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Ab Initio Study of the Reactions between a Series of Substituted Singlet Nitrenium Ions and Water

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Highly correlated ab initio molecular orbital calculations have been used to study the energetics and mechanisms governing the reactions of a series of substituted singlet nitrenium ions ($^1[R-N-H]^+$, R = H, Cl, F, CN, and Me) with water in gas phase and in solution. It was found that, in gas phase and in solution, the nitrenium ions react in a barrierless fashion to produce an intermediate $[HNR-OH_2]^+$, which in turn undergoes a 1,2-hydrogen shift to produce the corresponding protonated hydroxylamine $[RNH_2OH]^+$. Results obtained at the QCISD(T)/6-311++G**//QCISD/6-311++G** level indicate that in the gas phase, the intermediates are located between 27.7 and 339.6 kJ/mol below the reactants depending upon the substituent on the nitrenium ion. The transition states are located between 93.1 and 141.9 kJ/mol above the intermediates depending upon the substituent in question. Electrostatic interactions with the solvent increases the intrinsic barrier of the process, as it lowers the relative energy of the intermediates (and reactants) with respect to the transition state. It is also found that the reaction of water with the methyl nitrenium ion inhibits the decomposition of this species in gas phase. The effects of the substituent, the solvent, and the levels of theory employed on the reaction paths are discussed in detail. In addition, the reaction of singlet nitrenium ion with two water molecules is also studied and the results are discussed in the context of the importance of the explicit treatment of the solvent in the determination of the energetics and mechanisms of these processes.

Introduction

Nitrenium ions are highly reactive, electron-deficient intermediates with the general structure $[R-N-R']^+$. These azacations are isoelectronic analogues to the better-studied carbenes (R−C−R′), undergoing the same type of reactions such as addition, insertion, and rearrangements.[1]

Similar to their isoelectronic carbenes, nitrenium ions can exist in singlet and triplet states. The relative stability of these states is dependent on the substituents bonded to the central, electron-deficient atom. In the singlet state, the nonbonding electrons occupy an sp^2 orbital, leaving an empty p orbital on the nitrogen atom. The electronic structure of singlet nitrenium ions make them very reactive toward nucleophiles. In the triplet state, the nonbonding electrons have parallel spins and occupy an sp^2 orbital as well as an orbital with large p character, usually behaving as diradicals.

Nitrenium ions are generally produced in the singlet state, undergoing an intersystem crossing to the low lying triplet state.[2] Recent experimental studies[3] have indicated the possibility of stabilization of the singlet with respect to the triplet as a result of electrostatic interactions with the solvent. These observations are in agreement with results of a recent ab initio study by Gonzalez et al.[4] Given the highly electrophilic character of nitrenium ions, a facile reaction is expected with nucleophilic solvents such as water, yielding a protonated hydroxylamine. Recently, we have studied the reactions of a series of substituted singlet carbenes (isoelectronic to nitrenium ions) with water.[5] These substituted carbenes initially react with water to form an intermediate, which subsequently undergoes a 1,2 proton shift to yield the corresponding alcohol. This theoretical finding is strongly supported by numerous experimental studies of reactions between carbenes and nucleophiles.[6] The reaction profiles for these processes are highly affected by the substituents bonded to the carbon atom and by the presence of a polar solvent. Thus, more recently, Pliego and De Almeida[7] have reported that singlet dichlorocarbene, $:CCl_2$, does not form an ylide in the presence of water, and that instead, the reaction proceeds via a direct insertion into an O−H bond in the water moiety. However, they observe the formation of a stable ylide in the case of the reaction of $:CCl_2$ with HCHO.[8]

Unlike the isoelectronic carbenes, examples in the literature of nitrenium ions characterized by direct spectroscopic methods are scarce. Aryl-substituted nitrenium ions have been found to be relatively stable to allow their detection by UV−Vis spectrophotometry[9] and NMR spectroscopy.[10] In addition, the aminylium ion ($^+NH_2$) has been characterized by IR,[11] EPR[12] and laser spectroscopies.[13] Likewise, experimental examples of the reaction of nitrenium ions with nucleophiles directly involving the electron-deficient nitrogen atom are rare. Most reports in the literature indicate that, in the presence of nucleophiles, singlet, alkyl-substituted, aromatic nitrenium ions undergo a facile addition reaction, where the nucleophile attacks the aromatic ring.[14]

Most of the theoretical work on nitrenium ions has focused on the characterization of the relative stability of the singlet

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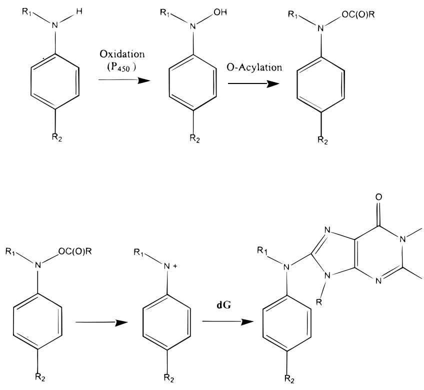
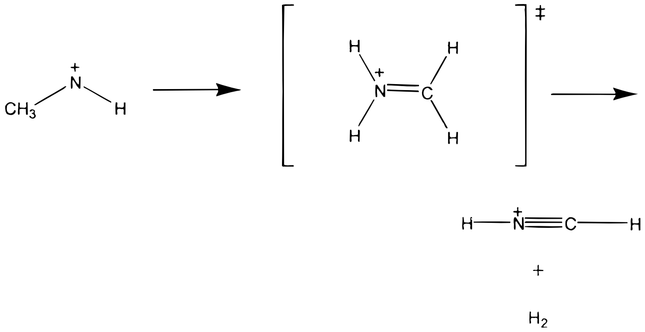
SCHEME 1



SCHEME 2



with respect to the triplet, and very few studies of the reactivity of these species in solution have been reported. Recently, we have used highly correlated ab initio methods combined with continuum solvation models to study solvent and substituent effects on the singlet−triplet gap of a series of small nitrenium ions and their isoelectronic carbenes.[4] Cramer et al.[15] have performed a DFT study combined with the semiempirical solvation model SM5.4/A[16] on the isoelectronic series methylphenylborenide, methylphenylcarbene, and methylphenylnitrenium, where solvent effects (in *n*-heptane and acetonitrile) on singlet−triplet gaps as well as 1,2-hydrogen migrations are reported.

