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Correlation of Azide/Solvent Selectivities for Nitrenium Ions with ab Initio Hydration Energies: Understanding the Kinetic Lability of Nitrenium Ions in Aqueous Solution

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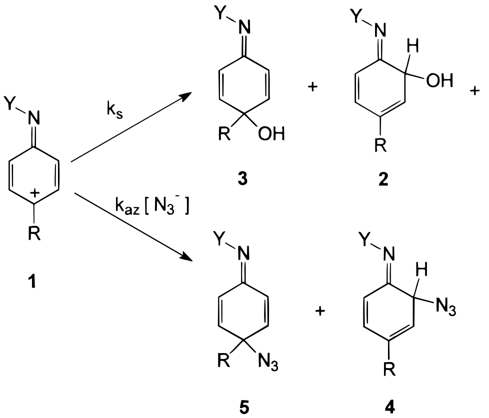
The experimentally determined azide/solvent selectivity data (log *S*) for 22 nitrenium ions (**1a**−**v**) were compared to the relative hydration energies (ΔE) calculated for these same ions at the RHF/6-31G*//3-21G level of theory. Except for the most reactive (least selective) of these ions (*N*-phenylnitrenium (**1a**), *N*-acetyl-*N*-phenylnitrenium (**1b**), and *N*-acetyl-*N*-(2-naphthyl)nitrenium (**1d**)), there is a good linear correlation of log *S* with ΔE that is broken only by the most selective ion for which the calculation was performed (*N*-(4′-methoxy-4-biphenylyl)nitrenium (**1r**)). The deviation from linearity of the highly reactive ions is likely caused by the onset of preassociation trapping by N_3^- for ions with rate constants for solvent trapping, k_s, of at least 10^{10} s^{-1}. The preassociation process leads to approximately constant and low azide/solvent selectivities (log $S \approx 0.0$) for these ions. Both the experimental log *S* values and the calculated ΔE values show that π-donor substituents in the para-position of the proximal ring of the ion have a remarkably strong stabilizing effect on the nitrenium ion that is not observed in carbenium ions of analogous structure, or in σ^+ parameters. Substituents in the distal ring of a series of N-(4-biphenylyl)nitrenium ions were previously shown by Ren and McClelland to behave in a way expected for a benzylic carbenium ion, and our calculated ΔE values for these same ions also show a pattern that is carbenium ion-like. These results add to the growing experimental data that suggests that the dominant canonical form of most *N*-arylnitrenium ions is the iminocyclohexadienyl cation-like structure **II**. Calculated charge densities and LUMO coefficients for the nitrenium ions are of some use in rationalizing the regioselectivities of the reactions of small anionic nucleophiles and H_2O with these ions, but this approach is not very useful in predicting the regioselectivities of softer carbon, nitrogen, or sulfur nucleophiles.

Over the last 30 years a good deal of empirical knowledge has been gathered concerning the relative reactivities of *N*-arylnitrenium ions and the regioselectivities of their reactions with a variety of nucleophiles.[1−7] An understanding of the basic principles underlying the observed reactivities and regioselectivities has been lacking, however.

Early on it was shown that the rates of solvolysis of *N*-arylnitrenium ion precursors could be adequately correlated by σ^+.[1,3a] The reactivities of the resulting ions, measured by azide/solvent selectivities (log(k_{az}/k_s)) in aqueous solution (eq 1),[3,4] or by direct measurement of log k_s on ions generated by laser flash photolysis methods,[5,6] produce highly scattered plots when correlations with σ^+ are attempted, with the notable exception of the 4-biphenylyl ions with substituents in the distal ring of the ions.[4a,6b] This is in contrast to substituted arylcar-



(1)

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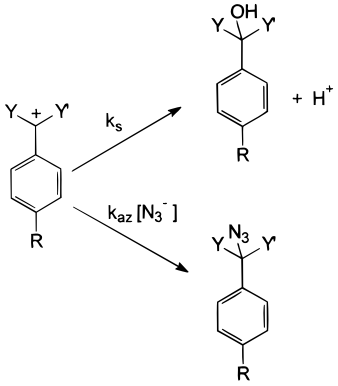
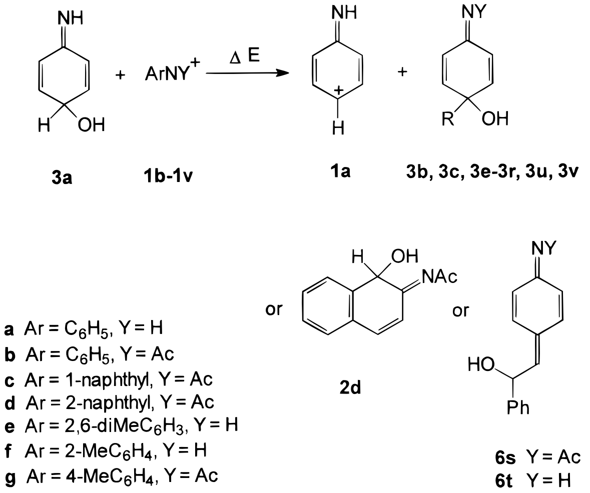
benium ions that do show good correlations of $\log(k_{az}/k_s)$ or $\log k_s$, with σ^+ or σ^{c+}.[8,9] Although the lack of correlation of nitrenium ion reactivity with σ^+ is understandable because of the very different fates of nitrenium ions (eq 1) and carbenium ions (eq 2),[4a] the inability to correlate nitrenium ion reactivity with familiar organic substituent constants has made it difficult to sort out the factors that influence that reactivity.



(2)

At the same time, the development of an understanding of the regioselectivities of the reactions of **1** with nucleophiles such as H_2O or N_3^- has been complicated by the fact that all of the initial products of nucleophilic attack (**2**−**5**) are unstable and yield a bewildering variety of stable, observed products.[1−7] At the present time most of the decomposition pathways of **2**−**5**, and similar intermediates, are understood,[1−7,10−12] so it is possible to ascribe most reaction products to one of these initial intermediates.[10] Complications still arise if R extends the π-conjugation because additional initial reaction products such as **6s** and **6t** are then formed.[13] Analogies to arylcarbenium ion regioselectivities are of little use because, with very few exceptions,[14] arylcarbenium ions undergo reaction at the benzylic carbon, while *N*-arylnitrenium ions undergo attack by N_3^-, Cl^-, H_2O and most other nucleophiles at carbons of the aryl rings.[1−9] Only certain sulfur, nitrogen, and carbon nucleophiles show a tendency to react at N of the nitrenium ions.[15−17] Included among these is deoxyguanosine which may react either through N-7 or C-8 to produce the familiar C-8 adduct.[16,17]

