text{1a} \) and \( \text{1b} \), prove that oxenium ion \( \text{21} \) is generated from uncatalyzed decomposition of \( \text{19} \) and that \( \text{21} \) is responsible for the formation of the hydration product \( \text{20} \) under these conditions. Based on the precedent of \( \text{2a},^6 \) it is also likely that the acid catalyzed decomposition of \( \text{19} \) generates \( \text{21} \). Unlike the 4-Ph and 4-(p-tolyl) substituents of cations \( \text{1a} \) and \( \text{1b} \), the 4-(benzothiazol-2-yl) substituent of \( \text{21} \) shows two significantly different electronic effects at different stages of the reaction. At the transition state for ionization of \( \text{19} \) the inductive electron-withdrawing effect of the 4-(benzothiazol-2-yl) substituent dominates and supresses the transformation of C-4 from a saturated tetrahedral carbon to a positively charged carbon with trigonal geometry. That makes the generation of \( \text{21} \) significantly slower than the generation of \( \text{1a} \) or \( \text{1b} \) at the same temperature. Once the cation is formed, the same substituent stabilizes \( \text{21} \) by electron delocalization through the \( \pi \)-system of the benzothiazole ring, confirmed by the magnitude of \( k_{\text{az}}/k_{\text{s}} \) and by the structure of the major azide trapping product \( \text{23} \). This stabilization lies between that of the 4-phenyl and 4-(p-tolyl) substituents of \( \text{1a} \) and \( \text{1b} \).

Compared to previously reported photochemistry of \( \text{2a} \) and \( \text{2b} \), photolysis of \( \text{19} \) is more complicated. Quinol \( \text{20} \) is no longer the major photoproduct indicating that the photo-ionization that generates cationic transient oxenium ion \( \text{21} \) is only a small component of the photochemistry of \( \text{19} \). Further studies with the emphasis on direct detection and structural characterization of \( \text{19} \) and the other related transients by laser flash photolysis methods will be continued in our group.

4.4 Experimental

4.4.1 Kinetic and product analyses:

Kinetic measurements were performed for the decomposition of \( \text{19} \) and \( \text{20} \) in 5 vol% CH\(_3\)CN-H\(_2\)O, \( \mu = 0.5 \) (NaClO\(_4\)), at 80 °C by monitoring the changes in the UV absorbance as a function of time at three or four wavelengths. The pH was maintained with HClO\(_4\) solutions (pH < 3.0), or with HCO\(_2\)H/NaHCO\(_2\), AcOH/AcONa, and NaH\(_2\)PO\(_4\)/Na\(_2\)HPO\(_4\) buffers. Reactions were initiated in the same way as used in other two projects (Chapter 2 and 3). The initial concentration of the reaction mixture was maintained as ca. \( 5 \times 10^{-5} \) M by using a 0.01 M stock
solution of 19 or 20 in CH₃CN. The hydrolysis rate constant for each reaction was obtained as an average of all rate constants determined at each wavelength. The wavelengths chosen to monitor the decomposition of 19 at pH 1.0-6.5 varied slightly due to slight shifts of the maximum absorbance changes observed in different solutions. In phosphate buffers at pH 7.1 and 7.5, the decomposition kinetics of 19 were monitored at wavelengths chosen from the UV range in which no observable absorbance change was found during the slow decomposition of 20 at the same pH. All wavelengths used for monitoring the decomposition of 19 at different pH are listed in Table 4.4. Kinetic studies of the acid-catalyzed decomposition of 20 were performed at pH < 3. The wavelengths used to follow the decomposition of 20 were 212, 233, and 260 nm. The standard first-order and consecutive first-order rate equations applied for kinetic data fitting have been described in Chapter 2.

**Table 4.4 Wavelengths used for monitoring the decomposition kinetics of 19 at different pH**

<table>
<thead>
<tr>
<th>Reaction solution</th>
<th>pH</th>
<th>UV wavelengths monitored (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HClO₄ solutions</td>
<td>1.0-2.5</td>
<td>212, 221, 235, 340</td>
</tr>
<tr>
<td>Formate buffer</td>
<td>3.0-4.0</td>
<td>217, 257, 340</td>
</tr>
<tr>
<td>Acetate buffer</td>
<td>4.5</td>
<td>217, 257, 340</td>
</tr>
<tr>
<td>Phosphate buffer</td>
<td>5.5-6.5</td>
<td>222, 257, 340</td>
</tr>
<tr>
<td>Phosphate buffer</td>
<td>7.1-7.5</td>
<td>250, 257, 265</td>
</tr>
</tbody>
</table>