Nitrenium ions are believed to play an important role in carcinogenic processes. They are presumed to be generated in the metabolic pathway of degradation of aromatic amines.[17] The carcinogenic ability of these highly reactive intermediates is attributed to their high electrophilicity which allows these species to readily bind to and modify DNA molecules.[18] Arylamines are known to readily react with deoxy guanosine, dG, via the metabolic pathway given by Scheme 1.[19]

The following mechanism has been postulated for this transformation: (1) the aromatic amine is enzymatically oxidized by the cytochrome P-450-dependent monooxygenase enzyme to form an intermediate hydroxylamine; (2) the hydroxylamine is then acetylated and deacetylated, by action of N,O-acetyltransferase and deacetylase respectively; (3) this process yields an arylnitrenium ion (the ultimate carcinogen), which attacks the nucleotide bases in DNA (dG in Scheme 1) causing severe mutations that ultimately lead to cancer tumors.[20] It is interesting to notice that, in this proposed scheme, the adduct formed by the nitrenium ion and DNA calls for formation of a bond between the electronically deficient nitrogen atom and a carbon atom from a base in the nucleotide.

Given the potential role of some nitrenium ions in carcinogenic processes, it is essential to have a clear understanding of solvent and polarity effects in the reaction of these species with nucleophiles, especially water, as water would be a competing nucleophile in biomolecular reactions. In this work, highly correlated ab initio molecular orbital calculations are used to evaluate the substituent and solvent effects on the energetics governing the reaction of the singlet nitrenium ions $[R-N-H]^+$ (R = H, Cl, F, CN, and CH_3) with water.

The nitrenium ions that have been proposed as ultimate carcinogens are derived from larger systems such as aromatic amines, and several mechanisms can account for the reactivity of these amines toward DNA. In this study, we will concentrate on the reaction of a series of smaller nitrenium ions with water, using the electronically deficient nitrogen atom as a reaction center. This model reaction can allow us to gain a better understanding of the chemistry of these azacations. It should be pointed out from the outset that we are mainly focusing on the electrostatic interactions between the solvent (bulk water) and the reacting system ($^1[R-N-H]^+ + H_2O$) and that the explicit interaction with the solvent molecules is totally neglected in the case where R = Cl, F, CN, and CH_3. The explicit treatment of an additional molecule of water in the first solvation shell is considered only in the case of the singlet nitrenium ion ($^1[NH_2]^+$), and the results are used to assess the importance of explicit waters in the mechanisms of the model reactions under study. This work may serve as a good reference for further investigations concerned with the structure and interactions with solvents of the more realistic and far more computationally demanding aromatic nitrenium ions.

Methodology

Geometries of all the reactants, intermediates, transition states, and products in the gas phase were fully optimized at the MP2-(Full)[21] and QCISD[22] levels of theory in conjunction with the 6-311++G** basis set. Vibrational frequencies at the MP2 level were used to characterize the stationary points as minima or saddle points and to compute their zero-point energies, ZPE. Relative energies were calculated at the QCISD(T)/6-311++G**//QCISD/6-311++G** and QCISD/6-311++G**//QCISD/6-311++G** levels in the gas phase and in solution, respectively. To simulate water as the solvent interacting with the substrate, a dielectric constant of 80.0 was used under the isodensity polarizable continuum model (IPCM) approach.[23] All calculations in this project were carried out using the Gaussian 94 suite of programs[24] on DEC Alpha AS/600 333 MHz computers at the Multidisciplinary Research Computer Facility at Florida Atlantic University, and a Cray C90 with six processors available at the National Institute of Standards and Technology, NIST.[25]

Results

With the exception of methyl nitrenium ion, the results obtained at the MP2 and QCISD levels indicate similar reaction profiles for all cases under study, both in gas phase and in solution. The singlet nitrenium ion $^1[H-N-R]^+$ readily reacts with the water molecule in a barrierless fashion, and forms an adduct, $^1[HNR - OH_2]^+$. This process is followed by a 1,2-hydrogen shift that leads to the formation of the protonated hydroxylamine $[NH_2ROH]^+$ (see Figure 1). This mechanism resembles the one previously found for the reaction between singlet methylene and water.[5a]

Methyl nitrenium ion, $^1[CH_3NH]^+$, was found to undergo a facile decomposition in the gas phase (see below), in agreement with results previously reported by others.[26] No transition state was found, and the reaction proceeds in a barrierless fashion following the decomposition mechanism shown in Scheme 2.

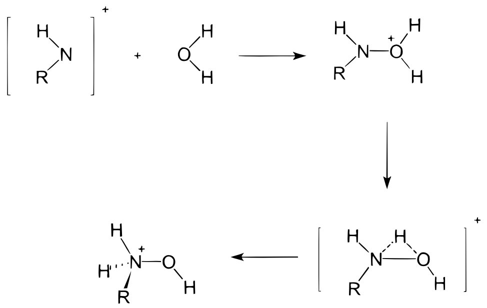


Figure 1. The steps of the mechanism in the reactions of a series of nitrenium ions and water.

