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Quantum Chemical Analysis of Heteroarylnitrenium Ions and Mechanisms for Their Self-Destruction

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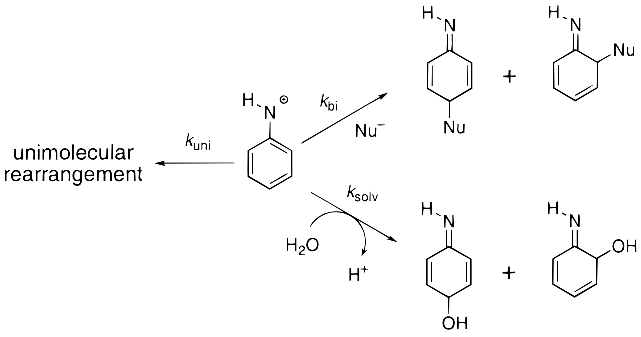
Abstract: Singlet−triplet state-energy splittings in arylnitrenium ions are substantially reduced when the aromatic system is heterocyclic with nitrogen atoms incorporated at ring positions that would otherwise better stabilize the formally exocyclic positive charge through resonance. Ring contraction rearrangements of singlet arylnitrenium ions with a nitrogen atom at an *ortho* position are predicted to proceed with barrier heights that become lower with increasing substitution of nitrogen atoms at other positions. Predilection to delocalize positive charge also controls the relative facility with which (i) *N*-acetylarylnitrenium ions undergo ring closure to form 2-oxazolium cations and (ii) arylnitrenium ions are subject to nucleophilic aromatic substitution by water.

1. Introduction

Arylnitrenium ions, $ArNR^+$, have been extensively studied because of their implication as in vivo reactive intermediates that covalently modify genetic material; such reactivity is carcinogenic.[1−8] These nitrenium ions derive from metabolic oxidation of aromatic amines[9−11] that can be ingested directly, e.g., as cooked food[12] or smokeless tobacco[13] components, or they can derive from in vivo reduction of nitroaromatic precursors.[14−16]

The reactivity of arylnitrenium ions is described in a schematic sense in Scheme 1. As powerful electrophiles, they can react in a bimolecular fashion with available nucleophiles (such as functionality present in nucleic acids). For in vivo reactivity, solvent water is a particularly important nucleophile present at high concentration, and solvolysis is listed as a distinct pathway in the scheme. Finally, unimolecular processes may be available to individual nitrenium ions that result in a loss of nitrenium ion character.

Scheme 1



Bimolecular reaction with nucleophiles usually results in aromatic ring substitution. This is rationalized by consideration of resonance structures available to arylnitrenium ions that localize positive charge onto *ortho* and *para* ring carbon positions (Figure 1). Such charge localization is favorable since nitrogen is more electronegative than carbon. Put differently, an arylnitrenium ion has a substantial degree of iminocyclohexadienyl cation character.

The kinetics of the various processes listed in Scheme 1 have been studied, primarily by laser flash photolysis, for a number of different arylnitrenium ions,[17,18] including parent and substituted phenyl-,[19−31] biphenyl-,[24,25,32−36] naphthyl-,[37]

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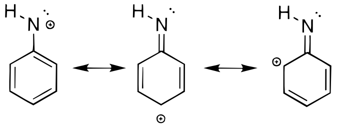

Figure 1. Three key resonance structures for arylnitrenium ions. The two mesomers on the right, formally available only to the singlet state of the nitrenium ion, rationalize trends in substitution effects for that state.

fluorenyl-,[24,32–35,38] and heterocyclic[39–42] nitrenium ions. Substantial experimental work has also examined the specificity with which nitrenium ions react with nucleic acids as nucleophiles.[14–16,28,35,38,39,43,44] In addition, the acid/base properties of nitrenium ions (which are amphiprotic, deriving on one hand from protonation of a nitrene but capable of conversion to the aniline dication) have been studied.[24,34,45–47]

Since the early 1980s, experimental studies of arylnitrenium ion reactivity have been complemented by substantial theoretical work.[48] One area where theory has played a particularly critical role is in the computation of nitrenium ion singlet−triplet state-energy (S−T) splittings. The reactivity in Scheme 1 and the resonance in Figure 1 presuppose a singlet nitrenium ion, but insofar as the parent nitrenium ion, NH_2^+, has an experimentally determined S−T splitting of 30 kcal/mol[49] (a positive sign corresponding to the *triplet* state being lower in energy), it is not necessarily obvious that the singlet state should dominate for arylnitrenium ions. Theoretical work, however, has illuminated the degree to which stabilization of the positive charge on nitrogen by π donation, which is operative to a significantly larger extent for the singlet state than the triplet, serves to reverse the relative energies of the spin states in substituted systems, particularly aryl-substituted systems.[26,50–64] Indeed, theoretical predictions helped guide the experiments leading to the first characterization of a substituted arylnitrenium ion possessing a *triplet* ground state.[21,22]

Computational studies have played a role in understanding the conformational behavior of nitrenium ions and the differing sensitivities of the singlet and triplet states to geometric constraints (e.g., incorporation into rings).[50,51,55,57,60,61,65,66] Theory has also rationalized (i) trends in the rates and regiochemistries of nucleophilic aromatic substitution as a function of nucleophile and nitrenium ion,[26,50,67,68] (ii) mechanistic details of 1,2-hydride shifts in *N*-aryl-*N*-alkylnitrenium ions as well as analogous carbenes and borenide anions,[61] and (iii) the nature of signature arylnitrenium infrared frequencies[69] and their sensitivity to aromatic ring substituents.[62,70] Finally, Ford and Herman have computationally characterized N−O bond heterolysis transition states in hydroxylamine precursors of nitrenium ions,[71] and Ford has explored relationships between computed nitrenium ion properties and their mutagenicity.[48,72]

Many aromatic amines that may be ingested are heterocyclic. These heterocyclic nitrenium ions have only recently begun to be the subject of experimental studies as detailed as those performed for substituted aromatic hydrocarbons.[39–42] Preliminary analysis suggests the chemistry of heterocyclic nitrenium ions can sometimes be quite different from hydrocarbon analogues. For instance, on the basis of product analysis, Takeuchi and co-workers[40] inferred the singlet and triplet states of 2′,6′-pyrimidylnitrenium (see Section 3 for nomenclature convention) to be nearly isoenergetic, in sharp contrast to the situation for phenylnitrenium.[57]

The focus of this paper is to better characterize several reactions of arylnitrenium ions, including unimolecular rearrangements that effectively eliminate the nitrenium ion functionality (and would thereby be expected to mitigate mutagenicity), and to examine the sensitivity of these reactions to the nature of the aromatic ring. In particular, for various systems we examine unimolecular ring contraction, unimolecular ring

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closure in *N*-acetyl-*N*-arylnitrenium ions, and nucleophilic trapping by a water molecule in aqueous solution. As part of this study, we also provide the first systematic characterization of the electronic structures of triazinylnitrenium ion and all isomeric pyridyl- and pyrimidylnitrenium ions.