Scheme 1



3a **1b-1v** **1a** **3b, 3c, 3e-3r, 3u, 3v**

2d

6s Y = Ac
6t Y = H

a Ar = C_6H_5, Y = H
b Ar = C_6H_5, Y = Ac
c Ar = 1-naphthyl, Y = Ac
d Ar = 2-naphthyl, Y = Ac
e Ar = 2,6-diMeC_6H_3, Y = H
f Ar = 2-MeC_6H_4, Y = H
g Ar = 4-MeC_6H_4, Y = Ac
h Ar = 4-MeC_6H_4, Y = H
i Ar = 4-MeC_6H_4, Y = Me
j Ar = 4-MeOC_6H_4, Y = Ac
k Ar = 4- MeOC_6H_4, Y = H
l Ar = 4-biphenylyl, Y = Ac
m Ar = 4-biphenylyl, Y = H
n Ar = 4-biphenylyl, Y = Me
o Ar = 3'-Me-4-biphenylyl, Y = H
p Ar = 4'-Me-4-biphenylyl, Y = H
q Ar = 3'-MeO-4-biphenylyl, Y = H
r Ar = 4'-MeO-4-biphenylyl, Y = H
s Ar = 4-stilbenyl, Y = Ac
t Ar = 4-stilbenyl, Y = H
u Ar = 2-fluorenyl, Y = Ac
v Ar = 2-fluorenyl, Y = H

The kinetics of the hydration of **1** (k_s of eq 1) are of critical importance to determining the reactivity patterns of nitrenium ions in aqueous solution because the magnitude of k_s governs how selectively the ion can react with nonsolvent nucleophiles such as N_3^- or deoxyguanosine. For example, the bimolecular rate constants for reaction of N_3^- with **1** (k_{az} of eq 1) are effectively at their diffusion controlled limits for moderately to highly reactive ions ($k_s > 10^4\ s^{-1}$)[5,6] so the selectivities of these ions for N_3^- are entirely governed by k_s. Similar considerations govern the selectivities of these ions for other nucleophiles.

In a preliminary report we suggested that insight into the kinetic lability of nitrenium ions in an aqueous environment could be obtained from the relative thermodynamic driving force for hydration of these ions, ΔE of Scheme 1, determined from ab initio calculations at the RHF/6-31G*//3-21G level.[4a] In that paper, data were available for only 10 ions. In this paper we report on the results of calculations involving 22 different ions **1a**−**v** (Scheme 1) that show we can predict the relative kinetic labilities of these ions in an aqueous environment to within an order of magnitude in most cases, provided that we know the identity of the major initial hydration product of the ions. LUMO coefficients and charge distributions determined by the calculations also provide insight into the regioselectivity of the reactions of these ions with H_2O and N_3^-. Some of our conclusions concerning the regioselectivity are similar to those previously made by Ford and Scribner from semiempirical calculations.[18]

Results and Discussion

During the last several years the Novak and McClelland groups have provided azide/solvent selectivity data

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Table 1. Results of ab Initio Calculations and Azide/Solvent Selectivities

	total energies (RHF 6-31G*//3-21G) in Hartrees			
ion	for ion	for H_2O adducts	ΔE (kcal/mol)[a]	log S[b]
1a	−284.84929	−360.54137 (**3a**) −360.53976 (**2a**)	0	0.00[c]
1b	−436.61909	−512.31781 (**3b**) −512.31665 (**2b**)	−4.2	−0.15[d]
1c	−589.29936 (anti)	−664.98377 (**3c**) −664.98224 (**2c**)	4.8	−0.15[e]
1d	−589.29433 (anti) −589.29240 (syn)	−664.98786 (**2d**) (C-1) −664.94864 (**2d′**) (C-3) −664.92824 (**3d**)	−0.9	0.18[e]
1e	−362.94330	−438.61811 (**3e**)	10.8	0.88[f]
1f	−323.89812 (anti) −323.89583 (syn)	−399.58061 (**3f**)	6.0	0.37[c]
1g	−475.67106	−551.35674 (**3g**)	4.0	0.04[g]
1h	−323.90113	−399.58028 (**3h**)	8.1	0.49[g]
1i	−362.93991	−438.60613 (**3i**)	16.2	1.66[g]
1j	−550.53417	−626.20023 (**3j**)	16.3	2.74[g,h]
1k	−398.76487	−474.42070 (**3k**)	22.7	3.18[i]
1l	−666.19657	−741.86367 (**3*l***)	15.7	2.97[j,k]
1m	−514.42620	−590.08747 (**3m**) −590.09014 (**2m**)	19.3	3.45[j,l] (3.55)[m]
1n	−553.46200	−629.11336 (**3n**)	25.6	4.15[g]
1o	−553.46472 (anti) −553.46515 (syn)	−629.12453 (**3o**)	20.5	3.79[m]
1p	−553.46906	−629.12460 (**3p**)	22.9	4.52[m]
1q	−628.30495 (anti) −628.30501 (syn)	−703.96634 (**3q**)	19.3	3.50[m]
1r	−628.31882	−703.96646 (**3r**)	27.9	6.59[m]
1s	−743.09918 (anti) −743.09910 (syn)	−818.75806 (**6s**) −818.75377 (**2s**) −818.74982 (**3s**)	20.8	2.45[n]
1t	−591.32823 (anti) −591.32787 (syn)	−666.97864 (**6t**)	26.1	3.08[o]
1u	−704.08839 (anti) −704.08887 (syn)	−779.73628 (**3u**)	28.0	4.77[k]
1v	−552.31786 (anti) −552.31810 (syn)	−627.95991 (**3v**) −627.97134 (**2v**) (C-3) −627.97041 (**2v′**) (C-1)	31.5	5.08[l]

[a] Calculated from the isodesmic reaction of Scheme 1. [b] Conditions: 5% CH_3CN-H_2O, $\mu = 0.5$ ($NaClO_4$), $T = 20$ °C, unless otherwise indicated. [c] Reference 4c: H_2O at 25 °C, $\mu = 1.0$. This value is derived from Br^- trapping, but it appears that $k_{Br} \approx k_{az}$. [d] Reference 4a; at 50 °C. [e] Reference 4b. [f] Reference 3c; H_2O at 40 °C, $\mu = 1.0$. [g] Reference 4a. [h] Measured for $4\text{-EtOC}_6H_4NAc^+$ and its hydration product. [i] Reference 6a; H_2O. [j] Reference 3b. [k] Reference 5a. [l] Reference 5b. [m] Reference 6b; 20% CH_3CN-H_2O, $\mu = 0.0$. [n] Reference 13. [o] Reference 6c; 20% CH_3CN-H_2O, $\mu = 0.0$.