TABLE 1: Optimized Geometries for a Series of Singlet Nitrenium Ions $[H-N-R]^{+\,a}$

	$dN-R^b$		$dN-H^b$		$\langle R-N-H^b$	
R	MP2	QCISD	MP2	QCISD	MP2	QCISD
H	1.048	1.052	1.048	1.052	107.1	107.0
Cl	1.542	1.573	1.041	1.043	108.5	108.3
F	1.223	1.240	1.055	1.060	105.1	104.9
CN	1.263	1.245	1.041	1.036	117.1	119.0
Me^c	1.380	1.380	1.030	1.030	109.5	108.7

[a] All calculations have been carried out using the 6-311++G** basis set. [b] All bond distances are given in angstroms and bond angles in degrees. [c] Taken from the point in the PES where the distance between the oxygen (water) and the nitrogen (methylnitrenium) is 2.0 Å.

Given this unusual behavior, a separate discussion of the reaction between singlet methyl nitrenium ion and water will be presented later in this paper.

Molecular Geometries. Intermediates. Tables 1−4 list the optimized geometry (gas-phase) parameters calculated at the MP2/6-311++G** and QCISD/6-311++G** levels of theory, for reactants, intermediates, transition states, and products for all the reactions under study. Overall, an excellent agreement between the MP2 results and the optimized parameters at the QCISD level is observed.

In the case of the singlet nitrenium ions (Table 1), the optimized geometries using MP2/6-311++G** and QCISD/6-311++G** are in very good agreement with highly correlated CASSCF calculations using a triplet-ζ plus polarization basis set, TZP, reported by Cramer et al.[27] In addition, the optimized geometries of the nitrenium ions obtained in this work are in good agreement with results obtained by Gobbi and Frenking at the MP2/6-31G(d) level.[28] These results are encouraging and support the validity of the use of MP2 and/or QCISD geometries on the rest of the potential energy surface for the reactions under study. Similar conclusions were reached in our recent study of the reaction of singlet methylene with water.[5a]

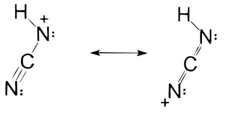
Table 2 shows the optimized geometries for the different intermediates, $^1[RNH-OH_2]^+$, obtained in this work. These species are characterized by N−O bond lengths 0.022−0.070 Å larger than single N−O bonds, such as in hydroxylamine (1.475−1.523 Å for nitrenium ions vs 1.453 Å for hydroxylamine). In general, the geometrical structures of the two moieties, H_2O and $^1[RNH]^+$, remain almost unchanged when forming an adduct, $[RNH-OH_2]^+$ (Tables 1 and 2). The largest variation in the geometries of these intermediates, were observed in the relative orientation of the substituent on the nitrogen atom (−R and −H) with respect to the hydrogens on the central oxygen in the H_2O fragment. This variation can be measured by the $<H^3ONR$ dihedral angle (see Table 2). This angle varies from 22.5° (an almost planar geometry for the reaction of the H_2N^+, $F-N^+-H$, and $Cl-N^+-H$) to 88.2° (a criss-cross geometry for the Me−NH and $NC-N^+-H$). This geometrical difference may be attributed to larger steric repulsions due to the bulkier substituents −Me and −CN. In these cases, the crisscross geometry is able to better accommodate the electron clouds of these bulky groups.

Transition States and Products. The intermediates $[RNH-OH_2]^+$ undergo a concerted 1,2-proton shift through a transition state, TS, whose geometry is shown in Table 3. Minimum reaction paths, computed by the Gonzalez−Schlegel intrinsic reaction coordinate method (IRC)[29] verified that these TS's are uniquely connected to the intermediates ($[RNH-OH_2]^+$) and products (the protonated hydroxylamines). The geometry of these transition states can be described as a three-centered reacting moiety, where the proton to be transferred (H^2) lies between the nitrogen and oxygen atoms. For the five reactions under study, the transition structures exhibit similar $N-H^2$ distances (1.24−1.26 Å), with larger variations on the corresponding $O-H^2$ bond lengths (1.17−1.21 Å). In contrast to the case of the intermediates, small changes in the relative orientation of the different substituents (−R, −H) with respect to the hydrogens on the H_2O fragment are observed (ca. 116°−122° for $<RNOH_2$).

At the TS, the N−O bond is slightly elongated when compared to the intermediate, and it does not change substantially with the substituent (1.54−1.61 Å). This distance is significantly longer than the corresponding N−O bond distances observed in the products (see below). No significant changes in the $N-H^1$ bond lengths are observed when compared to the corresponding values in the intermediates.

As explained before, the intermediates $^1[R-N-OH_2]^+$ undergo 1,2-proton shifts to form the corresponding substituted protonated hydroxylamines $^1[R-N(H)-OH]^+$. The results shown in Table 4 indicate that, on the average, the N−O distances are approximately 11.5% shorter than the N−O bond lengths at the transition state, in keeping with the fact that the hydrogen (H^2) has already being transferred to the nitrogen, and a normal σ bond has been formed.

The geometry of the cyanonitrenium cation deserves special attention. At the QCISD level, the N≡C and the $C-N^+$ bond distances were calculated to be 1.233 and 1.245 Å, respectively. By way of contrast, analogous distances for the protonated cyanohydroxylamine are 1.160 and 1.416 Å, respectively. These results indicate that, in the case of the electron deficient cyanonitrenium cation, there is a significant contribution of structure **I** (see below), an isoelectronic nitrenium cation analogue, where the nitrogen of the substituent group bears the positive charge and is electronically deficient.

