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Theoretical studies on the iminium ion-forming reaction

Chang Kon Kim, In Young Lee, Chan Kyung Kim and Ikchoon Lee*

Department of Chemistry, Inha University, Inchon, 402–751, Korea

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ABSTRACT: The iminium ion forming reactions of $YC_6H_4NHCH_2NH_3^+$ **(I)** and the corresponding carbon analog, $YC_6H_4CH_2CH_2NH_3^+$ (**II**) were studied theoretically at the MP2/6–31G*//RHF/6–31G* level. The iminium ion-forming reactions are favored mainly due to a large amount of electron donation (0.05–0.06e) from the nitrogen to the antibonding orbital of the cleaving bond, $n_N \rightarrow \sigma^*(r_3)$, by a first-neighbor vicinal charge-transfer interaction. At *ca* 50% progress of reaction, *i.e.* bond cleavage in the S_N1 transition state (TS), bond contraction of the geminal bond (r_2) is greater by *ca* 10% (60%), which is also greater than bond stretching of a vicinal bond (50%). The reaction through the imbalanced TS provides the minimum energy path in accordance with the basic laws of nature. The Hammett ρ values for the iminium ion-forming activation and equilibrium processes are *ca* -1.3 and -4.3, respectively. The negative activation energies for the S_N2 processes with **I** in the gas phase are consistent with the experimental direct nucleophilic displacement by a strong nucleophile at the iminium ion-forming substrate in water. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: *ab initio* calculations; iminium ion-forming reactions; S_N1–S_N2 processes; first-neighbor vicinal interactions; Hammett ρ values

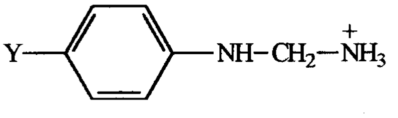
INTRODUCTION

Iminium ions are intermediates in many chemical-and enzyme-catalyzed reactions.[1] For example, in the synthesis of thymidine the biological reaction proceeds through an iminium ion derived from tetrahydrofolate.[2] The iminium ion has a short lifetime in water and it is known to have an even shorter lifetime in the presence of a strong nucleophilic reagent.[3] Hence there is no chemical barrier for reaction of a nucleophile with the iminium ion intermediate and a concerted bimolecular substitution (S_N2) reaction was observed when a nucleophilic reagent was added to the substrate.[4]

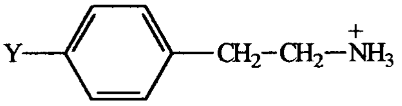
In this work, we investigated theoretically the gas-phase reactivities of iminium ion-forming reactions involved in the S_N1 and S_N2 processes of **I** (and its carbon analog **II**) in which NH_3 is the leaving group: In direct displacement (S_N2) processes, NH_3 was used as a nucleophile. Two types of products are possible in the S_N1 process of **I**, a phenonium ion (P1) and arylmethylene ammonium ion (P2), but for **II** only the phenonium ion product is formed (Scheme 1).

CALCULATION

Geometries were optimized at the RHF/6–31G* level using the Gaussian 92 and 94 programs.[5] The numbering of heavy atoms and bonds is shown in Scheme 2. Vibrational frequency calculations were carried out in order to confirm stationary states including transition state (TS) structures.[6] The energies were estimated from MP2/6–31G* calculations on the 6–31G* optimized geometries, MP2/6–31G*//RHF/6–31G*.[6] The differences in bond lengths in TS between the Hartree–Fock and MP2 levels were relatively small by about 0.1 Å in



I



II

Correspondence to: I. Lee, Department of Chemistry, Inha University, Inchon, 402–751, Korea.
E-mail: ilee@dragon.inha.ac.kr