for about 30 carbocyclic *N*-arylnitrenium ions under similar conditions in aqueous solution.[3−6,10,13] These measurements were made either by classical competition experiments or by direct measurement of k_{az} and k_s on ions generated by laser flash photolysis. Heterocyclic ions are not considered here because of a lack of reactivity and regioselectivity data for a sufficient number of ions at the present time. Initial products of the reaction of these ions with H_2O can be inferred from product study data,[3,4,10,13] or by analogy to closely related ions. Data for six halogen-substituted (CF_3ArNY^+, $ClArNY^+$) ions were excluded from this study because a preliminary correlation of ΔE calculated from the ab initio results and the semiempirical AM1 method showed large deviations (>10 kcal/mol, with the ab initio method consistently producing a more negative ΔE) for the halogen-substituted ions that were not observed for any other cations. This result suggests that our neglect of electron correlation in the ab initio calculations (vide infra) is not justified for the halogen-substituted ions. All other ions except those with relatively trivial structural differences (OEt or OMe substituents, for example) were included in this study. The 22 ions chosen for this study span a very broad range of structures (see Scheme 1) and about 7 orders of magnitude in reactivity toward H_2O.

The structures of all ions and hydration products were fully optimized at the RHF/3-21G level of theory.[19] Only singlet electronic states of the nitrenium ions were considered because calculations at various levels of theory indicate that *N*-arylnitrenium ions are singlet ground states unless substituted with strongly electron-withdrawing aryl substituents or with bulky substituents that increase the Ar−N−Y bond angle.[18,20] Some initial calculations were performed at the semiempirical level with the AM1 method to generate initial geometries that were subsequently refined by the 3-21G calculations. Most of the ions **1** have minimal structural freedom because the aryl rings and N−Y bonds lie in the same plane, or nearly so, with the exception of the biphenylyl ions in which the distal ring twists out of the plane of the proximal ring by 10° to 26°. For nonsymmetric aryl substituents the N−Y bond can take on two conformations. Ford and Herman have previously referred to these conformations as syn and anti, the syn conformation being that in which

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the N−Y bond is directed toward the source of asymmetry.[21] We have followed the same formalism. In agreement with Ford and co-workers' previous calculations,[18,22] we find that at this level of theory the acetyl groups for **1** in which Y = Ac are rotated out of the plane of the aryl ring by ca. 25°−35° with the carbonyl oxygen directed toward the ring. The planar structures are only 1−2 kcal/mol less stable than the nonplanar ground states at either the RHF/3-21G or RHF/6-31G*//3-21G level. Energies for all ions, including syn and anti conformations where applicable, at the RHF/6-31G*//3-21G level,[23] are reported in Table 1. Electron correlation effects were not considered in these calculations because we are predominantly interested in the energetics of isodesmic reactions such as Scheme 1, which should be relatively insensitive to the inclusion of electron correlation.[24] Indeed, Ford and Herman have previously shown that inclusion of electron correlation at the MP2 level had little effect on the calculated energetics of isodesmic reactions involving *N*-arylnitrenium ions and the corresponding amines or amides at the 6-31G*//3-21G level.[22a] Our successful correlation of ΔE calculated from the AM1 and 6-31G*//3-21G results (except for the halogen substituted cases noted above) also suggests that electron correlation effects on ΔE are minimal.

Ford and co-workers have previously reported energies for some of these ions (**1a**, **1b**, **1v**) at the RHF/3-21G or RHF/6-31G*//3-21G levels.[21,22] Our results are in agreement with the previous calculations. More details of the structures and other features of **1** are described below with respect to the regioselectivities of their reactions with H_2O and N_3^-.

The hydration products have greater conformational freedom than the corresponding ions. The rings of the ortho- or para-addition products, **2** or **3,** deviate considerably from planarity, and there is rotational mobility about the C−O and C−R bonds in both structures. The N−Y bond of all structures **2** and structures **3** that have nonsymmetric aryl substituents can also take on syn or anti conformations. In several cases there are multiple conformations that lie within 2−3 kcal/mol of each other at the RHF/3-21G and RHF/6-31G*//3-21G levels. These structures are summarized for **2m** and **3m** in Figures 1 and 2. The energies at the RHF/6-31G*//3-21G level of the most stable conformer located for the observed major hydration products of each ion are reported in Table 1. For selected ions, energies of minor or unobserved hydration products are also reported. In those cases the energies of the observed or most abundant hydration products are reported first in the Table. A table of Cartesian coordinates for the lowest energy structure of all species listed in Table 1 is provided in the Supporting Information.

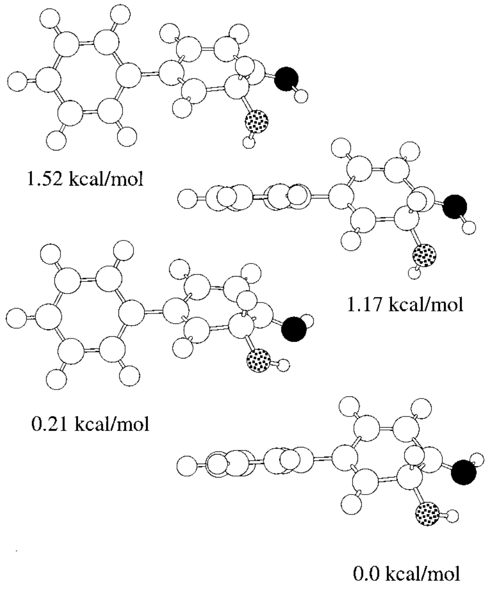


Figure 1. Low energy conformations located at the RHF/3-21G level for **2m**. Energies listed are the relative energies for each conformer at the RHF/6-31G*//3-21G level of theory.

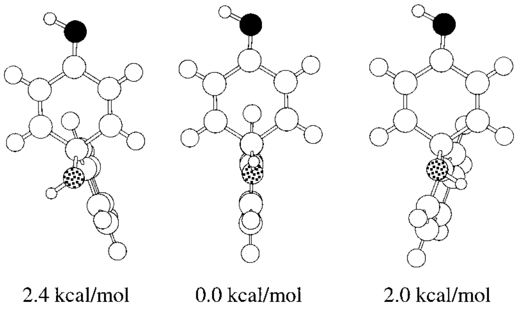
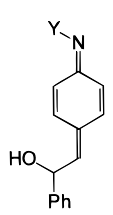
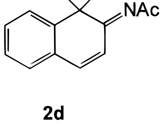


Figure 2. Low energy conformations located at the RHF/3-21G level for **3m**. Energies listed are the relative energies for each conformer at the RHF/6-31G*//3-21G level of theory.