Computations are carried out using density functional theory (DFT), which has been demonstrated to predict S−T splittings accurate to within about 2 kcal/mol, as compared either to experiment or well converged electronic structure calculations at alternative levels of theory, for a variety of analogous systems.[57,58,60−63,65,66,73−81] Furthermore, since nitrenium ion chemistry is primarily of interest in vivo, condensed-phase effects are taken into account using an SM5.42R aqueous solvation model,[82] in particular one designed for the DFT level of theory.[83]

2. Computational Methods

All geometries were optimized using the gradient-corrected functionals of Becke[84] for exchange and of Perdew and Wang[85] for correlation (BPW91) with the correlation-consistent polarized valence double-ζ[86] (cc-pVDZ) basis set. At this level, analytic frequency calculations were performed to verify the nature of all stationary points (minima and transition state structures), and these frequencies were used to compute zero-point vibrational energies (ZPVE) and 298 K thermal contributions to the enthalpies and standard-state (1 atm) gas-phase free energies of all species using standard statistical mechanical approximations.[87]

Standard state solvation free energies ΔG°_{S} in water (dielectric constant $\epsilon = 78.3$) were calculated using the SM5.42R/BPW91/DZVP aqueous model[83] based on Class IV charges[88] obtained with the DZVP basis set;[89] these calculations employed gas-phase BPW91/cc-pVDZ geometries (the "R" in SM5.42R implies that the model was designed to use gas-phase geometries kept *R*igid in the liquid solution phase). All calculations were carried out with Gaussian 98[90] augmented with MN-GSM version g1.[91]

The standard state used for all solvation free energies in this article involves the ideal gas or ideal solution at a concentration of 1 mol L^{-1}.

3. Results

We adopt a nomenclature system that numbers the aromatic ring such that the point of exocyclic nitrenium ion substitution is 1, and numbering around is dictated by which direction provides the lowest number to the first endocyclic nitrogen atom. While this scheme turns out to generate compound names equivalent to standard convention for the pyridylnitrenium ions, it does not for the pyrimidyl- or triazinylnitrenium ions; to emphasize this point, we will use a prime on our numbers. Thus, for instance, compound **4** (Figure 2) will be named 2′,4′-pyrimidylnitrenium in contrast to its conventional name of 4-pyrimidylnitrenium. Our scheme ensures *ortho*, *meta*, and *para* positions have equivalent numbers for different heterocycles and this facilitates comparison between species.

Heterocyclic Nitrenium Ions. Optimized geometries were obtained for the singlet and triplet states of the three isomeric pyridylnitrenium ions, the three isomeric pyrimidylnitrenium ions, and the triazinylnitrenium ion (Figure 2). For the 2′- and 3′-pyridyl- and 2′,4′-pyrimidyl- cases, both syn and anti rotamers of the exocyclic NH bond were examined (we will define syn to imply the NH rotated to the same side as the 2′ or 3′ nitrogen atom). All geometries were verified as minima by computation of analytic frequencies. We will refer to individual structures by number, using **s** or **t** as a suffix to indicate the singlet or triplet state, respectively.

With the exception of *syn*- and *anti*-**1s**, all singlets were found to deviate somewhat from planarity (Figure 2). We examined the energetic consequences of constraining the singlets to C_s symmetry. For **2s**−**5s**, symmetric structures were found to be only 0.1 to 2.6 kcal/mol higher in energy; however, **6s** constrained to C_s symmetry was 15.5 kcal/mol higher in energy. Moreover, the constrained structure possessed a CNH bond angle at the exocyclic nitrogen of 158.9°. The implications of this geometry for the electronic structure of **6s** are discussed in Section 4. Given the particulars of the optimized structures, the states for *syn*- and *anti*-**1s** are A′ while those for the remaining singlets are simply A. All triplets were found to be planar with A″ electronic states. For the triplets, Figure 2 provides Fermi contact integrals for key heavy-atoms X,

$$\rho(\mathrm{X}) = \sum_{\mu\nu} P^{\alpha-\beta}_{\mu\nu} \phi_{\mu}(\boldsymbol{R}_{\mathrm{X}})\, \phi_{\nu}(\boldsymbol{R}_{\mathrm{X}}) \tag{1}$$

where $\mathbf{P}^{\alpha-\beta}$ is the BPW91/cc-pVDZ one-electron spin density matrix, and evaluation of the overlap between basis functions ϕ_μ and ϕ_ν is only at the nuclear position, $\boldsymbol{R}_{\mathrm{X}}$. These are discussed in more detail below.

Table 1 provides the 298 K aqueous free energies of solvation and relative free energies in the gas phase and aqueous solution of the different pyridyl and pyrimidyl isomers by spin state. Table 2 lists selected geometric details involving the exocyclic nitrogen and S−T splittings in the gas-phase and aqueous solution (as 298 K free energies) for all structures/states.