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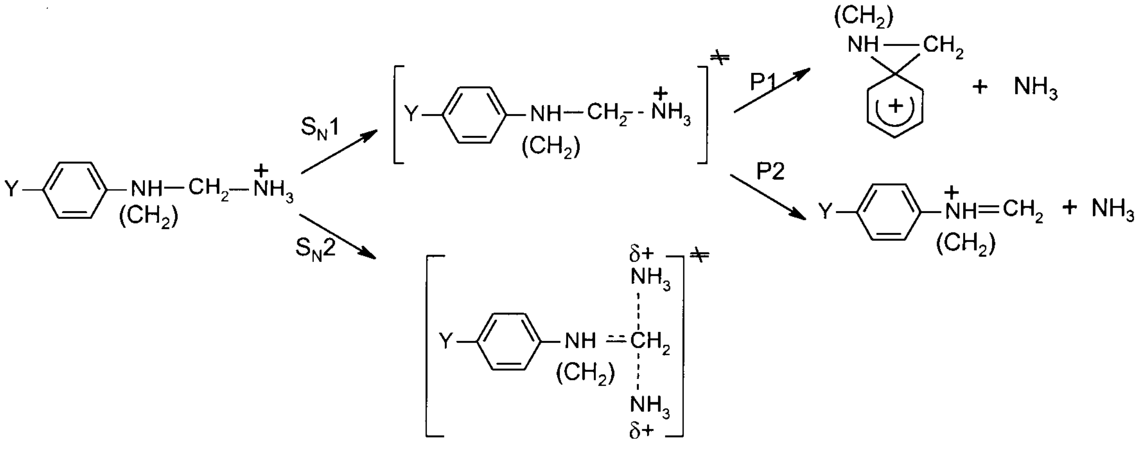
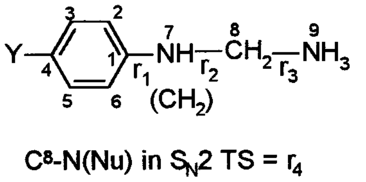


Scheme 1

the identity S_N2 reactions;[7] hence it is expected that the discussion of N—C bond lengths using HF/6–31G* optimized geometries is little affected, especially in view of large differences in bond lengths between S_N1 and S_N2 processes or between reaction systems **I** and **II**.)



Scheme 2

RESULTS AND DISCUSSION

We employed a cationic substrate, RNH_3^+, which has NH_3 as the leaving group. Because the ionogenic heterolytic bond cleavage involved in an S_N1 process is computationally difficult to model in the gas phase owing to the strong endoergic nature in the absence of stabilization by solvent, we chose a cationic substrate with a neutral leaving group.

Cationic species with a neutral leaving group are often used in both experimental and theoretical studies of gas-phase S_N1 and/or S_N2 reactions. For example, experimentally in the gas-phase studies of nucleophilic substitution reactions, cationic species with HCl, HF and H_2O as leaving groups were used.[8] Also, dimethylsulfonium cations with dimethyl sulfide as a leaving group have been used in solution.[9] Various cationic species with N_2 as a leaving group were extensively used in theoretical work by Simonetta and co-workers.[10] There are examples of gas-phase S_N1 studies of cationic species with H_2O and HF as leaving groups.[11] Most recently, Schleyer and co-workers[12] reported high-level MO theoretical studies of the solvolysis of the 2-norbornyl system (cation) with H_2O as a leaving group. We found that NH_3 was most suitable as a leaving group in the present studies of gas-phase iminium ion-forming reactions.

The optimized bond lengths are summarized in Table 1. The percentage changes of the bond orders, $\%\Delta n^{\neq}$, defined by the Eqn (1)[13] where $n^{\neq}$, n_R and n_P are the bond orders of the TS, reactant and product, respectively, were calculated and are shown in Table 2. The

$$\%\Delta n^{\neq} = \{[\exp(-r^{\neq}/a) - \exp(-r_R/a)]/[\exp(-r_P/a) - \exp(-r_R/a)]\} \times 100 \qquad (1)$$

Table 1. Bond lengths (Å) involved in the iminium ion-forming reactions of $YC_6H_4NHCH_2NH_3$ (**I**), and $YC_6H_4CH_2CH_2NH_3$ (**II**) with NH_3 as nucleophile

		S_N1											S_N2			
		R			TS			P1			P2		TS			
System	Y	r_1	r_2	r_3	r_1	r_2	r_3	r_1	r_2	r_3	r_1	r_2	r_1	r_2	r_3	r_4
I (NH)	NH_2	1.431	1.383	1.576	1.431	1.315	1.917	1.468	1.410	1.522	1.428	1.265	1.439	1.272	2.797	2.708
	H	1.416	1.391	1.551	1.429	1.309	1.984	1.484	1.376	1.616	1.443	1.264	1.439	1.274	2.747	2.694
	NO_2	1.406	1.394	1.548	1.427	1.303	2.074	1.488	1.350	1.767	1.444	1.265	1.435	1.278	2.704	2.653
II (CH_2)	NH_2	1.513	1.526	1.525	1.529	1.446	2.285	1.553	1.453	1.553			1.514	1.514	2.137	2.222
	H	1.513	1.526	1.523	1.561	1.422	2.673	1.609	1.424	1.611			1.517	1.513	2.140	2.216
	NO_2	1.516	1.527	1.520	1.597	1.412	3.121	1.642	1.412	1.643			1.517	1.512	2.143	2.209