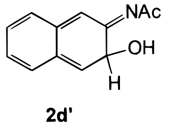
For all the ions in this study except **1d**, **1s**, and **1t**, the para-addition product **3** is the major or exclusive initial hydration product based on the observed structures of the stable hydrolysis products or by analogy to ions of similar structure.[3,4,10] For the stilbenyl ions **1s** and **1t** the initial hydration products are **6s** and **6t**,[6c,13] while the major hydration product of **1d** is the product of attack of H_2O on C-1, **2d**.[4b] The product of attack of H_2O at C-3, **2d′**, is not observed, but the product of attack of H_2O on C-4a, **3d**, is apparently produced as a minor hydration product.[4b]



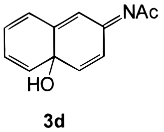
6s Y = Ac
6t Y = H



2d



2d'



3d

The relative thermodynamic driving force for hydration of the cations to generate the major observed product,

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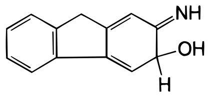
Table 2. Relative Energies of Possible Hydration Products, and Observed Product Ratios

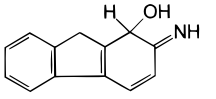
ion	ΔE_i (kcal/mol)[a]	product ratios
1a	1.0 (**3a** $\rightleftarrows$ **2a**)	>50/1 (**3a**/**2a**)[b]
1b	0.7 (**3b** $\rightleftarrows$ **2b**)	34/1 (**3b**/**2b**)[c]
1c	1.0 (**3c** $\rightleftarrows$ **2c**)	>25/1 (**3c**/**2c**)[d]
1d	−37.4 (**3d** $\rightleftarrows$ **2d**)	0.6/1 (**3d**/**2d**)[d]
	24.6 (**2d** $\rightleftarrows$ **2d′**)	>25/1 (**2d**/**2d′**)[d]
1m	−1.7 (**3m** $\rightleftarrows$ **2m**)	>50/1 (**3m**/**2m**)[e]
1s	5.2 (**6s** $\rightleftarrows$ **3s**)	>20/1 (**6s**/**3s**)[f]
	2.7 (**6s** $\rightleftarrows$ **2s**)	>20/1 (**6s**/**2s**)[f]
1v	−7.2 (**3v** $\rightleftarrows$ **2v**)	>10/1 (**3v**/**2v**)[g]
	−6.6 (**3v** $\rightleftarrows$ **2v′**)	>10/1 (**3v**/**2v′**)[g]

[a] Isomerization energies for the indicated reactions from the RHF 6-31G*//3-21G calculations. [b] Reference 4c. [c] Reference 10. [d] Reference 4b. [e] Reference 3b. [f] Reference 13. [g] Novak, M. Unpublished data; see also ref 10 for similar results of the *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion, **1u**.

from the isodesmic reactions of Scheme 1, is calculated from the energies of the lowest energy conformations of both **1** and the products, **2d**, **3a**−**c**, **3e**−**r**, **3u**, **3v**, **6s**, or **6t**, and reported in Table 1. The ΔE values calculated for three of the 10 ions previously reported on (**1l**, **1n**, **1u**) are 1−2 kcal/mol less positive than reported earlier.[4a] This was caused by the location of somewhat lower energy conformations of the hydration products **3l**, **3n**, and **3u**. These small changes do not materially affect the conclusions of the previous paper. No corrections for zero point energies, vibrational or rotational enthalpies, or entropic terms are included. These were estimated from the thermodynamic features of GAUSSIAN[25] for several of the ions and their products and were found to largely cancel in calculating ΔE. The ΔE values range from −4.2 kcal/mol for **1b** to 31.5 kcal/mol for **1v**. For the same aryl substituent, ΔE consistently increases for the Y substituents in the order Ac < H < CH_3. This is the order one would intuitively expect from the predicted relative stability of the nitrenium ions due to electron-donating effects of those substituents. Ford and Herman have suggested that the destabilizing effect of the acetyl group in the nitrenium ion is caused by the loss of resonance energy that is present in the neutral precursor or product, not to an inductive effect.[22a] The effects amount to an average $\Delta(\Delta E)$ of 4.5 ± 1.1 kcal/mol for the replacement of Y = Ac by Y = H, and 7.2 ± 1.3 kcal/mol for the replacement of Y = H by Y = CH_3. The data in Table 1 suggest that these Y substituent effects decrease slightly as ΔE becomes more positive. ΔE is also more positive for ions with π-donating substituents placed in the para-position of the aryl ring proximal to the N. This can be seen clearly in a comparison of ΔE for **1g**, **1h**, and **1i** to that for **1l**, **1m**, and **1n**, respectively. The 2-fluorenyl ions **1u** and **1v**, in which the distal aromatic ring is kept coplanar with the proximal ring by the methylene bridge at C-9, show large positive ΔE of 28.0 and 31.5 kcal/mol, respectively. These values are ca. 12 kcal/mol more positive than those for the corresponding biphenylyl ions, **1l** and **1m**. This difference is likely due to a combination of the stabilizing effect on the ions of enforced coplanarity in the fluorenyl ions, the stabilizing substituent effect of the methylene bridge in the ions, and the destabilization of **3u** and **3v** caused by ring strain in the five-membered ring introduced by the hydridization changes at C-4a. The ring strain in **3v** destabilizes that compound by 5.5 kcal/mol relative to its more stable ortho-isomer, **2v,** when compared to **3m** and **2m** in which the five-membered ring is absent (see Table 2).



2v



2v'

Also included in Table 1 are literature values for log *S*, the logarithm of the observed azide adduct/hydration product concentration ratio extrapolated to 1 M N_3^- for **1a**−**v**. For log $S \geq 2.0$, log *S* is functionally equivalent to $\log(k_{az}/k_s)$ of eq 1, but for log $S < 2.0$ trapping by N_3^- is complicated by terms arising from ion pairs and preassociation.[10] It is possible to derive estimates of k_{az}/k_s from trapping data at log $S < 2.0$, but these estimates depend on assumptions about the trapping mechanism, and on the magnitudes of individual rate constants that cannot be directly determined.[4c,10] In any case, the deviations between log *S* and $\log(k_{az}/k_s)$ are not large until log *S* approaches 0. For ions with log $S \geq 2.0$, measurements were made from direct observations of k_{az} and k_s on the ions generated by laser flash photolysis methods,[5,6] or by classical competition experiments.[3,4] Averages are reported where both types of data are available under the same reaction conditions. For ions with log $S < 2.0$, all values were obtained from competition experiments that rely on measurement of the yields of azide- and solvent-derived products as a function of $[N_3^-]$.[3,4] In general, directly measured k_{az} and k_s are not available for these more reactive ions.