Singlet heterocyclic arylnitrenium ions with a nitrogen at the 2′-position can undergo a unimolecular ring contraction to generate a protonated heteroarylcarbonitrile as illustrated in Figure 3. The process, which eliminates all nitrenium ion character, is stepwise for **1s**, **4s**, **5s**, and **7s** (the four cases with a nitrogen atom in the appropriate position); in each case a [3.1.0] bicyclic intermediate is formed which then opens with a barrier of about 5 kcal/mol in aqueous solution. Figure 3

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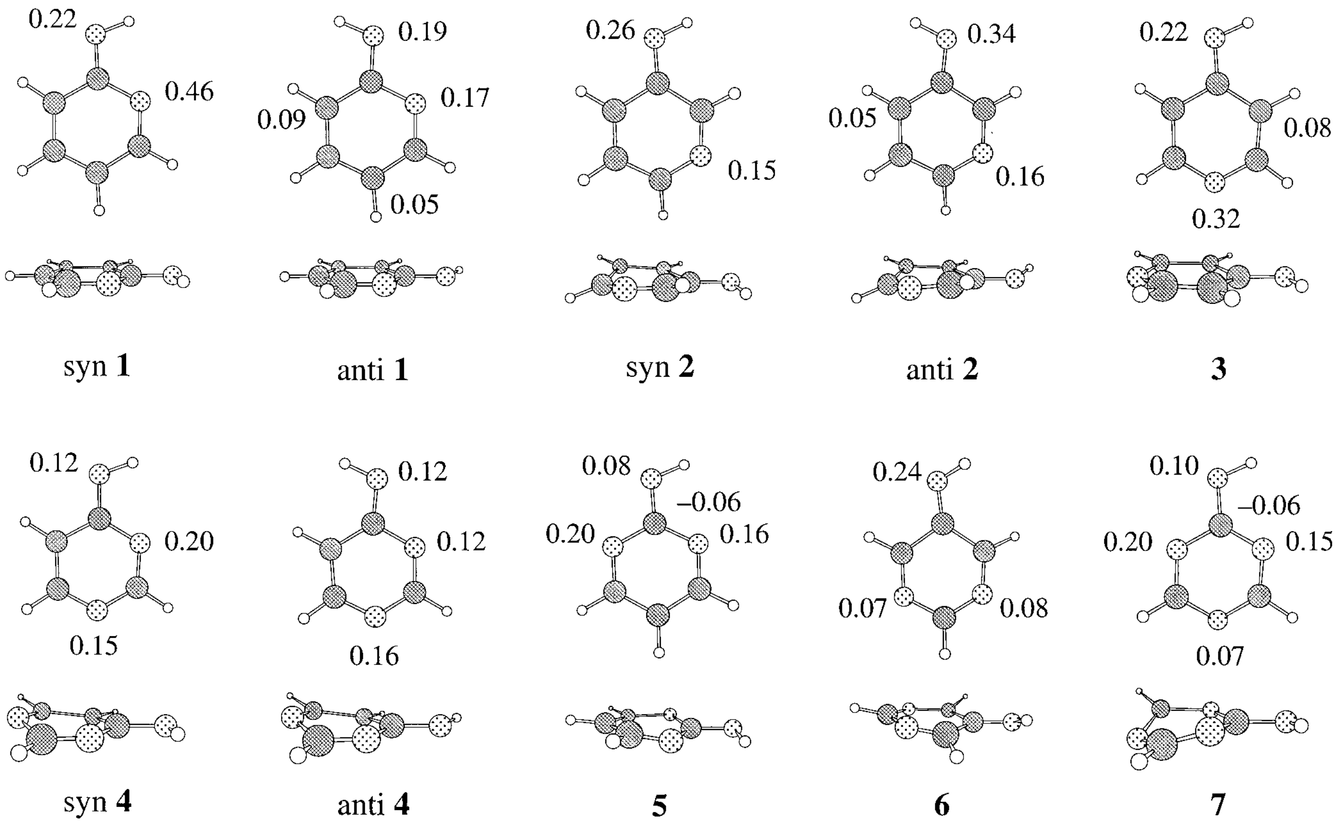


Figure 2. Ball-and-stick structures for **1**−**7**. Triplet Fermi contact integrals ≥0.05 au in magnitude are indicated at atomic positions. Side views of the optimized singlet structures are provided (all triplets are planar).

Table 1. Relative Free Energies and Absolute Free Energies of Solvation (298 K, kcal/mol) for **1**−**7**[a]

molecule	rel $G°$, gas	$\Delta G°_S$	rel $G°$, aq
	pyridyl singlets		
syn-**1s**	0.5	−61.6	0.1
anti-**1s**	5.7	−64.8	2.0
syn-**2s**	0.0[b]	−61.1	0.0
anti-**2s**	0.1	−61.2	0.0
3s	13.1	−61.5	12.7
	pyridyl triplets		
syn-**1t**	9.0	−58.6	9.9
anti-**1t**	5.2	−61.1	3.6
syn-**2t**	0.0[c]	−59.5	0.0
anti-**2t**	3.3	−59.0	3.8
3t	10.6	−60.2	9.9
	pyrimidyl singlets		
syn-**4**	12.9	−62.7	12.7
anti-**4**	17.2	−65.7	14.1
5	11.3	−65.3	8.6
6	0.0[d]	−62.6	0.0
	pyrimidyl triplets		
syn-**4**	8.3	−61.4	8.7
anti-**4**	9.0	−63.9	6.9
5	5.1	−63.8	3.0
6	0.0[e]	−61.8	0.0

[a] BPW91/cc-pVDZ for gas phase and SM5.42R/BPW91/DZVP//BPW91/cc-pVDZ for free energies of solvation. [b] $G°_{298}(E_h) = -302.620\,24$. [c] $G°_{298}(E_h) = -302.610\,61$. [d] $G°_{298}(E_h) = -318.661\,82$. [e] $G°_{298}(E_h) = -318.663\,05$.

Table 2. Selected BPW91/cc-pVDZ Geometrical Data and S−T Splittings ($G°_{298}$, kcal/mol) for Arylnitrenium Ions

molecule	electr. state	rCN, Å	rNH, Å	∠CNH, deg	$G°_{S-T}$, gas (aq)[a]
		pyridylnitrenium ions			
syn-**1**	$^1A'$	1.310	1.046	108.7	
	$^3A''$	1.355	1.042	116.7	−14.5 (−17.5)
anti-**1**	$^1A'$	1.312	1.043	110.8	
	$^3A''$	1.306	1.032	119.2	−5.6 (−9.3)
syn-**2**	^1A	1.301	1.042	111.9	
	$^3A''$	1.300	1.031	125.5	−6.0 (−7.7)
anti-**2**	^1A	1.302	1.042	111.9	
	$^3A''$	1.286	1.030	128.0	−9.2 (−11.5)
3	^1A	1.314	1.044	111.3	
	$^3A''$	1.338	1.038	117.9	−3.6 (−4.9)
		pyrimidylnitrenium ions			
syn-**4**	^1A	1.320	1.047	109.2	
	$^3A''$	1.356	1.044	110.4	5.4 (4.0)
anti-**4**	^1A	1.321	1.043	110.5	
	$^3A''$	1.334	1.038	112.5	9.0 (7.2)
5	^1A	1.318	1.047	108.3	
	$^3A''$	1.316	1.039	109.7	7.0 (5.5)
6	^1A	1.289	1.040	114.0	
	$^3A''$	1.293	1.033	122.0	0.8 (0.0)
		triazinylnitrenium ions			
7	$^1A^b$	1.325	1.047	108.6	
	$^3A''$	1.326	1.042	109.7	10.9 (10.5)