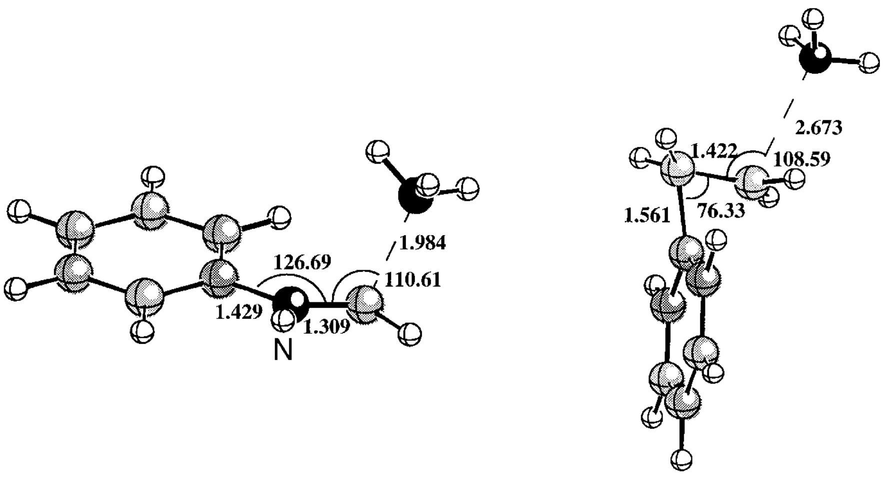
Table 2. Percentage bond-order changes, $\%\Delta n^{\neq}$ [Eqn. (1)] for the S_N1 and S_N2 processes

System	Y	S_N1 (P2) r_1	r_2	r_3	S_N2 $r3$
I	NH_2	21.0	53.3	43.3	86.9
	H	51.3	59.5	51.4	86.4
	NO_2	55.4	66.1	58.4	85.4
II	NH_2			71.8[a]	64.0
	H			85.3	64.3
	NO_2			93.1	64.7

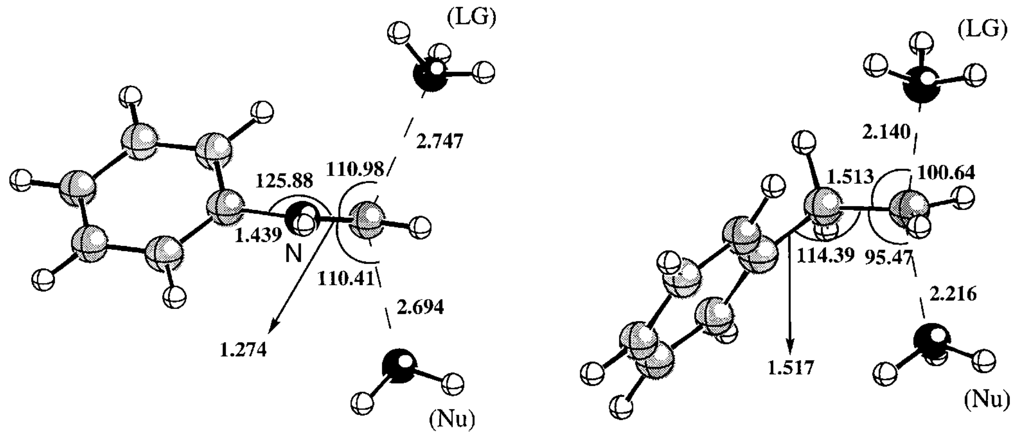
[a] For the P1 path.

constant$a$ was fixed at 0.3 for r_1 and r_2 but for the cleaving bond, r_3, $a = 0.6$ was used.[13] We note that leaving group (NH_3) departure ($\%\Delta n^{\neq}$ for r_3) in the S_N1 TS for the 2-phenylethyl derivative **II** is almost complete (85%), in contrast to *ca* half-way (51%) towards bond scission for the iminium ion-forming process of **I**. The later TS along the reaction coordinate for **II** is due to the greater endothermicity of the reaction, *i.e.* the product (phenonium ion) is relatively unstable in the gas phase so that the reaction is highly endothermic and hence the TS resembles closely the product state.[14] By contrast, in the S_N2 processes, the TS is later for **I** (86%) than for **II** (64%) because of the greater stability of the iminium-like TS of **I**.