Figure 3 is a plot of log *S* vs ΔE for all 22 ions included in this study. Except when log $S \approx 0$, there is a good linear correlation of log *S* with ΔE. The point for the 4′-methoxy-4-biphenylyl ion, **1r**, also deviates considerably from the linear correlation exhibited by most other ions. The correlation line ($r = 0.94$) was calculated for 18 of the 21 data points (**1a**, **1b**, **1d**, and **1r** excluded). For those 18 points the observed log *S* is always within 1.0 unit of the value calculated from the correlation line, and the mean absolute deviation of log *S* for the 18 data points is 0.45. The correlation is remarkably good considering that the points were collected under a variety of cosolvent conditions (0−20% CH_3CN), ionic strengths (0−1.0), and temperatures (most data were collected at 20 °C but some measurements were made at 25, 40, or 50 °C). No attempts were made to correct the log *S* data for these variations in experimental conditions. The plot is similar to that previously reported for only 10 ions,[4a] but the correlation has been extended over a much wider range of nitrenium ion structures.

The positive deviations from the correlation line for the highly reactive and unselective ions **1a**, **1b**, and **1d** are understandable. Since k_{az} is diffusion-limited at ca. 5 ×

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(25) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzales, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92, Revision B*; Gaussian, Inc.: Pittsburgh, PA, 1992. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stafavor, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzales, C.; Pople, J. A. *Gaussian 94, Revision E2*; Gaussian, Inc.: Pittsburgh, PA, 1995.

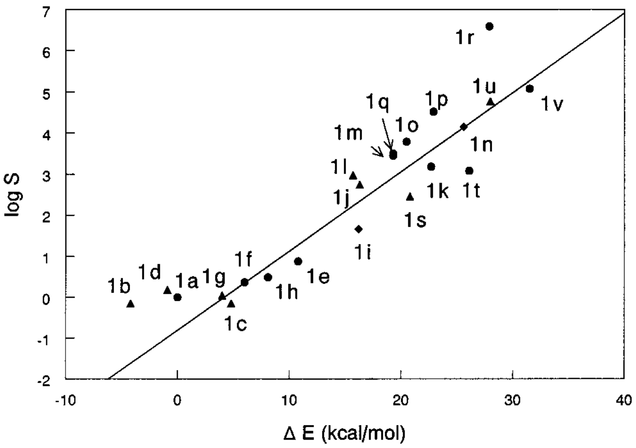


Figure 3. Correlation of log S with ΔE of Scheme 1. The least-squares correlation line, log $S = (-0.81 \pm 0.33) + (0.19 \pm 0.02)$ ΔE, was calculated from all points except those for **1a**, **1b**, **1d**, and **1r**. Ions are labeled according to Y substituents: Y = H (●), Y = Ac (▲), Y = Me (♦).

10^9 M^{-1} s^{-1} (for $\mu = 0.5$ and $T = 20$ °C) for all the ions for which the direct measurement has been made,[5,6] the correlation line can be used to predict an approximate value of k_s for each of these ions based on ΔE. The extrapolated values are 3.2×10^{10} s^{-1} for **1a**, 2.1×10^{11} s^{-1} for **1b**, and 4.8×10^{10} s^{-1} for **1d**. All of these ions are predicted to be too short-lived for efficient trapping by nonsolvent nucleophiles. Instead, most of the N_3^- trapping observed in these cases is likely due to a preassociation process.[10] We have previously shown that the N_3^- trapping of **1b** can be quantitatively accounted for by a preassociation mechanism,[10] and Fishbein and McClelland have shown that a large proportion of the trapping of **1a** by nonsolvent nucleophiles can be accounted for by a preassociation process.[4c] They estimated a value for k_s of 8×10^9 s^{-1} for **1a** from their trapping data if preassociation trapping is included in the reaction scheme.[4c] This value is within a factor of 4 of our extrapolated value based on the correlation of Figure 3.

Preassociation trapping is very inefficient and will contribute significantly to the overall trapping process only in cases in which the lifetime of the ion is so short that trapping of the free ion also becomes very inefficient. The transition for N_3^- trapping of nitrenium ions from predominately trapping of the free ion to predominately a preassociation process appears to occur at $k_s \approx 10^{10}$ s^{-1}. A similar transition has been observed for N_3^- trapping of carbenium ions at $k_s \approx 10^{10}$ s^{-1}.[8] Since the efficiency of the preassociation process is, to a first approximation, independent of the structure of the ion,[10] the effect of the preassociation trapping will be to produce a small and relatively constant value of log S for highly reactive ions. This effect can be clearly seen in Figure 3.

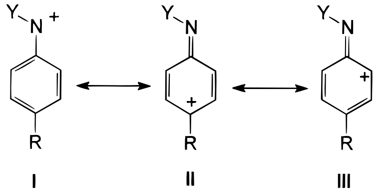
The reasons for the deviation of the point for **1r** are less clear. The measured value of k_{az} for this ion is only slightly smaller than that for **1m** under the same conditions (6.12×10^9 M^{-1} s^{-1} for **1r** and 9.6×10^9 M^{-1} s^{-1} for **1m** at $\mu = 0.0$),[6b] so the observed k_s for this ion is about 10^2 smaller than that predicted by the correlation line. The major hydrolysis products of **1r** have not been experimentally determined. We assumed, based on analogy to **1m**, that the initial hydration product would be **3r**. If that is not correct, our prediction of log S would be invalid.

Interestingly, this ion also showed the greatest deviation from linearity in a plot of log k_s vs σ^+ for a series of 4-biphenylylnitrenium ions with substitution in the distal ring.[6b] The observed value of log k_s for **1r** is about 1.5 units below the correlation line calculated from the points for 3′-substituted ions.[6b] This was interpreted to mean that the σ^+ scale underestimated the π-donor effect of the 4′-MeO substituent (and to a lesser extent other 4′-substituents) in stabilizing the fully formed cation. This seems reasonable because the σ^+ scale is based on transition state energies for the ionization of cumyl chlorides, and the resonance interactions in a transition state are not likely to be as fully developed as those in a fully formed cation. Unfortunately, the same argument cannot apply in our case because ΔE is based on the energies of the fully formed cations and hydration products, not on transition state energies.