[a] From data in Table 1. [b] $G°_{298}(E_h) = -334.669\,71$ and $\Delta G°_S$(aq, kcal/mol) = −62.9.

provides details on changes in the heavy atom bond lengths along the gas-phase reaction coordinate for the particular case of *syn*-**1s**. Energies relative to the reactant six-membered rings for stationary points on the ring contraction reaction coordinates are listed in Table 3.

An alternative unimolecular rearrangement that also effectively eliminates nitrenium ion character is available to *N*-acetylarylnitrenium ions, namely ring closure to form a *C*-protonated benzoxazole (Scheme 2). As *N*-acetylation is common in biologically relevant arylnitrenium ions, we have characterized the activation and reaction free energies for this

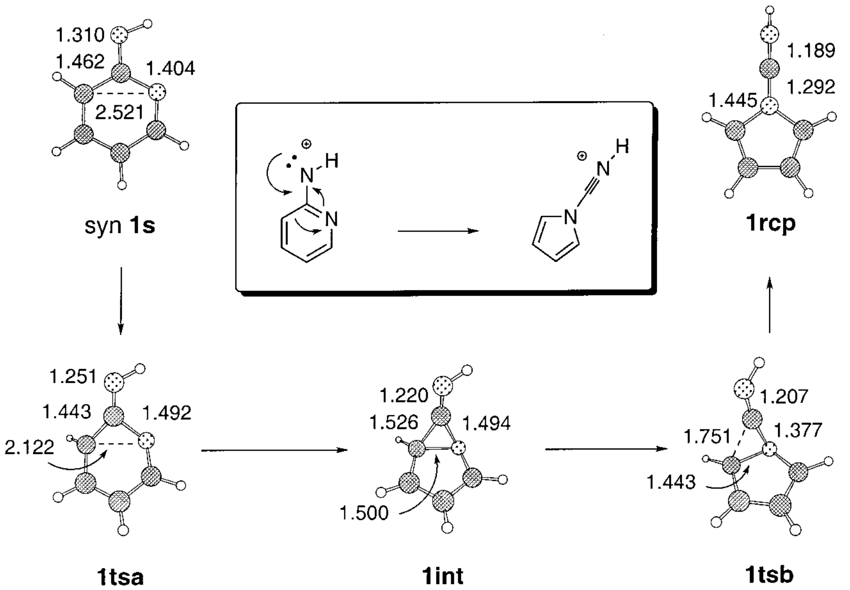


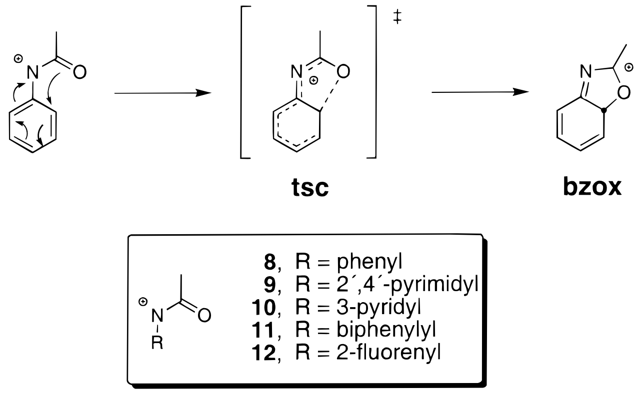
Figure 3. Ball-and-stick structures for stationary points along the gas-phase ring contraction coordinate for *syn*-**1s** with selected heavy-atom bond lengths in angstroms. This reaction generalizes to other six-membered-ring heteroarylnitrenium ions with a nitrogen at the 2′ position.

Table 3. Energies (kcal/mol) Relative to Arylnitrenium Ion Reactants along the Ring Contraction Reaction Coordinate[a]

reactant	tsa	int	tsb	rcp
syn-**1s**	25.0 (24.9)	4.7 (5.7)	7.6 (12.2)	−16.1 (−5.8)
anti-**1s**	22.2 (23.4)	−1.5 (2.7)	−0.4 (6.1)	−21.3 (−7.8)
syn-**4s**	14.3 (11.9)	−8.1 (−10.0)	−6.2 (−5.6)	−34.4 (−28.6)
5s	12.2 (14.4)	−5.1 (2.2)	−1.7 (7.3)	−25.2 (−14.9)
7s	3.4 (3.5)	*b*	−14.2 (−10.1)	−41.1 (−37.3)

[a] BPW91/cc-pVDZ for gas phase and SM5.42R/BPW91/DZVP//BPW91/cc-pVDZ for free energies of solvation. Energies are reported as gas phase (aqueous solution). [b] Not located.

Scheme 2



process in the gas phase and aqueous solution for *N*-acetylphenylnitrenium (**8**), -2′,4′-pyrimidylnitrenium (**9**), -3-pyridylnitrenium (**10**), -4-biphenylnitrenium (**11**), and -2-fluorenylnitrenium (**12**); the data are given in Table 4. We find this reaction to operate only in the case of the singlet state; triplet optimizations starting from ring-closed geometries smoothly open to the *N*-acetylarylnitrenium ions. S−T splittings for **8**−**12** are also listed in Table 4. The *C*-protonated benzoxazole is highly acidic, and would not be expected to persist after ring closure. To provide some quantitative measure of its acidity, we note that the rearomatized *N*-protonated benzoxazole is 36.9 kcal/mol lower in energy than the *C*-protonated isomer. Cyclizations in **10** and **12** were to the 4- and 3-positions, respectively (note that we here use conventional aryl ring numbering: the 4 position of *N*-acetyl-3-pyridylnitrenium would be the 6′ position of *N*-acetyl-3′-pyridylnitrenium). We note that in the optimized structures for the singlets, the plane defined by the two carbons and the oxygen of the acetyl group is essentially perpendicular to the plane of the aromatic ring, so there is no syn/anti distinction for **9s**, **10s**, and **12s** (**8s** and **11s** would lack this distinction in any case by symmetry); Ford and Scribner have discussed this point based on semiempirical calculations for analogous compounds.[50] The triplets, on the other hand, have the heavy atoms of the acetyl group essentially coplanar with the aromatic ring (Ford and Scribner[50] found rotation about the C(O)−N bond to be very facile for analogous triplets at the semiempirical level): we restricted our consideration to those rotamers placing the acetyl oxygen syn to the carbon to which cyclization takes place in the singlet.