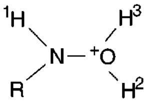


I

In the analogue **I**, the carbon atom shares double bonds with both nitrogen atoms, thus explaining the similarities in the bond distances noted above. This effect of the cyano substituted electronically deficient species has been observed experimentally for the diphenylcyanocarbocation in superacid solution at −78 °C.[30]

Energetics. Table 2 lists the relative energies for all the species involved in the reactions between the substituted nitrenium cations $^1[R-N-H]^+$ and water, in gas phase and solution. In general, MP2 was found to predict energies relative to reactants (gas phase) to be significantly lower than the values

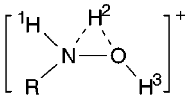
TABLE 2: Optimized Geometries for the Intermediates in the Reactions of Singlet Nitrenium Ions and Water[a]



R	*d*NO	*d*NH^1	*d*NR	*d*OH^2	*d*OH^3	<H^{3}OH^2	<H^{2}ON	<H^{3}ON	<H^{1}NR	<H^{1}NO	<RNO	δH^{3}ONR
						A. MP2						
H	1.461	1.020	1.021	0.979	0.977	111.7	108.3	117.3	109.9	102.3	106.0	24.5
Cl	1.505	1.026	1.709	0.980	0.985	110.1	106.3	114.3	107.7	98.9	109.0	25.0
F	1.490	1.031	1.357	0.982	0.986	110.7	107.2	113.6	104.0	99.6	104.2	29.7
CN	1.483	1.025	1.367	0.981	0.983	113.0	108.4	116.5	113.1	106.4	107.1	87.1
Me	1.500	1.022	1.461	0.977	0.979	111.3	107.8	116.9	111.0	103.3	106.6	86.3
						B. QCISD						
H	1.475	1.022	1.023	0.975	0.976	111.4	108.2	117.2	109.4	101.6	105.2	22.5
Cl	1.523	1.027	1.718	0.977	0.981	110.1	106.6	114.6	107.5	98.3	108.7	23.8
F	1.500	1.032	1.356	0.979	0.983	110.6	107.5	113.7	104.0	99.4	103.8	28.9
CN	1.487	1.024	1.375	0.978	0.980	112.8	108.7	116.7	112.8	106.1	107.0	87.1
Me	1.516	1.024	1.470	0.974	0.976	110.9	107.6	116.9	110.7	102.5	106.1	88.2

[a] All calculations have been carried out using the 6-311++G** basis set. Bond distances are given in angstroms and bond angles in degrees.

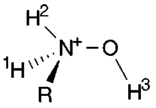
TABLE 3: Optimized Geometries for the Transition States in the Reactions of Singlet Nitrenium Ions and Water[a]



R	*d*NO	*d*NR	*d*NH^1	*d*NH^2	*d*OH^2	*d*OH^3	<H^{3}OH^2	<H^{2}ON	<H^{3}ON	<RNH^1	δRNOH^2	δH^{1}NOH^2	δH^{3}ONH^2
							A. MP2						
H	1.547	1.022	1.022	1.273	1.160	0.981	109.8	53.8	107.2	112.9	−119.6	119.9	102.2
Cl	1.606	1.676	1.027	1.255	1.184	0.985	110.0	50.8	105.1	112.3	−118.5	121.3	99.8
F	1.551	1.330	1.031	1.241	1.213	0.987	109.1	51.6	105.4	109.0	−114.4	129.2	102.4
CN	1.593	1.362	1.029	1.248	1.202	0.987	109.5	50.7	105.7	116.0	−116.7	117.5	102.6
Me	1.577	1.458	1.023	1.289	1.144	0.981	107.8	53.8	105.5	114.0	−122.7	115.8	100.9
							B. QCISD						
H	1.552	1.022	1.022	1.257	1.167	0.977	110.6	52.8	107.8	113.0	−119.2	120.2	102.7
Cl	1.593	1.690	1.026	1.242	1.187	0.980	108.5	50.5	109.3	112.4	−117.9	121.6	100.8
F	1.543	1.332	1.030	1.237	1.210	0.983	110.8	51.7	102.3	109.1	−113.7	129.7	104.0
CN	1.575	1.373	1.027	1.242	1.198	0.982	111.0	51.0	106.7	116.0	−115.7	118.1	103.8
Me	1.582	1.469	1.022	1.264	1.156	0.977	108.8	52.2	106.5	114.2	−122.2	116.3	101.3

[a] All calculations have been carried out using the 6-311++G** basis set. Bond distances are given in angstroms and bond angles in degrees.

TABLE 4: Optimized Geometries for the Protonated Substituted Hydroxylamines in the Reactions of Singlet Nitrenium Ions and Water[a]



R	*d*NO	*d*NR	*d*NH^1	*d*NH^2	*d*OH^3	<NOH^3	<H^{2}NO	δH^{2}NOH^3	<RNH^2	<H^{1}OH^2	<RNH^1
						A. MP2					
H	1.397	1.029	1.029	1.027	0.971	106.7	104.9	180.0	108.3	108.3	110.4
Cl	1.377	1.746	1.030	1.031	0.974	107.2	111.7	60.8	108.1	109.1	108.2
F	1.340	1.374	1.033	1.035	0.976	108.2	112.2	51.2	105.1	112.2	106.2
CN	1.409	1.407	1.036	1.035	0.975	106.4	103.6	174.9	110.0	107.9	110.4
Me	1.402	1.491	1.026	1.028	0.971	106.2	109.8	69.6	114.9	107.2	110.6
						B. QCISD					
H	1.400	1.029	1.029	1.028	0.970	106.7	105.0	180.0	108.4	108.4	110.3
Cl	1.381	1.753	1.029	1.030	0.972	107.2	111.6	59.9	108.3	109.0	108.3
F	1.350	1.367	1.033	1.034	0.975	107.9	113.9	51.9	105.7	119.9	106.7
CN	1.410	1.416	1.035	1.034	0.974	106.4	103.9	175.4	109.8	107.9	110.2
Me	1.402	1.499	1.026	1.028	0.969	106.4	109.9	69.0	115.6	107.1	110.5

[a] All calculations have been carried out using the 6-311++G** basis set. Bond distances are given in angstroms and bond angles in degrees.