To determine the product yield by HPLC quantification, same solutions used for kinetic measurements were subjected to HPLC examination after 8 half-lives of the hydrolysis reactions. HPLC conditions were: 20 μL injections on a 4.7 mm × 250 mm C-8 reverse phase column, 65/35 MeOH/H₂O elution solvent, flow rate 1.0 mL/min, monitoring wavelengths: 212, 235 nm. The major hydrolysis product of 19, quinol 20, was isolated from large scale hydrolysis of 19 in 0.02 M pH 4.61 acetate buffer with initial concentration of 19 of ca. 7 × 10⁻⁴ M, and was characterized afterwards. The detailed procedure for the isolation is described in Section 4.4.3, synthesis.
4.4.2 Azide trapping experiments:

Hydrolysis of 19 in the presence of N$_3^-$ at 80 °C were performed in 0.02 M 1/1 NaH$_2$PO$_4$/Na$_2$HPO$_4$ buffer (pH 6.6, 5 vol% CH$_3$CN-H$_2$O, $\mu = 0.5$ (NaClO$_4$)) at various N$_3^-$ concentrations (0.1, 0.01, 0.008, 0.006, 0.004, 0.002 M). Kinetics were determined by monitoring the change in the UV absorbance at 310 and 330 nm. For each individual run, absorbance vs. time data were fit to a standard first-order rate equation. The reported rate constant is the average of those taken at both wavelengths. The yields of products were determined after two hours reaction time by HPLC quantification method using the same conditions as those described above. The yields were determined after two hours instead of after the completion of the reaction, because some of the products decompose slowly in the reaction media. The residual concentration of 19 was monitored by HPLC to assure that the individual reactions had proceeded to the same extent. Control experiments that tested the reactivity of quinol 20 toward N$_3^-$ were carried out in the same solution at 80 °C. These control experiments were allowed to proceed for 2 hours then the reaction mixtures were immediately moved into the refrigerator (5 °C) to terminate any possible reaction and subjected to HPLC analyses. The major azide adduct was isolated as described below. The ester 19 (50.0 mg, 0.18 mmol), dissolved in 1 mL of CH$_3$CN, was added in 0.1 mL aliquots every 1 h to 250 mL of a 0.02 M phosphate buffer (pH 6.7, 5 vol% CH$_3$CN-H$_2$O, $\mu = 0.5$ (NaClO$_4$)) containing 0.008 M NaN$_3$ that was incubated in the dark at 80 °C. After the last addition, the mixture was incubated in the dark at 80 °C for an additional 3.5 h. The mixture was then refrigerated overnight and was allowed to reach room temperature before extracting with CH$_2$Cl$_2$ (5 × 50 mL). The combined extract was dried over anhydrous Na$_2$SO$_4$, filtered, evaporated to dryness, and subjected to multiple radial chromatography with two solvent systems (5:1 CH$_2$Cl$_2$:EtOAc, then 20:1 CH$_2$Cl$_2$:CH$_3$CN). The major azide adduct was separated as a low melting point solid.

4-(6-Azidobenzothiazol-2-yl)phenol (23): IR 3062, 2097, 1606, 1557, 1451, 1435, 1279, 1225, 1168 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 6.93 (2H, d, $J = 8.5$ Hz), 7.22 (1H, dd, $J = 8.8$ Hz, 2.3 Hz), 7.91 (2H, d, $J = 8.5$ Hz), 7.93 (1H, d, $J = 2.0$ Hz), 7.97 (1H, d, $J = 8.5$ Hz), 10.22 (1H, s); $^{13}$C NMR (125.8 MHz, DMSO-$d_6$) $\delta$ 112.63 (7.93), 116.37 (6.93), 118.66 (7.22), 123.55 (7.97), 124.13, 129.24 (7.90), 136.05, 136.63, 151.59, 160.81, 167.61; LC-MS (ESI, positive) m/e 241
(M - N₂ + H)⁺, (ESI, negative) m/e 239 (M - N₂ -H); high-resolution MS (ES, positive) C₁₃H₉N₄OS (M + H) calcd 269.0492, found 269.0512.