Table 4. Energies (kcal/mol) for Stationary Points along the Ring Closure Reaction Coordinate and Triplets Relative to Singlet *N*-Acetylarylnitrenium Ion Reactants[a]

reactant[b]	tsc	bzox	G°_{S-T}
8s	6.9 (8.2)	−16.1 (−15.7)	−6.8 (−11.7)
9s	6.7 (6.6)	−31.2 (−33.9)	6.0 (2.8)
10s	4.5 (6.2)	−8.0 (−8.9)	−1.0 (−4.9)
11s	11.1 (14.2)	−1.7 (−3.0)	−10.0 (−15.9)
12s	10.4 (14.0)	−2.2 (−2.0)	−10.1 (−16.1)

[a] BPW91/cc-pVDZ for gas phase and SM5.42R/BPW91/DZVP//BPW91/cc-pVDZ for free energies of solvation. Energies are reported as gas phase (aqueous solution). [b] **8s**: $G^{\circ}_{298}(E_h) = -439.204\ 12$ and ΔG°_S(aq, kcal/mol) = −54.7. **9s**: $G^{\circ}_{298}(E_h) = -471.270\ 23$ and ΔG°_S(aq, kcal/mol) = −59.0. **10s**: $G^{\circ}_{298}(E_h) = -455.245\ 75$ and ΔG°_S(aq, kcal/mol) = −57.6. **11s**: $G^{\circ}_{298}(E_h) = -670.203\ 05$ and ΔG°_S(aq, kcal/mol) = −48.4. **12s**: $G^{\circ}_{298}(E_h) = -708.324\ 24$ and ΔG°_S(aq, kcal/mol) = −48.6.

Finally, we have examined for both **8** and phenylnitrenium ion (which might be named *des*-acetyl **8**) the reaction paths for nucleophilic trapping by a water molecule at the position *para* to the nitrenium ion. Figure 4 illustrates the reaction energetics as a function of C−O separation for the gas phase and aqueous solution. In the gas phase, “kinks” in the reaction coordinate near C−O distances of 2.7 Å arise because of a large change in the preferred structure of the complex. At shorter C−O distances, the water molecule is situated over the face of the π system, descending toward the *para* carbon atom to form a tetrahedral center. At longer C−O distances, the water oxygen

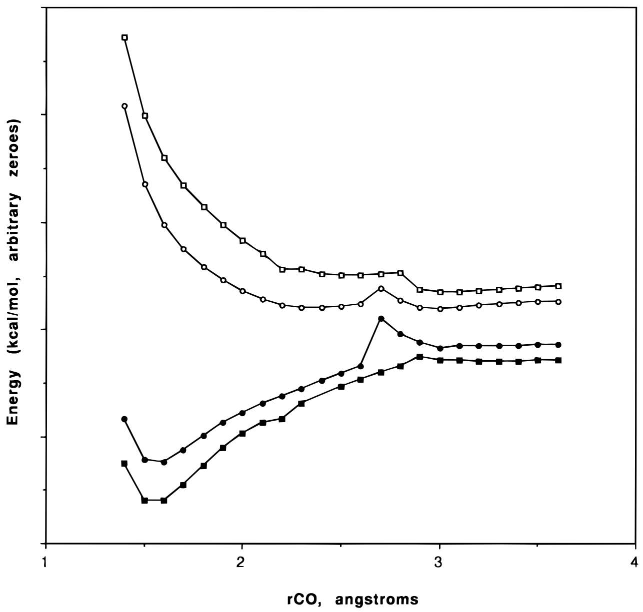


Figure 4. Reaction coordinates for addition of water to the *para* position of phenylnitrenium ion (circles) and **8** (squares); gas-phase values (open symbols) are from BPW91/cc-pVDZ calculations, and values in aqueous solution (filled symbols) refer to solvating the gas-phase reaction coordinate with the SM5.42R/BPW91/DZVP aqueous solvation model.

atom prefers to lie in the plane of the aromatic ring interacting with the aromatic protons in a loose hydrogen-bonding fashion. Near 2.7 Å, these two possibilities are nearly equal in energy, so the one-dimensional representation of the reaction coordinate does not appear smooth. This kinking is maintained for the potential energy curves in aqueous solution, although it is much more pronounced for phenylnitrenium ion than for **8**. In aqueous solution, the oxonium ion products derived from water addition lie about 11 kcal/mol below separated reactants for phenylnitrenium ion and 13 kcal/mol below separated reactants for *N*-acetylphenylnitrenium ion.

4. Discussion

Isomer Energetics and S−T Splittings. Irrespective of spin state, the most stable pyridyl and pyrimidyl isomers in Table 1 are inevitably those that lack nitrogen atoms at *ortho* or *para* positions. When a nitrogen atom *is* present at those positions, 5 times out of 6 it is more energetically destabilizing for the singlet state than the triplet. This is consistent with the extent of the resonance stabilization depicted in Figure 1 (which is most effective for the singlet state) being reduced by the presence of electronegative nitrogen atoms at the ring positions that delocalize positive charge.

Certain trends within isomeric series are of particular interest. We ascribe the fairly large difference in energy between *syn*- and *anti*-**1s** to a combination of (i) a stabilizing anomeric effect available to the former and (ii) the more favorable electrostatics of having the NH proton adjacent to the endocyclic nitrogen lone pair in the syn isomer. The latter effect is trivially evident. Support for the former effect derives from analysis of off-diagonal matrix elements in the Kohn−Sham matrix constructed using the natural bond orbital basis;[92] second-order perturbation theory indicates the magnitude of the anomeric interaction $n_{\mathrm{N(exo)}} \rightarrow \sigma^*_{\mathrm{CN(endo)}}$ to be 10.5 kcal/mol in **1s** but only 2.7 kcal/mol in **1a**. This same differentiation is seen for *syn*- and *anti*-**4s** with equivalent energetic magnitude.