obtained at QCISD(T). In the case of the intermediates $^1[\mathrm{R{-}N{-}OH_2}]^+$ this discrepancy ranges from 30 kJ/mol for R = −Me, to 57 kJ/mol for R = −CN. Similar trends are observed in the case of the transition states and products. It is noticeable that MP2 predicts a transition state lying 8 kJ/mol below reactants for the reaction of $^1[\mathrm{Cl{-}N{-}H}]^+$, whereas QCISD and QCISD(T) predict TS's lying 21 kJ/mol to 29 kJ/mol above reactants. This is an indication of the importance of electron correlation and poses serious doubts regarding the validity of the MP2 formalism in the proper description of the energetics of these processes. The results of Table 2 also show that, in general, QCISD tends to overestimate the in-

TABLE 5: Relative Energies (in kJ/mol) of the Reactions between Several Nitrenium Ions and Water

substituents	MP2 gas phase	QCISD gas phase	QCISD(T)//QCISD gas phase	QCISD solution
		A. R = H		
reactants	0.00	0.00	0.00	0.00
intermediate	−369.74	−332.54	−339.62	−327.36
TS	−263.51	−213.01	−229.12	−201.00
products	−477.06	−436.73	−443.59	−443.29
intrinsic barrier[a]	106.23	119.54	110.50	126.36
overall barrier	−263.51	−213.01	−229.12	−201.00
		B. R = Cl		
reactants	0.00	0.00	0.00	0.00
intermediate	−114.01	−94.68	−92.72	−112.68
TS	−7.99	29.16	20.84	38.07
products	−204.89	−182.13	−178.07	−177.82
intrinsic barrier[a]	106.02	123.80	113.47	150.71
overall barrier	−7.99	29.16	20.84	38.07
		C. R = F		
reactants	0.00	0.00	0.00	0.00
intermediate	−224.97	−200.71	−204.22	−204.26
TS	−89.62	−49.71	−62.30	−35.35
products	−305.68	−276.60	−279.03	−270.45
intrinsic barrier[a]	135.35	151.00	141.92	168.91
overall barrier	−89.62	−49.71	−62.30	−35.35
		D. R = CN		
Reactants	0.00	0.00	0.00	0.00
intermediate	−194.30	−142.51	−137.44	−182.13
TS	−81.71	−12.59	−19.25	−8.45
products	−254.39	−202.13	−196.52	−203.33
intrinsic barrier[a]	112.59	129.96	118.16	173.68
overall barrier	−81.71	−12.59	−19.25	−8.45
		E. R = Me		
reactants[b]	0.00	0.00	0.00	0.00
intermediate	−47.86	−31.97	−27.70	−46.36
TS	39.37	70.84	65.44	71.13
products	−172.97	−152.76	−147.49	−158.28
intrinsic barrier[a]	87.24	102.80	93.09	117.49
overall barrier	39.37	70.84	65.44	71.13

[a] All calculations using 6-311++G** basis sets and corrected with gas-phase MP2 ZPEs. [b] Intrinsic barrier computed as the energy difference between the intermediate and the TS. [c] From the point in the PES in which the distance between the fragments is 2.0 Å.

trinsic barriers for the 1,2-proton shifts by 9−12 kJ/mol when compared to the QCISD(T) results, indicating the importance of triple excitations in the treatment of the three center interactions existent in these reactions. It is interesting to notice that, despite the problems encountered with the MP2 relative energies, the 1,2-proton shift barriers predicted by this method are only 5−7 kJ/mol lower than their respective QCISD(T) values, exhibiting a better agreement with QCISD(T) than the corresponding results obtained at the QCISD level.

The results presented in Table 5 show that the relative stabilization energies of the intermediates $^1[H-N-X-OH_2]^+$ increase in the order X = −Me < −Cl < −CN < −F < −H. This trend can be attributed to factors such as the strength of "π donor−π acceptor" interactions between the substituents and the central nitrogen atom, as well as their electron withdrawing character. Thus, in the case of fluorine, the retrodonation of π electronic density from one of its lone pairs causes significant electronic repulsions with the σ N−O bond being formed, leading to a smaller stabilization energy of the intermediate compared with the intermediate $^1[H-NH-OH_2]^+$. This effect gets amplified by the significant electron affinity of fluorine, which tends to destabilize the formal charge on the molecule. The same rationale can be used to explain the lower stabilization energy of the adducts corresponding to X = −Cl, −CN, and −Me. However, it is surprising to see that the relative energy of $^1[NC-NH-OH_2]^+$ is lower than the corresponding value for $^1[Cl-HN-OH_2]^+$. This extra stabilization could be the result of contributions of resonance structures similar to the one existent in the parent ion (see above).

The reactions of $[Me-NH]^+$ and $[Cl-NH]^+$ with water to produce their respective protonated methyl- and chlorohydroxylamines are predicted to have an overall positive barrier, whereas the other members of the series proceed through transition states lying below reactants. In addition, the gas-phase intrinsic barriers involved in the 1,2-proton shifts from the intermediates toward their protonated hydroxylamines follow the trend: $F-NH-OH_2 > NC-NH-OH_2 > Cl-NH-OH_2 > H-NH-OH_2 > Me\text{-}NH-OH_2$. In all cases, these barriers are sufficiently high to give a reasonable stability to theintermediates. It is noticeable that the magnitude of these barriers are substantially larger than the corresponding value found in a previous study of the reaction between singlet methylene and water (5.98 kJ/mol).[5a] Besides the effect of the substituent noted above, there seems to be a correspondence between the size of the substituent bonded to the nitrogen atom and the energetics of the corresponding nitrenium ions. The bulkier groups yield higher relative energies for the intermediates, transition states, and products in our model reactions.

A graphical summary of the results listed in Table 5 is presented in Figure 3, where QCISD(T)//QCISD gas-phase energy profiles are shown. Despite the energy differences, the profiles for these reactions show similar features, indicating the formation of an intermediate that undergoes a proton 1,2-proton shift to produce the corresponding protonated hydroxylamine.