4.4.3 Synthesis:

4-(Benzothiazol-2-yl)phenol (22): 4-Hydroxybenzaldehyde (3.66 g, 23 mmol) and 2-aminothiophenol (7.51 g, 60 mmol) were dissolved in 100 mL of Et₂O. Silica gel (30 g) was added to the mixture, and the solvent was slowly evaporated under vacuum. The dry mixture was divided into four portions, placed into four sealable Teflon vessels and subjected to microwave heating at a maximum power of 650 watts for 3 min. The silica gel was washed with 9:1 hexanes:EtOAc (4 × 50 mL), EtOAc (4 × 50 mL), and EtOH (4 × 50 mL). Silica gel (15 g) was added to the EtOAc wash again and the solvent was removed. The dry residue was washed again with 9:1 hexanes:EtOAc (2 × 50mL), EtOH (2 × 50mL), followed by hot EtOH (1 × 50mL). The hexanes/EtOAc washes were discarded. All the EtOH filtrates were combined and evaporated to dryness under vacuum to yield crude 22. A clean sample of 22 was obtained by recrystallization from EtOH: m.p.226.5-227.5 °C, lit \(^{152}\) m.p.227 °C; \(^1\)H NMR (300 MHz, DMSO-d₆) δ 6.93 (2H, d, J = 8.5 Hz), 7.39 (1H, td, J = 7.5 Hz, 1.2 Hz ), 7.49 (1H, td, J = 7.7 Hz, 1.2 Hz), 7.92 (2H, d, J = 8.7 Hz), 7.97 (1H, d, J = 7.8 Hz), 8.07 (1H, d, J = 7.8 Hz), 10.21 (1H, s); \(^1\)³C NMR (125.8 MHz, DMSO-d₆) δ 116.04, 122.05, 122.25, 124.01, 124.84, 126.36, 128.99, 134.07, 153.69, 160.48, 167.40.

4-Acetoxy-4-(benzothiazol-2-yl)-2,5-cyclohexadien-1-one (19): 22 (0.455g, 2 mmol) was dissolved in 30 mL of AcOH, and the resulting solution was stirred and kept in a water bath at 30-33 °C as a solution of PIDA (0.708g, 2.2 mmol) in 15 mL of AcOH was added dropwise over a period of 1.5 h. The reaction solution was stirred for another 30 min at room temperature after completion of the addition. AcOH was removed by rotary evaporation under vacuum and the residue was left on the vacuum pump overnight. The dry residue was dissolved in ca. 25 mL of EtOAc followed by filtration. The filtrate was collected and evaporated to dryness, and then subjected to trituration with hot 75/25 Hexanes/EtOAc. The solvent was removed and oily yellow 19 was obtained. Further purification was performed by multiple application of radial chromatography on silica gel with 2:1 hexanes:EtOAc (yield: 10-20%): m.p. 98-100 °C; IR 3065, 3050, 2930, 1751, 1668, 1629, 1432, 1370, 1214, 1163, 1040 cm⁻¹; \(^1\)H NMR (300 MHz, DMSO-d₆) δ 2.19 (3H, s), 6.43 (2H, d, J = 10.2 Hz), 7.36 (2H, d, J = 9.9 Hz), 7.47-7.52 (2H, m),
8.02 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.16 (1H, dd, J = 7.5 Hz, 1.5 Hz); $^{13}$C NMR (75.5 MHz, DMSO-$d_6$) δ 20.46, 75.66, 121.85, 122.76, 125.50, 126.18, 128.60, 134.22, 144.38, 151.89, 166.83, 167.90, 184.02; high-resolution MS (ES, positive) C$_{15}$H$_{12}$NO$_3$S (M + H) calcd 286.0532, found 286.0549, C$_{15}$H$_{11}$NO$_3$SNa (M + Na) calcd 308.0352, found 308.0370.