In both the singlets and the triplets, it is more energetically costly to have a nitrogen atom at the *para* position than at an *ortho* position, suggesting that π-resonance is most effective at this position, probably because the exocyclic nitrenium nitrogen withdraws electron density in an inductive fashion from the *ortho* positions and this reduces their ability to accommodate additional positive charge from π delocalization. There is also an interesting difference in the relative energies of *syn*- and *anti*-**1t**, which we ascribe to a substantial difference in spin localization, as described in more detail below.

Aqueous solvation free energies are large in magnitude, as expected for these ionic systems. Differential solvation effects within series are primarily associated with isomers having a nitrogen atom at an *ortho* position. In that case, solvation favors anti isomers from cooperative solvation of the eclipsing nitrogen lone pairs, this effect being worth about 3 kcal/mol for both spin states of **1** and **4**. Across all isomers, there is a general trend for singlet states to be better solvated than their corresponding triplet states by an average of 1.8 kcal/mol. This is consistent with results obtained previously for *para*-substituted phenylnitrenium ions[61,62] and some nonarylnitrenium ions.[63]

As noted above, singlet states are more destabilized by nitrogen atoms at the *ortho* and *para* positions of the aromatic ring than are triplet states. Compared to phenylnitrenium, which has an aqueous S−T splitting of −20.6 kcal/mol at the same level of theory employed in this paper,[62] they are more destabilized by nitrogen atoms at *meta* positions as well, the effect being worth roughly 10 kcal/mol per nitrogen atom (Table 2). Thus, for **6**, which has two *meta* nitrogen atoms, the singlet and triplet states are predicted to be degenerate. In general, the singlet state becomes still more destabilized relative to the triplet, by an average of about 4 kcal/mol per nitrogen atom, when a nitrogen atom is moved from a *meta* to an *ortho* or *para* position. Some exceptions exist for *ortho* cases where anomeric and spin anomeric effects can combine to have a large effect on the splitting of a particular rotamer. The net effect of nitrogen-atom incorporation in the aromatic ring is such that all pyridylnitrenium ions are predicted to remain ground-state singlets, all pyrimidylnitrenium ions are predicted to be ground-state triplets (except **6**, which has degenerate singlet and triplet states), and triazinylnitrenium is predicted to be a ground-state triplet by 10.5 kcal/mol in aqueous solution. Takeuchi et al.[40] recently inferred a thermally accessible triplet state for **5** (they did not speculate on which state was the ground state), which is consistent with our predictions. We note that replacing the proton of the nitrenium nitrogen in phenylnitrenium with a methyl group reduces the S−T gap by about 7 kcal/mol, primarily from steric destabilization of the singlet, so it is certainly possible that some *N*-alkylpyridylnitrenium ions could be ground-state triplets. Acetylation of the nitrenium ion is discussed in more detail below.

Geometric Implications for Charge/Spin Localization in 1−7. The singlet states of **1**−**7** are all well described by an electronic configuration where the lone pair of the exocyclic nitrogen is oriented in the plane of the ring (i.e., it is sp^2-like). Of course, this can be inferred from the nature of the occupied Kohn−Sham orbitals in the DFT calculations, but it also follows from the geometric similarities between these heterocyclic nitrenium ions and phenylnitrenium, which may be regarded as the "unperturbed" parent arylnitrenium ion.

Geometric analysis is additionally useful for evaluating the extent to which the resonance stabilization indicated in Figure

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[92] Reed, A. E.; Weinhold, F.; Curtiss, L. A.; Pochatko, D. J. *J. Chem. Phys.* **1986**, *84*, 5687.

1 is operative in the different heterocycles. Phenylnitrenium, which can delocalize positive charge to its *ortho* and *para* positions, has a C−N bond length of 1.308 Å.[60,62] When one of those ring positions is occupied by a nitrogen atom, as is the case for **1** and **3**, the exocyclic C−N bond length gets longer by 0.002 to 0.006 Å (Table 2), suggesting a decreased contribution from imine-like mesomers. When two *ortho/para* positions are nitrogen atoms, as is the case for **4** and **5**, the exocyclic C−N bond length is found to be about 0.01 Å longer than in phenylnitrenium. Finally, when all 3 positions are nitrogen atoms, as found for **7**, the exocyclic C−N bond length is 0.017 Å longer—the longest such singlet bond length. Conversely, when a single nitrogen atom is found at a *meta* position, as in **2**, the exocyclic C−N bond length shortens by 0.006 Å, suggesting an enhanced contribution from imine-like mesomers, and when both *meta* positions are nitrogen atoms, as in **6**, the bond length is very short indeed, at 1.289 Å.

The same analysis can be made for the CNH bond angles. In phenylnitrenium, the bond angle at nitrogen is 111.2°.[60] In the cases where contributions from imine-like mesomers are enhanced, one would expect this angle to increase to the more nearly sp^2-like value of 120°, while in the cases where such mesomers are less important contributors, one would expect a decrease in bond angle. This trend is, for the most part, observed (Table 2), although the magnitude of the effect is considerably smaller than were changes in bond lengths, so other influences may obscure the otherwise common trend.

As for deviations from ring planarity in singlets **2**−**5** and **7**, an analysis of Charge Model 2[88] (CM2) partial atomic charges indicates that in every case such distortion slightly reduces positive charge localization onto nitrogen atoms, typically by 0.02 to 0.04 charge units (data not shown). As noted above, the energetic consequences of ring distortion are fairly small, consistent with the small changes in charges; nevertheless, they appear to be sufficient to outweigh some loss of aromaticity associated with this phenomenon. Nitrenium ion **6s** is more interesting. In this case with two nitrogen atoms, the π system seems to be sufficiently electron-withdrawing that, when constrained to planarity, it is energetically preferable for the exocyclic nitrogen lone pair to be part of the π system rather than in the plane of the ring. Thus, as noted above, the CNH bond angle becomes nearly linear (for the described electronic configuration the nitrogen atom would be formally sp hybridized). [As a technical point, the large change in energy computed for this planar structure relative to the nonplanar minimum is probably something of an artifact. It is likely that the two alternative electronic configurations, in-plane vs π lone pair, are quite close in energy for planar **6**, and a single-determinantal method like DFT is poorly suited for such a situation.[93−95] As the planar structure is not of much chemical interest, we have not characterized it with multideterminantal methods.] It is important to point out that **4** and **5** also have two nitrogen atoms in the aromatic ring, but a similar change in electronic configuration is not predicted on enforcement of planarity. We ascribe this to anomeric stabilization available to the in-plane lone pair in these isomers, as already noted above. In the case of **7**, the SCF equations could not be coaxed to converge for a planar structure, which is consistent with two alternative configurations that are close in energy causing numerical instability.