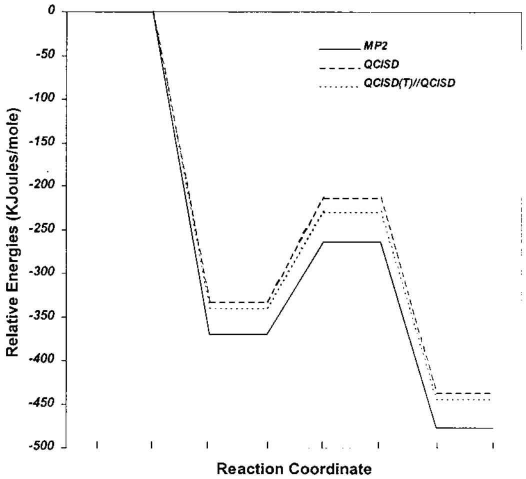


Figure 2. Effect of the electron correlation on the gas-phase energy profiles for the reaction of $[NH_2]^+$ with water.

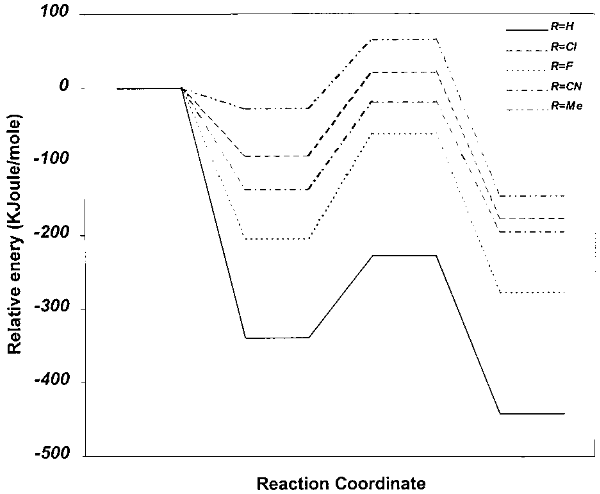


Figure 3. Effect of the substituent in the QCISD(T)/6-311++G**//QCISD/6-311++G** gas-phase energy profiles for the reactions of a series of substituted nitrenium ions and water.

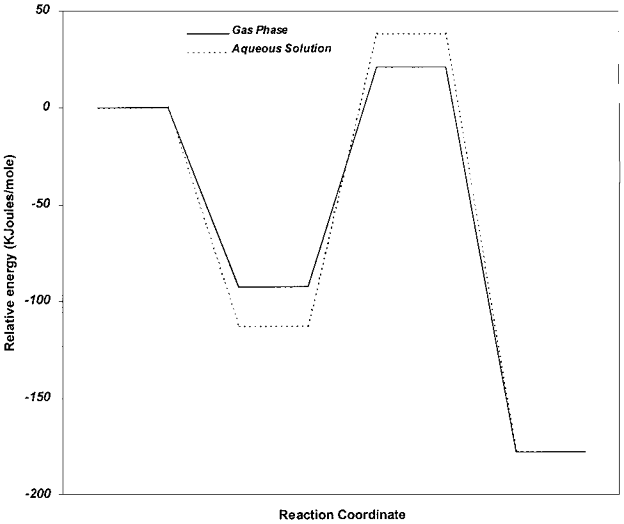


Figure 4. Effect of the solvent in the QCISD/6-311++G** energy profile for the reaction of $[ClNH]^+$ with water.

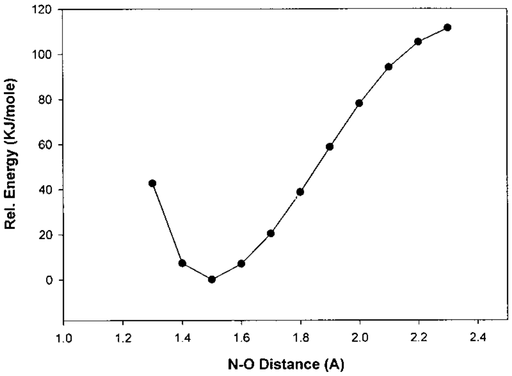


Figure 5. Potential energy surface for the interaction of the methylnitrenium ion and water. Calculations were carried out at the MP2-(Full)/6-311++G** level.

Figure 4 shows energy profiles for the reaction of $[Cl-NH]^+$ with water in the gas phase and in solution. Electrostatic interaction with the solvent, increases the intrinsic barrier of the process, as it stabilizes the reactants and the intermediates relative to the transition state. This trend was also observed for the reaction of the other nitrenium ions in this series (see Table 5), and agrees with results obtained by similar calculations carried on the reaction of a series of substituted carbenes and water.[5] In general, the solvent results are in qualitative accord with gas-phase findings. Caution must be exercised when interpreting the results in solution, given the limitations of the IPCM solvation model (i.e., lack of treatment of implicit solvent molecules) used in the present work.[23c,23d]

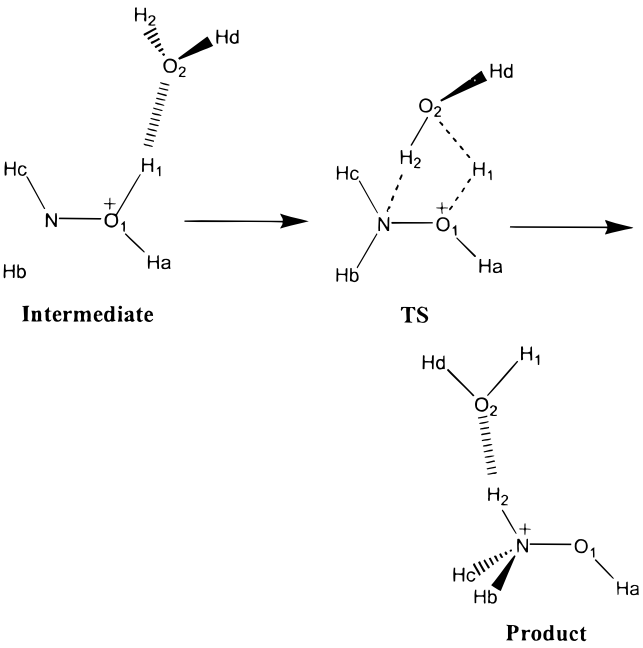
The relative stability of the intermediates and the large intrinsic barriers suggest that the intermediates could be characterized spectroscopically. We have previously reported that an analogous methyleneoxonium intermediate can exist as a stable intermediate for the reaction of $:CH_2$ with water.[5a] This theoretical finding confirmed the experimental results reported by Wesdemiotis and co-workers, as they were able to detect this intermediate by mass spectrometry.[31] The intrinsic barrier of the reaction singlet methylene ($:CH_2$) and water was predicted to be 5.98 kJ/mol in gas phase at the QCISD(T)/6-311++G**//QCISD/6-311++G** level; the analogous reaction of $[NH_2]^+$ with water has an intrinsic barrier of 110.50 kJ/mol (Table 5). Therefore, it is very likely that the intermediates can be readily detected in the reactions of our series of nitrenium ions with water.