4-(Benzothiazol-2-yl)-4-hydroxy-2,5-cyclohexadien-1-one (20): 20 was obtained from large scale hydrolysis of 19. The procedure is as follows. 250 mL of 0.02 M, 1/1 AcOH/AcONa buffer (pH 4.61 5 vol% CH$_3$CN, μ = 0.5 (NaClO$_4$)) was prepared and incubated in a water bath at 80 °C prior to the addition of 19. A freshly made solution of 19 (50 mg, 0.175 mmol) in 1 mL of CH$_3$CN was added in 0.1 mL aliquots every 1 h to the incubated acetate buffer over a period of 10 h. After the last addition, the reaction mixture was kept in the dark at 80 °C for another 5 h before refrigerating overnight. It was brought back to room temperature the next day and extracted with CH$_2$Cl$_2$ (5 × 50 mL). The combined CH$_2$Cl$_2$ extract was dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated to dryness under vacuum. The crude product was purified by radial chromatography with 3:2 hexanes:EtOAc. (yield: 71 %): m.p.108-109.5 °C, lit m.p.63-66 °C; IR 3168, 1674, 1607, 1494, 1434, 1386, 1147, 1069, 1055 cm$^{-1}$; $^1$H NMR (300 MHz, CD$_2$Cl$_2$) δ 4.35 (1H, s), 6.32 (2H, d, J = 9.9 Hz), 7.01 (2H, d, J = 9.9 Hz), 7.42-7.55 (2H, m), 7.93 (1H, dd, J = 8.7 Hz, 0.6 Hz), 8.01 (1H, dd, J = 8.5 Hz, 0.8 Hz); $^{13}$C NMR (75.5 MHz, CD$_2$Cl$_2$) δ 71.76, 122.68, 124.06, 126.55, 127.24, 129.37, 136.82, 148.04, 153.51, 171.45, 185.00; high-resolution MS (ES, positive) C$_{13}$H$_{10}$NO$_2$S (M + H) calcd 244.0427, found 244.0439.

4.4.4 Calculations:

Density functional calculations were carried out using the Gaussian 03 suite of programs. Geometry optimization of the ground state oxenium ions 21 and 1a and the quinols 20, 3a, and 3b were executed at the B3LYP/6-31G(d) level and their verification as a minimum, as well as derivation of IR vibrational frequencies and normal modes of vibration were executed using a harmonic frequency analysis, which afforded all real frequencies. Calculations at this level were previously reported for 1b. Vibrational frequencies for comparison with experimental data were scaled by a factor of 0.9614 according to Scott and Radom.
CHAPTER 5

Summary
The initial research goal, centered on the detection and characterization of reactive aryloxenium ions 1 generated from different sources was achieved. In this dissertation, focusing on 4’-methyl-4-biphenylyloxenium ion 1b, the decomposition chemistry of two potential precursors, 4-acetoxy-4-(4’-methylphenyl)-2,5-cyclohexadien-1-one 2b and O-(4-(4’-methylphenyl)phenyl)-N-methanesulfonylhydroxylamine 13b were carefully studied and compared to that of 4-acetoxy-4-phenyl-2,5-cyclohexadien-1-one 2a.\(^{67,68}\) It was determined by N\(_3^-\)trapping experiments that, 1b can be generated from both 2b and 13b via a heterolytic C-O bond or O-N bond cleavage under solvolytic conditions, at acidic and neutral pH. In the absence of any nucleophile other than water, quinol 3b that comes from the attack of water on oxenium ion intermediate 1b was identified as the major decomposition product for both 2b and 13b. In the presence of added nucleophile N\(_3^-\), the same kinetic pattern as well as the same azide adduct were observed for the decomposition of 2b and 13b, indicating a two-step mechanism in which a cationic intermediate is formed in a rate-limiting step, and then is trapped by either N\(_3^-\) or H\(_2\)O in the next step.

However, generation of 1b is not the only mechanism involved in the decomposition of 13b. In addition to 3b there are two more major hydration products, rearrangement product 14 and phenol 6b not arising from 1b. The yields of these products vary differently with pH. The pH dependence of the decomposition of 13b is consistent with the uncatalyzed decomposition of both the neutral 13b and its conjugate base 13b\(^-\). The kinetically determined pK\(_a\) of 13b is in good agreement with the spectrophotometrically observed pK\(_a\).\(^{73}\) It was proposed that at pH < pK\(_a\) the dominant decomposition pathways for 13b include ionization of 13b, concerted intramolecular rearrangement, and homolytic dissociation leading to phenoxy radical 5b (3:3:1). At pH > pK\(_a\), 13b\(^-\) undergoes a stepwise base-catalyzed \(\alpha\)-elimination decomposing into the final product phenol as its conjugate base 6b\(^-\) and sulfonylnitrene 15. The nitrene 15 decomposes into methylsulfonamide, 16, through hydrogen trapping of the triplet nitrene.