The geometries of the triplets are also noteworthy in several instances. Again, the exocyclic C−N bond length is diagnostic of the character of the exocyclic nitrogen atom. In many nitrenium ions, triplet C−N bond lengths are shorter than singlet C−N bond lengths,[51,55,56,58,60,61,63,73] as in *anti*-**1**, for instance. This bond shortening, together with an observed increase in the CNH bond angle, is indicative of increased nitrogen s character in NX bonding orbitals, which is to be expected when the remaining non-bonding orbitals are both formally singly occupied.

However, with multiple nitrogen atoms in the system, there is no a priori requirement that the electron that is promoted (with spin flip) into the π system derives from the lone pair of the *exo*cyclic nitrogen: it could come from an *endo*cyclic nitrogen atom as well, or involve a “hole” delocalized over multiple nitrogen atoms. Since the nitrogen lone pairs have high s character, nitrogen Fermi contact integrals (FCI) in the triplets are diagnostic for the contribution each nitrogen atom makes to providing the necessary spin. For instance, in *syn*-**1** the FCI at the endocyclic nitrogen is more than twice that at the exocyclic nitrogen (Figure 2), suggesting that the triplet nitrenium ion is primarily endocyclic in character. Consistent with this picture is the very long exocyclic C−N bond length in *syn*-**1**. By contrast, in *anti*-**1**, the two nitrogen FCI values are nearly equal, suggesting an even delocalization of spin, and the much shorter C−N bond length bears this out. The large difference between *syn*- and *anti*-**1** appears to derive from a one-electron anomeric effect, although in a direction opposite to that more typically observed. Thus, the exocyclic nitrogen lone pair orbital, which is singly occupied, serves as an aggressive acceptor orbital for opposite spin density from the antiperiplanar ring σ bond. In *syn*-**1**, the antiperiplanar bond is the C−N bond, and this increases the spin density on the endocyclic nitrogen; in *anti*-**1**, the antiperiplanar bond is the C−C bond, and the FCI at carbon 6′ is a substantial 0.09 (note that the C−C bond is also antiplanar to the endocyclic nitrogen lone pair orbital, so delocalization is further enhanced and this is the largest carbon FCI observed in **1**−**7**). This spin-anomeric effect is also evident in *anti*-**2**, **3**, and *syn*-**4**. In the other systems, spin localization onto endocyclic nitrogen atoms and/or competition for anomeric delocalization with other nitrogen atoms diminishes the effect.

Analysis of FCI values, triplet C−N bond lengths, and CHN bond angles indicates that **2** and **6** are the only species heavily localizing in-plane spin on the exocyclic nitrogen atom. This is consistent with the greater ability of these systems, which have no nitrogen atoms at *ortho* or *para* positions, to better stabilize exocyclic positive charge. The case of **2t** is interesting, since there is a large difference in energies between the syn and anti isomers that is not found in the singlets. Analysis of FCI values suggests that the in-plane hole is shared between the exo- and endocyclic nitrogens in the syn isomer via their overlap through the mutually parallel C1′−C2′ σ system, and this stabilizes the syn isomer relative to the anti, where the in-plane hole is much more localized on the exocyclic nitrogen.

Ring Contractions. The transformation of 2′-azaarylnitrenium ions to protonated *N*-cyanopyrrole derivatives represents a nitrenium ion self-destruct mechanism in the sense that the product, which is more thermodynamically stable than the reactant, would not be expected to be a particularly aggressive electrophile (particularly after deprotonation of the acidic nitrile). The barrier height for the rate-determining ring closure to an azabicyclo[3.1.0]hexane, which is the first step in the process, is sufficiently high in the 2′-pyridyl case that the unimolecular reaction is unlikely to compete with bimolecular nucleophilic

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(93) Cramer, C. J.; Smith, B. A. *J. Phys. Chem.* **1996**, *100*, 9664.
(94) Cramer, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 6261.
(95) Gräfenstein, J.; Kraka, E.; Cremer, D. *Chem. Phys. Lett.* **1998**, *288*, 593.

substitution reactions occurring at diffusion-controlled rates (vide infra). It is possible, however, that this reaction might be observable in a 2′-pyridylnitrenium ion that is substituted at the 4′ and 6′ positions to decrease the facility of nucleophilic aromatic substitution.

As increasing nitrogen incorporation in the aromatic ring destabilizes the reactant nitrenium ion, the barrier to ring closure drops by about 10 kcal/mol per nitrogen atom. For **7**, the barrier is predicted to be only 3.4 kcal/mol, which is sufficiently low that, if the singlet can be generated, ring contraction might compete with intersystem crossing to the ground-state triplet provided spin−orbit coupling is small.

Aqueous solvation decreases the overall exergonicity of ring contraction, but has relatively little effect on the rate determining free energy of activation. Solvation also stabilizes the azabicyclohexane intermediate relative to **tsb**, but the second barrier remains very small in every instance. In the case of **7**, exhaustive efforts to find **7int** were undertaken to no avail, a rather odd situation given the identification of **7tsa** and **7tsb**, but probably attributable to a very shallow minimum in the potential energy surface.

We note that the exergonicity of the ring contraction pathway derives in part from the aromatic nature of the product heterocycle. Thus, this pathway is unlikely to be observed unless a heteroatom, which can contribute one electron to the π system of the reactant and two electrons to the π system of the product, is present at the *ortho* position to which migration/contraction takes place.