Close inspection of Figure 3 suggests that each major structural variant of the nitrenium ions may form a slightly different correlation line. For example, log S for the biphenylyl ions for which Y = H all fall somewhat above the calculated correlation line for the entire set. If k_{az} is diffusion-limited for the biphenylyl ions as suggested by the available data,[5b,6b] k_s is somewhat smaller for these ions than predicted by the correlation line. This could be due to steric hindrance to attack of H_2O on the para-position caused by the distal ring that according to our calculations does not lie in the plane of the proximal ring in the lowest energy structures of the cations, and is also fairly free to rotate about the C−C bond connecting the two rings. The point for **1r** lies only 0.62 units above the correlation line calculated for **1m**, **1o**, **1p**, and **1q**. If this structural variant effect does exist it is small enough that it does not mask the overall correlation for most ions.

It is clear that the overriding factor in determining the kinetic lability of these ions in aqueous solution is their thermodynamic stability toward hydration. The slope of the correlation line (0.19 ± 0.02) shows that about 25% of $\Delta(\Delta E)$ is observed in the transition states for cation hydration at 20 °C. This is a substantial amount of the available thermodynamic stabilization of the cations. The difficulty in rationalizing the kinetic lability of *N*-arylnitrenium ions arises because the substituent effects for the stabilization of nitrenium ions are very different from those of the corresponding carbenium ions.

The effect of substituents on ΔE is quite interesting. Although there are limited data available, it appears that para-substituents exert a significantly stronger effect on ΔE than do ortho-substituents. This can be seen in ΔE for hydration of **1e**, **1f**, and **1h** of 10.8, 6.0, and 8.1 kcal/mol, respectively to yield **3e**, **3f**, and **3h**. The effect of the *p*-Me substituent of **1h** is midway between that of the *o*-Me substituent of **1f** and the 2,6-diMe substituents of **1e**. Comparison of substituent types in the para-position shows that π-donor substituents, particularly aryl and vinyl groups, have an unusually large stabilizing effect on the nitrenium ions. This can be seen in a comparison of ΔE for **1h** (*p*-Me, 8.1 kcal/mol), **1k** (*p*-MeO, 22.7 kcal/mol) and **1m** (*p*-Ph, 19.3 kcal/mol). The experimental log S values show a similar trend. The unusual stabilization of nitrenium ions by π-donor substituents in the para-position has been noted previously and has been used as evidence that the dominant canonical form of the nitrenium ion is **II** (eq 3) in which the positive charge is localized at the para-carbon.[3b,4a,5,6b]



(3)

The magnitude of the π-donor stabilization effect seen in nitrenium ions is not reproduced in σ_p^+: σ_p^+ for Me, MeO, Ph are −0.311, −0.778, −0.179, respectively.[26] This is the major reason that plots of log S or log k_s vs σ^+ are so highly scattered for nitrenium ions. Recently Ren and McClelland noted that substituent effects for log k_s in 4-biphenylylnitrenium ions substituted in the distal ring were very similar to those observed for benzylic-type cations.[6b] A plot of log k_s vs σ^+ did show a significant negative deviation from the correlation line for **1r**, but the data were not highly scattered, and an excellent correlation was observed using the two parameter Yukawa−Tsuno equation.[6b] The parameters obtained from this fit were very similar to those obtained for a fit of log k_s for triarylmethyl cations to the Yukawa−Tsuno equation.[6b] A comparison of ΔE values for the 4-biphenylylnitrenium ions **1m** and **1o**−**r** shows that ΔE increases in the order 3′-MeO ~ H < 3′-Me < 4′-Me < 4′-MeO. A plot of ΔE vs σ^+ (not shown) for the distal substituent exhibits a good correlation ($r = 0.998$) with a large slope of −10.6, so substituents in the distal ring affect nitrenium ion stability in much the same way that these same substituents affect the stability of arylcarbenium ions when they are placed in the proximal ring. The results of Ren and McClelland and our substituent effect results for ΔE suggest the importance of the canonical structure **II**. A recently published IR spectrum of the diphenylnitrenium ion is also consistent with a predominant iminocyclohexadienyl cation-like structure such as **II**.[27]

The RHF/3-21G structures of several of the nitrenium ions (**1l**, **1m**, **1s**, **1t**, **1v**) are summarized in Figure 4. A number of characteristics are evident. The C−N bond is quite short (ca. 1.27 Å), and the C−C bonds in the ring proximal to N exhibit strong alternation (up to 0.14 Å difference between adjacent bonds). Both of these features are consistent with the predominant canonical structure **II**. This same trend in bond lengths has been noted previously in semiempirical MNDO calculations[18] and in high level density functional theory calculations on **1a** (BVWN5/cc-pVDZ).[20a] Bond length alternation in the distal rings of **1l**, **1m**, **1s**, **1t**, and **1v** is much weaker (<0.04 Å difference between adjacent bonds). The C−N bond lengths reported here are about 0.03 Å shorter than those reported in the previous semiempirical and density functional theory calculations.[18,20a] The C−C bond lengths also tend to be about 0.02 to 0.03 Å shorter than those reported in the previous calculations,[18,20a] but trends in bond length changes are consistent with the previous results. Replacement of Y = H by Y = Ac has remarkably little effect on the structure of the cation. For example, the C−N bond length changes by less than ±0.003 Å on replacement of Y = H by Y = Ac. As noted above, the carbonyl oxygen is twisted significantly out of the plane of the aromatic ring in the N-acetylnitrenium ions. This feature was previously noted in MNDO and AM1 calculations, although larger dihedral angles of ca. 70° (MNDO) and 40° (AM1) were observed in those calculations.[18,22b]