Experimental studies in the gas phase of the reaction of $^+NH_2$ with water at near room-temperature conditions have concentrated on H or H^+ exchange to form $^+NH_3$ or NH, respectively.[32,33] These reactions have been described as very fast processes, which is in accord with the observation that nitrenium ions are extremely difficult to detect due to their very high reactivity. These experimental studies have been carried out under conditions that are quite different from the ones assumed in our study, i.e., for our calculations we have assumed that in the gas phase, these reactions occur for isolated molecules at 0 K. Furthermore, as in the case of the reaction of methylene with water, the detection of the intermediates requires specific experimental conditions not applied to the to the study of nitrenium ions.

The dramatic difference in the energetics of the reactions of water with nitrenium ions with the isoelectronic carbenes, can be attributed to the formal positive charge in the nitrenium ions. This charge enhances the electrophilicity of these species and increases the relative stability of their corresponding intermediates.

Reaction of the Methylnitrenium Ion. The reaction between methylnitrenium ion and water represents an anomaly in this series of reactions. As stated above, we have found that the methylnitrenium cation experiences a rapid gas-phase decom-

SCHEME 3



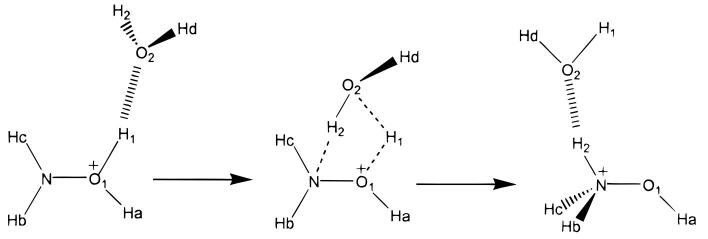
position, leading to the formation of $^1[HC{=}NH]^+$ and H_2. However, our results show that when a water molecule is present, the water addition competes with the H_2 elimination process. The presence of the water inhibits the elimination as the methyl nitrenium ion is present at N−O distances less than 2.3 Å. At an optimal intermoiety distance (ca. 1.5 Å), the corresponding adduct is formed! This remarkable result seems to indicate the possibility of producing a stable ylide as soon as singlet methyl nitrenium ion is formed in solution. To compute the reaction profile of this cation with water, we started with the geometry of the intermediate and calculated a potential energy surface using the N−O bond distance as the reaction coordinate. Figure 5 shows the result of an MP2(Full)/6-311++G** scan optimization of the potential energy surface of the interaction between methylnitrenium ion and water. The scan optimization was carried out by fully optimizing the molecular geometries at different fixed N−O distances ranging from 1.3 to 2.3 Å. In this potential energy surface two competitive reaction pathways can occur. At N−O distances less than 2.3 Å, there is a strong interaction between the methylnitrenium fragment and the oxygen atom of the water and the reaction profile resembles the formation of the intermediate. During this stage, the interaction of the fragments inhibits the H_2 elimination. As the reaction coordinate increases, the energy increases steadily up to 111 kJ/mol at a distance of 2.3 Å. At this point of the PES, the energy begins to drop and the nitrenium fragment begins to undergo the H_2 elimination to produce the hydrated ion $^1[HC{=}NH]^+$. We have also explored an alternate path where the water molecule assists a 1,2-proton shift from the methyl group to the nitrogen atom, to form the hydrated ion $^1[H_2C{=}NH_2]^+$. Although preliminary calculations indicate that all these reactions paths are competitive, their detailed study is beyond the scope of this work, and the results will be presented in a future publication.

Reaction of Singlet Nitrenium Ion with Two Water Molecules. As explained before, the use of the IPCM model describes only electrostatic interactions between the solute ($^1[NH_2]^+ + H_2O$) and the solvent (water) and does not consider explicit hydrogen bonding between water and this system. The neglect of explicit waters could lead to predicted mechanisms that might be too different from the real processes taking place in solution. To address this issue, an extra water molecule was added to the reaction of $[^1NH_2]^+$ with H_2O, and the energetics as well as the mechanism were computed with the same methodology used for the previous calculations. Full optimizations[34] at the QCISD/6-311++G** level (see Table 6), indicate that the addition of a second water molecule leads to the formation of a stable intermediate, where the second water molecule hydrogen bonds to the adduct $^1[NH_2{-}OH_2]^+$. This complex undergoes a proton transfer to the nitrogen to form the solvated molecule $[NH_3OH]^+$. This process can be summarized by Scheme 3.

It is interesting to notice that the second water molecule acts a catalyst, whereby it abstracts a proton from the water moiety in $^1[NH_2{-}OH_2]^+$ and donates another proton to the nitrogen atom. The transition state structure involves a five-member ring which contains the second water molecule and the molecular plane $N{-}O_1{-}H_1$. (We found a similar mechanism in the case of $:CH_2 + 2H_2O$.) The results listed in Table 6 indicate an elongation of approximately 0.49 Å in the $O_1{-}H_1$ bond length, accompanied by a corresponding shortening of the $N{-}H_2$ distance by 1.14 Å when the TS structure is compared to the solvated intermediate.