Ring Closure of Acetylated Nitrenium Ions. An *N*-acetyl group can serve as an intramolecular nucleophile in a different nitrenium ion self-destruct reaction. This process is also strongly exergonic, particularly if one recognizes the high acidity of the product *C*-protonated benzoxazole. Novak et al.[96] have isolated benzoxazole products from ring closure of **12** in MeOH-d_4; such products do not appear ever to have been isolated from aqueous reaction mixtures.

Although **8**−**12** are all ground-state singlets, an *N*-acetyl group reduces the S−T splitting compared to N−H substitution by 5−10 kcal/mol for **8**−**10**. The tendency for the acetyl group *not* to conjugate with the aromatic pi system may reflect the unfavorability of two electron-poor π systems interacting, or unfavorable steric interactions with *ortho* hydrogen atoms, or both. Large CNC bond angles and less electron-poor π systems in the triplets mitigate the magnitude of any such destabilization, and thus S−T gaps in the *N*-acetylarylnitrenium ions are smaller than those in their nonacetylated congeners.

The acetyl ring closure reaction coordinate conforms to the Hammond postulate.[97] The forming C−O bond is very long (reactant-like) in the strongly exergonic reactions and much shorter (product-like) in the weakly exergonic reactions. In **8**, for instance, the forming C−O bond length is 2.426 Å while in **11** it is 2.009 Å.

Exergonicities to produce **bzox** reflect the degree to which positive charge localizes on the carbon to which cyclization occurs. Taking **8** as a standard, having nitrogen atoms in an *ortho* and *para* position, as in **9**, strongly increases the tendency for the remaining *ortho* carbon atom to carry positive charge (since the nitrogen atoms prefer not to) and the exergonicity increases substantially. With an aromatic system offering *additional* sites for charge localization, on the other hand, as found in **11** and **12**, the exergonicity is very much reduced, since the *ortho* carbon has *less* concentrated positive charge. Increased free energies of activation through **tsc** in **11** and **12** are further consistent with this analysis. For various substitution patterns, acetyl group ring closure would again appear to be a reaction that might compete effectively with bimolecular nucleophilic aromatic substitution reactions so long as the latter are not operating at diffusion controlled rates.

Nucleophilic Aromatic Substitution by Water. In the gas phase, addition of water to the aromatic ring of phenylnitrenium or of **8** is not a favorable process because of the concentrated charge that would be present in the product oxonium ion. Instead, two loose ion dipole complexes are found, one with the water *over* the plane of the aromatic ring and one with the water *in* the plane of the aromatic ring; the intermolecular distance is slightly larger in the latter complex.

Aqueous solvation, however, strongly stabilizes the oxonium ion relative to the more delocalized nitrenium ion and, as illustrated in Figure 4, minimum energy structures having C−O bond lengths on the order of 1.5 Å are predicted. In the case of **8**, the curve derived from solvation of the gas-phase structures shows effectively no barrier to water addition, i.e., the reaction would be expected to be diffusion controlled. In the case of phenylnitrenium, the aqueous curve does appear to have a barrier, but this is probably not realistic. Rather, it reflects the less good solvation of the in-plane ion−dipole complex compared to the over-plane complex. In the gas phase, the two geometries are close to one another in energy at 2.7 Å, but in water the over-plane is considerably more stable. We presume that if we could generate over-plane geometries for C−O bond lengths of 2.8, 2.9, 3.0 Å, etc. (which for technical reasons is challenging), we would not see any appreciable barrier.

It should be emphasized, however, that a continuum solvation model cannot be used to identify subtle cooperative changes in solvation shell structure that may lead to small barriers in otherwise diffusion-controlled reactions. Thus, while there is no barrier in the continuum to bringing a water molecule smoothly up to phenylnitrenium, in the presence of an actual complete solvation shell it may be that rearrangement of some portion of the full network of surrounding hydrogen bonds will introduce a small barrier. Such an analysis is consistent with the experimental results of Fishbein and McClelland[98−100] who, on the basis of water/azide trapping product ratios in water (also measured by Novak and co-workers[37,67,101]), have assigned phenylnitrenium an aqueous lifetime of 125−250 ps (no transient for this species has ever been observed in laser flash photolysis experiments).

The discussion above is quite similar to an earlier analysis by Ford and Scribner[50] performed at the semiempirical level for addition of water to **8**. In that instance, a gas-phase minimum was predicted for the oxonium ion, albeit of higher energy than separated reactants. The absence of available solvation models required those authors to estimate hydration energies from fragment analysis and as a result no barrier estimates were offered. It should be noted that Marquez et al.[64] have used continuum solvation models to investigate reactions between non-arylnitrenium ions and water that ultimately lead to hydroxylamines, but theory[50] suggests this pathway is not competitive for arylnitrenium ions and product studies have not identified hydroxylamines in such instances.

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[101] Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; James, T. G. *J. Org. Chem.* **1995**, *60*, 8294.

5. Conclusions

Incorporation of nitrogen atoms into an aromatic ring substituting a nitrenium ion leads to significant changes in chemical properties; these are primarily dictated by perturbations in resonance interactions which make a greater contribution to stabilizing the singlet state than the triplet state. Thus, replacing *ortho* or *para* carbons with more electronegative nitrogens decreases resonance stabilization of the singlet more than the triplet, and singlet−triplet state energy splittings are reduced; pyrimidylnitrenium ions are predicted to be ground state triplets. A secondary effect that influences the relative stability of different heteroarylnitrenium ion isomers is anomeric delocalization that can operate in both spin states and is particularly strong when a nitrogen atom is present at an *ortho* position.

As the singlets become less stable, they undergo more facile reactions that destroy their nitrenium ion character. When a nitrogen atom is present at an *ortho* position, a ring contraction pathway leading to protonated *N*-cyanopyrrole derivatives is accessible. In the case of *N*-acetylarylnitrenium ions, ring closure to form a *C*-protonated oxazolium cation via internal electrophilic attack of the aromatic ring on the acetyl oxygen becomes increasingly facile as positive charge is concentrated (via resonance) at an *ortho* position. Finally, nucleophilic attack by water at the unsubstituted *para* position of phenylnitrenium and *N*-acetylphenylnitrenium is predicted to be unfavorable in the gas phase, but to proceed with little or no activation barrier in aqueous solution, consistent with conclusions drawn from experimental azide/solvent trapping ratios.

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Supporting Information Available: Cartesian coordinates (Å) and electronic energies (E_h) for all structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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