Photogeneration of 1b from those two precursors was also explored. 2b and 13b showed different photochemistry leading to a variety of photoproducts but still share something in common: they both generate phenoxy radical 5b with \(\lambda_{\text{max}}\) 360 nm during the photolysis process, but only 2b generates the oxenium ion 1b with \(\lambda_{\text{max}}\) 460 nm during photolysis in aqueous buffer. Direct measurements of the decay kinetics of 1b in the absence and presence of N\(_3^-\) by laser flash photolysis is in good agreement with the indirect kinetic measurement using the azide clock.
method, confirming that the lifetime of 1b is 170 ns and the ratio of $k_{as}/k_s$ for 1b is $1 \times 10^3$ M$^{-1}$.

The nature of 1b was further elucidated by its directly observed time-resolved resonance Raman (TR$^3$) spectrum. The experimental spectrum is consistent with the simulated vibrational spectrum of 1b at the B3LYP/6-31G(d) level of theory, indicating strong cyclohexadienyl character in the phenyl ring and carbonyl character in C-O bond. The carbocationic resonance form 1(III) (see Chapter 1, Figure 1.1) dominates its chemistry. The other transient species phenoxy radical 5b was assigned based on the comparison of its UV absorbance to that of the known phenoxy radical 5a. Its biphasic decay kinetics can be fitted by a mechanism that has been used to rationalize the decay of 5a and other aryloxy radicals.

In water arylnitrenium ions are intermediate in stability between nitrenium and carbenium ions of similar structure. Compared to analogous 4-biphenylnitrenium ions 8, the 4'-methyl substituents stabilize both oxenium ion and nitrenium ion (1b and 8b) toward hydration relative to the unsubstituted ions (1a and 8a) to approximately the same extent, ca. 10-fold. However, 8b is ca. 30-fold more stable than 1b (the observed lifetime of 8b is 0.63 μs). Oxenium ion 1 has more positive charge delocalized into the π-system because of the stronger electronegativity of the oxygen atom than that of nitrogen atom according to calculations, and it is more sensitive to the stabilization by π-donors on the phenyl ring than nitrenium ions.

The results of this dissertation work make it possible to critically evaluate previous claims for generation of 1. Based on a previous investigation into the generation of 4-alkyl substituted aryloxenium ions from corresponding quinol esters and O-aryl-N-sulfonylhydroxylamines performed by our group, it is concluded that 4-alkylaryloxenium ions are unlikely to exist because of the lack of electronic stabilization. Therefore in those cited examples in Chapter 1 of this dissertation, only a few, including the electrochemical and chemical oxidation of 4-(2-alkenylphenyl)-phenols, and the synthesis of natural alkaloids (±)-stepharine and (±)-pronucipharine via oxidative coupling reactions, are likely to proceed through the intermediacy of the proposed aryloxenium ion. In other cases concerted mechanism or radical process are more likely to be responsible for the formation of the final products.

In another related project, oxenium ion 21 was shown to be the reactive intermediate involved in the decomposition of 4-acetoxy-4-(benzothiazol-2-yl)-2,5-cyclohexadien-1-one 19 in aqueous buffers at acidic and neutral pH. Compared to the generation of 1b, the generation of 21 is much slower under the same conditions indicating that 4-(benzothiazol-2-yl) substituent acts as an...
electron-withdrawing group destabilizing the transition state for ionization of 19 and slowing down the reaction. However, once the cationic intermediate 21 is formed, the resonance effect of the same substituent takes over stabilizing cation 21 by charge delocalization into the benzothiazole system. This stabilizing effect is between that of p-phenyl substituent and p-tolyl substituent, indicated by their azide/solvent selectivity (the \( k_{az}/k_s \) ratio for 1a, 21, and 1b are, 77, 310, and \( 1 \times 10^3 \) M\(^{-1} \), respectively). In all three ions, the positive charge is essentially on the 4-C and on the 4-aryl substituent, rather than on the oxygen atom. Based on the assumption that the reaction between oxenium ion and N\(_3^-\) is diffusion limited, lifetime of 21 is ca. 20 ns at 80 °C. Attempted photogeneration of 21 from 19 was successful but in very low yield based on photoproducts analyses.\(^{145}\) This is probably due to the electron withdrawing effect of 4-(benzothiazol-2-yl) group that destabilizes the transition state and increases the energy barrier of the heterolytic dissociation leading to 21.
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