Table 7 lists the relative energies (in gas phase and in solution) of the different stationary points of the corresponding potential energy surface for this process. The gas-phase intrinsic barrier is computed to be 17.6 kJ/mol at both, QCISD/6-311++G** as well as at the QCISD(T)/6-311++G** level, suggesting that the inclusion of triple excitations might not be important. Comparing with the gas-phase results previously obtained in the case of $^1[NH_2{-}OH_2]^+ \rightarrow {}^1[NH_3OH]^+$, it is clear that the intrinsic barrier corresponding to the proton transfer decreases substantially (by ca. 93 kJ/mol) when a second molecule of water is treated explicitly. This significant decrease

TABLE 6: Optimized Geometries for Minima and Transition State in the Reaction of Singlet Nitrenium Ion and Two Waters[a]



Species	RNO_1	RO_1H_1	RO_2H_1	RO_2H_2	RNH_2	$<H_1O_1N$	$<O_2H_1O_1$	$<O_2H_2N$	$\delta H_1O_2H_2N$	$\delta H_bNH_2H_c$
intermediate	1.448	1.105	1.296	0.965	3.297	107.9	177.7	72.2	−2.2	178.5
TS	1.432	1.595	1.011	0.987	2.062	97.6	138.7	116.5	−9.3	−144.9
product	1.401	3.467	0.962	1.609	1.060	70.1	68.0	173.5	−2.7	−120.7

[a] Geometries optimized at the QCISD/6-311++G** level.

TABLE 7: Relative Energies (in kJ/mol) of the Reactions between Nitrenium Ions and Two Waters[a,b]

species	QCISD[e]	QCISD(T)[e]	IPCM[e]	?ZPE[c]	QCISD[f]	QCISD(T)[f]	IPCM[f]
Inter[d]	0.00	0.00	0.00	0.00	0.00	0.00	0.00
TS[d]	12.39	12.36	12.38	5.19	17.58	17.55	17.57
Product[d]	−71.66	−69.76	−73.43	6.15	−65.51	-63.61	-67.28

[a] IPCM calculations carried out at the QCISD/6-311++G** level on the geometries optimized at the QCISD/6-311+G** level, using a dielectric constant of 80.0. [b] QCISD(T) calculations carried out at the QCISD(T)/6-311++G**//QCISD/6-311++G** level. [c] Zero-point energy corrections computed at the QCISD/6-311++G** level. [d] See Table 3 for the optimized geometries of the intermediate (Inter), transition state (TS), and product. [e] Relative Energies without ZPE corrections. [f] Relative Energies with ZPE corrections.

in the barrier is mainly due to a change in the mechanism as a result of the hydrogen bonding of the second water moiety to the substrate.

The results listed in Table 7 also show that in the case of two water molecules, the electrostatic interactions with the solvent do not seem to have any effect on the intrinsic barrier. This is an indication of how hydrogen bonding of the second water molecule with the $^1[NH_2-OH_2]^+$ system offsets the stabilizing electrostatic interactions with the solvent, as observed in the calculations with just one H_2O (see Table 5).

It is expected that in the case of the substituted nitrenium ions studied in this paper, similar mechanisms as the one described in Scheme 2, will be found. Despite the fact that hydrogen bonding by an extra molecule decreases the intrinsic barrier for the proton transfer significantly, the stability of the intermediates might be strong enough to be detected experimentally, specially in the halogenated nitrenium ions where strong "π donor $-$ π acceptor" interactions are present. A systematic study, where up to four water molecules are explicitely treated, is currently underway and the results will be reported soon.

Conclusions

Highly correlated ab initio molecular orbital calculations predict the formation of stable intermediates in the reactions of nitrenium ions $^1[R-NH]^+$ ($R = -H, -F, -Cl, -CN$, and $-Me$) with water, in gas phase, and in solution. The same results show that these intermediates undergo a 1,2-proton shift to produce their corresponding protonated hydroxylamines. Gas-phase intrinsic barriers for these processes range from 93 kJ/mol in the case of $^1[Me-NH]^+$ to 142 kJ/mol in the case of $^1[F-NH]^+$. Electrostatic interactions with the solvent (via IPCM calculations) significantly increase the 1,2-proton shift barriers by up to 56 kJ/mol, enhancing the stability of the intermediates. In general, the results presented in Table 5 show that the relative stabilization energies of these intermediates $^1[H-N-X-OH_2]^+$ increase in the order $X = -Me < -Cl < -CN < -F < -H$. These results could be attributed to an interplay between the strength of "π donor$-\pi$ acceptor" interactions between the substituents and the electron deficient nitrogen atom, and the electron-withdrawing power of the substituents. It has also been shown that despite the fact that methyl nitrenium ion readily decomposes in gas phase, it reacts with water to form a stable intermediate. As with the other cases discussed in this work, the stability of the intermediate increases in solution.

Even though our results in solution obtained with the continuum IPCM model, indicate an enhanced stability of the intermediates, these results should be considered with caution as the use of explicit water molecules in our system could substantially change the mechanism of the reaction. This is confirmed by the calculations on the reaction of $^1[NH_2]^+$ with two water molecules, where hydrogen bonding plays a crucial role in the proton-transfer mechanism. Work is in progress, in which explicit waters are included in the reactions of a series of nitrenium ions and carbenes.

The results reported here are the initial steps toward understanding the reactivity of these species. The methodology employed here can be used to study the energetics and mechanisms of the reactions of aromatic nitrenium ions with water and other important biological nucleophiles. These studies are necessary before any conclusions can be drawn on the role played by these species in carcinogenic processes.

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