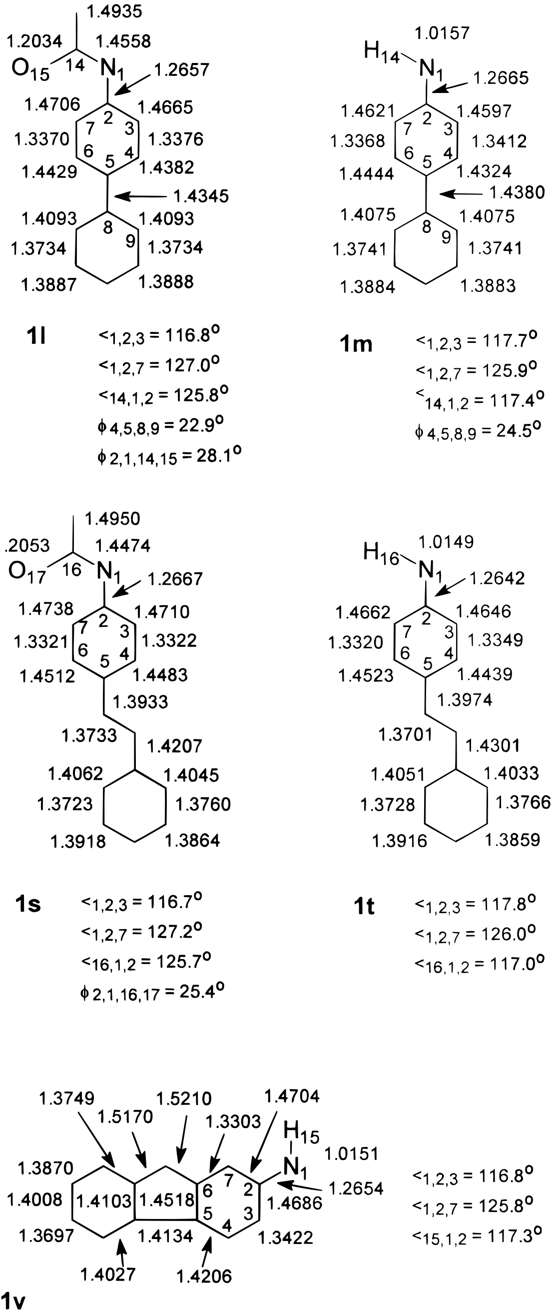


Figure 4. Calculated (RHF/3-21G) geometries for **1l**, **1m**, **1s**, **1t**, and **1v**. Bond lengths are expressed in angstroms. Selected bond angles and dihedral angles are also listed.

The attack of small anionic nucleophiles such as N_3^- and Cl^- on the nitrenium ions **1a**−**v** should be a charge controlled process.[28] This would suggest, based on the apparent dominant canonical form, **II**, that in most cases these nucleophiles should preferentially attack the para-position of the proximal ring of the ion. Indeed, Natural

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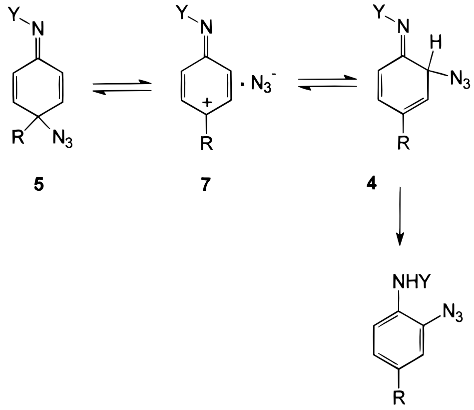
Bond Order (NBO)[29] calculations, based on the 6-31G* wave functions of the nitrenium ions, identify the para-carbon as either the most electron deficient site (Y = H) or second most electron deficient site (Y = Ac) in the ring (Figure 5). For the *N*-acetyl ions the ipso-carbon has a greater positive charge, but no products of attack by small nucleophiles at that site of a nitrenium ion have been reported. This is not surprising since attack at the ipso-carbon, though it may occur, is not likely to lead to a stable product since that would require preferential expulsion of NH_3 or $AcNH_2$.

Unfortunately, for most of these ions attack at the para-position by a nucleophile that is also a good leaving group (N_3^-, Cl^-, Br^-) cannot be detected because the product of such an attack will undergo ionization and conversion into other products. This is illustrated for the N_3^- addition product **5** in eq 4. Unless R is a good leaving group or H, this product will ionize to generate the ion pair, **7**, because it cannot tautomerize to a stable aromatic product or expel R^- as a leaving group. Because the reaction of all of these nitrenium ions with N_3^- is diffusion limited, or nearly so, **7** will either return nonproductively to **5** or generate another product such as the ortho-addition product **4** that can readily tautomerize to a stable product. For the ions **1a**−**v** the relative amounts of attack at the ortho- and para-positions by N_3^-, Cl^-, or Br^- can only be readily evaluated for the two unsubstituted ions **1a** and **1b**, and **1c** and **1f**. For **1b** the observed ortho/para product ratio for attack of N_3^- is 0.59 ± 0.01,[10] while for **1a** the ortho/para product ratio for attack of Cl^- is 0.44 ± 0.02, and 0.61 ± 0.02 for attack of Br^-.[4c] As predicted, attack at the para-carbon is preferred. The statistically corrected preference for para-attack ranges from 3.3/1 for attack of Br^- on **1a**, to 3.4/1 for attack of N_3^- on **1b**, and 4.5/1 for attack of Cl^- on **1a**. Steric effects are probably responsible for some of this preference, but those effects should not be large for N_3^-. For **1c** the preference for attack of N_3^- at the para-position relative to the ortho-position is 3.9/1.[4b] This is very similar to the preferences exhibited by **1a** and **1b**. For **1f** the preference for attack of Cl^- at the para-position is 11.2/1.[4c] This unusually high preference for attack at the para-position was attributed, in part, to the steric congestion introduced by three substituents on adjacent carbons if attack occurred at the ortho-position.[4c] For the limited number of ions for which it is possible to evaluate the prediction of preferential para-attack by N_3^-, Cl^- or Br^-, the prediction is correct.



(4)

Since the product of attack of H_2O on the para-carbon, **3**, does not undergo ionization under normal reaction conditions,[3,4,10] it is possible to determine the preference for attack on the para-position for this nucleophile in all of the ions **1a**−**v**. Data in the literature, concerning the attack of H_2O on ring substituted 1-phenylethyl carbocations of similar lifetimes to the nitrenium ions discussed in this paper, indicate that the observed hydration products of **1a**−**v** are the kinetically controlled products.[30] Attack of H_2O on these carbocations proceeds without observable catalysis although attack of less basic alcohols such as CF_3CH_2OH proceeds with general base catalysis.[30] This observation is consistent with rate-limiting attack of H_2O, followed by rapid deprotonation of the resulting oxonium ion to form the alcohol product (specific acid catalysis in the reverse direction to form the cation from the alcohol product) (eq 5). General base catalysis of attack of H_2O on carbocations is only observed for much more kinetically stable species than those considered here.[31]

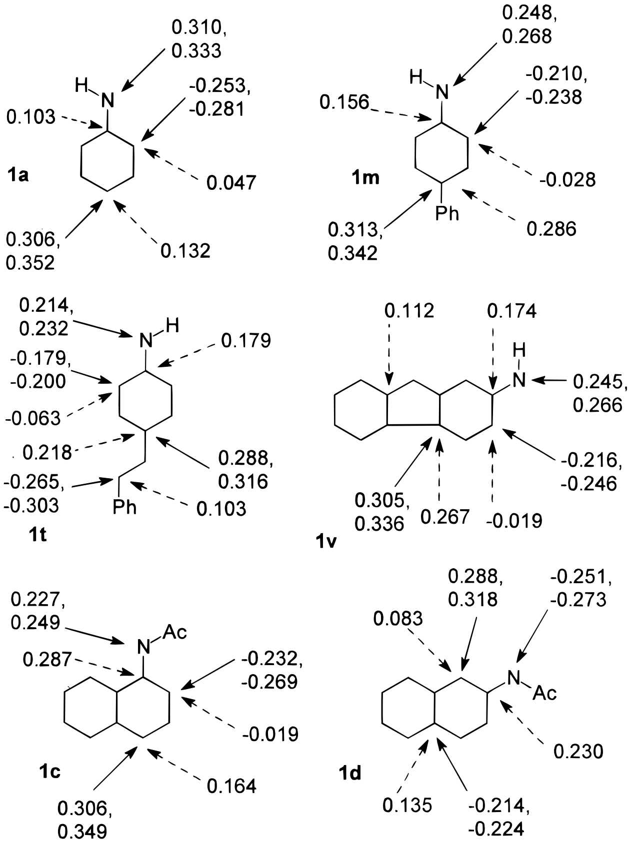


Figure 5. Selected LUMO coefficients ($2p_z$, $3p_z$ for the planar ion at the RHF/6-31G*//3-21G level) for several nitrenium ions (→). Selected charge densities calculated by the NBO method utilizing the 6-31G* wave functions are also included (- - -→).

$$R^+ \xrightarrow{k_s} ROH_2^+ \underset{}{\overset{K_a}{\rightleftharpoons}} ROH + H^+ \qquad (5)$$

Since Δ*E* measures the relative thermodynamic driving force for both steps of eq 5, the relative driving force available to k_s will be modulated by the structural dependence of K_a if attack of H_2O is the rate-limiting step of the hydration reaction. Linear free energy relation-

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(30) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1396−1401. Ta-Shma, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040−8050.

(31) Gandler, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 8218−8223.

ships suggests that pK_a could vary by as much as 3.0 units (4.0 kcal/mol at 20 °C) within the series of conjugate acids of the hydration products of **1a**−**v**.[31,32] This variation in pK_a would be insufficient to disrupt the overall correlation of log S with ΔE, but an attempt will be made to consider this effect in a future publication.

With only three exceptions, the major, if not exclusive, product of hydration of the cations **1a**−**v** are the para-addition products **3**. The data in Table 2 indicate that this preference is not governed by the thermodynamic stability of the possible hydration products. In most cases the initial ortho- and para-addition products are of similar stability according to the RHF 6-31G*//3-21G calculations, but the **3**/**2** product ratio exceeds 25/1. Even in the case of the 2-fluorenyl ion, **1v**, in which the para-addition product is significantly destabilized relative to the ortho-product by ring strain, the para-product, **3v**, predominates over the possible ortho-products **2v** and **2v′**. In the cases in Table 2 in which the para-product does not predominate, **1d** and **1s**, the products that do predominate, **2d** and **6s**, respectively, are the most stable of the possible hydration products. Product stability may influence the identity of the kinetically controlled hydration products of **1d** where the major product, **2d**, is calculated to be more stable than **3d** by 37.4 kcal/mol and more stable than **2d′** by 24.6 kcal/mol. The preference for the para-product can be seen even in this case because **3d** is a minor but significant hydration product even though it is strongly destabilized relative to **2d**.[4b]

The reaction of H_2O with **1a**−**v** is less obviously a charge-controlled process than is the reaction of N_3^- with the same ions. In fact, the magnitude of the coefficients of the LUMO of the cations are somewhat better predictors of the site of attack of H_2O than are the charge densities on the individual atoms (Figure 5). The LUMO coefficients were determined for the planar ions because symmetry requires that the LUMO is a pure π-type orbital only for the planar ions. For Y = H the planar ions are the calculated lowest energy structures except for the biphenylyl ions. For **1m** at the RHF 6-31G*//3-21G level the planar ion is only 0.53 kcal/mol above the ground state in which the two aryl rings are twisted by 24.5° with respect to each other. For the *N*-acetyl ions the planar structures are calculated to be above the ground-state structures by 1.96 kcal/mol for **1b**, 1.49 kcal/mol for **1c**, 1.36 kcal/mol for **1d**, and 1.02 kcal/mol for **1s**. The LUMO coefficients correctly predict the preferred site of attack of H_2O on **1d** while the calculated charge distribution does not. At this level of theory the LUMO coefficients for the para-carbons and β-carbons of **1s** and **1t** are nearly equivalent. In these cases the greater thermodynamic stability of the product of attack on the β-carbon (**6s** and **6t**, see Table 2) may stabilize the transition state for the formation of that product over the product of para-attack. Again, the LUMO coefficients do a better job of predicting the site of attack of H_2O on **1s** and **1t** than do the charge distributions. For all the other ions the LUMO coefficients and charge distributions identify the para-position as the most reactive site whether the reaction is orbital controlled or charge controlled.

Ford and Scribner previously came to similar conclusions concerning the preference for para-attack for either charge-controlled or orbital-controlled nucleophilic attack on most nitrenium ions from semiempirical calculations, but they were not able to evaluate how well their predictions correlated with observed product distributions for attack of simple nucleophiles because of a lack of such fundamental data on those reactions at that time.[18]

The reactions of carbon, nitrogen, and sulfur nucleophiles with nitrenium ions are considerably more complicated than those of N_3^-, Cl^-, Br^-, or H_2O. All of these soft nucleophiles show at least some tendency to react with the nitrogen of the nitrenium ion,[15−17] and, except for deoxyguanosine, very little selectivity for attack at any one position on the nitrenium ion.[15] Although it is possible to rationalize the products of reaction of the simple, harder nucleophiles with nitrenium ions by the use of charge distribution or frontier orbital arguments, these simple approaches are of little use in predicting the sites of attack of softer nucleophiles.

Experimental Section

Initial structures used for subsequent optimizations were obtained by utilizing the AM1 Hamiltonian available in MOPAC 4.0.[33] Ab initio calculations were carried out with the GAUSSIAN 92 or 94 programs[25] on a Cray Y-MP8/864 computer at the Ohio Supercomputer Center or on a SGI Power Indigo-2 workstation. All geometry optimizations were performed by restricted Hartree−Fock calculations employing the 3-21G basis set.[19] Frequency calculations were performed on optimized structures to confirm that the optimization had produced a true energy minimum rather than saddle point. Single point calculations at the 6-31G* level[23] were performed on all optimized structures. In most cases several local minima were optimized at the RHF/3-21G level, and the energies of these structures were subsequently evaluated at the RHF/6-31G* level to determine the lowest energy conformation for a given structure. Natural Bond Order (NBO) calculations[29] were performed by utilizing the NBO routine within GAUSSIAN 94.

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Supporting Information Available: Table of Cartesian coordinates for the most stable structures of all species listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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