Another interesting aspect of the bond order changes in Table 2 is that the progress of bond cleavage (r_3) in the S_N1 TS for **I** (51%) is surpassed by that of the bond contraction of r_2 (60%), which is also greater than that of the bond stretching of r_1 (51%). This sort of imbalance in the structural reorganization is well known and seems to



(I) S_N1 TS (II) S_N1 TS



(I) S_N2 TS (II) S_N2 TS

Figure 1. Geometrical structures of transition state for the S_N1 and S_N2 processes in systems **I** and **II**. Bond lengths and angles are in angstroms and degrees, respectively

Table 3. Group charges in electron units by NPA involved in the iminium ion-forming reactions

		S_N1															S_N2				
		R				TS				P1			P2			TS				
System	Y	Y-ring	NH (CH_2)	CH_2	NH_3	Y-ring	NH (CH_2)	CH_2	NH_3	Y-ring	NH (CH_2)	CH_2	Y-ring	NH (CH_2)	CH_2	Y-ring	NH (CH_2)	CH_2	NH_3	NH_3 (Nu)
I (NH)	NH_2	0.227	−0.310	0.530	0.553	0.255	−0.200	0.640	0.305	0.876	−0.210	0.334	0.386	−0.004	0.618	0.303	−0.107	0.748	0.025	0.031
	H	0.186	−0.295	0.521	0.588	0.252	−0.186	0.667	0.267	0.690	−0.165	0.475	0.344	−0.022	0.678	0.290	−0.115	0.761	0.030	0.034
	NO_2	0.164	−0.286	0.527	0.595	0.244	−0.166	0.700	0.222	0.521	−0.171	0.650	0.324	−0.030	0.706	0.270	−0.123	0.778	0.035	0.040
II (CH_2)	NH_2	0.557	0.017	0.313	0.613	0.275	0.079	0.510	0.136	0.667	0.166	0.167				0.037	0.033	0.578	0.194	0.158
	H	0.048	0.019	0.315	0.618	0.328	0.140	0.489	0.043	0.506	0.246	0.248				0.030	0.035	0.580	0.194	0.161
	NO_2	0.033	0.025	0.317	0.625	0.349	0.204	0.434	0.013	0.425	0.287	0.288				0.014	0.042	0.582	0.195	0.167

Table 4. Activation energies ($\Delta E^{\neq}$) and reaction energies (ΔE°) (kcal mol^{-1})

			S_N1			
				ΔE°		S_N2[b]
System	Y	E(R)[a]	$\Delta E^{\neq}$	P1	P2	$\Delta E^{\neq}$
I	NH_2 (RHF)	−435.18527	5.53	31.33	12.80	−10.87
	(MP2)	−436.55927	3.87	40.36	17.89	−6.80
	H (RHF)	−380.15353	4.77	56.38	15.79	−10.23
	(MP2)	−381.36211	4.06	60.44	22.01	−6.66
	NO_2 (RHF)	−583.61425	7.07	69.91	21.64	−7.30
	(MP2)	−585.35408	6.41	68.18	26.37	−5.18
II	NH_2 (RHF)	−419.19726	26.46	20.59		17.88
	(MP2)	−420.53915	26.64	28.18		16.18
	H (RHF)	−364.16570	34.73	42.37		17.67
	(MP2)	−365.34284	35.61	46.12		16.04
	NO_2 (RHF)	−567.62556	44.88	54.64		17.81
	(MP2)	−569.33564	42.51	53.06		16.16

[a] In hartree.

[b] The energies of NH_3 are −59.18435 (RHF) and −56.35371 (MP2) hartree.

be a universal phenomenon.[15] In the so-called imbalanced TS, the energy gain by bond contraction is ‘paying’ for the energy loss or energy required in bond stretching and/or bond cleavage.[15g] However, the reaction through such an imbalaced TS in the gas phase is not a higher intrinsic barrier pathway than that through a balanced TS, but is a minimum energy path through the fully optimized transition structure in accordance with the basic laws of nature.[15g]

The geometrical structures of transition states with Y = H for the S_N1 and S_N2 processes are represented in Fig 1.

The charges by natural population analysis are shown in Table 3. The population changes on going from the reactant to the phenonium ion place cationic charges of *ca* +0.50 in the ring for both **I** and **II**. On the other hand, the cationic charge in the arylmethyleneammonium ion becomes almost evenly distributed over the ring (+0.16), NH (+0.27) and CH_2 (+0.16).

The energetics are summarized in Table 4. We note that both the S_N1 and S_N2 processes are more favored with **I** than with **II**. One of the factors that determines this lowering of activation barriers for **I** is the greater stability of the arylmethylene iminium ion (P2) than the 2-phenylethyl cation. The iminium ion is more stable with an electron donor (Y = NH_2) in the ring, which no doubt stabilizes the cationic charge on N (Table 3). It is interesting that the iminium ion stability decreases by *ca* 5–6 kcal mol^{-1} (1 kcal = 4.184 kJ) when the electron correlation effect is accounted for. This is due to a well known trend that electron correlation enhances delocalization[16] or conversely the localized state is disfavored energetically by the electron correlation effect; on going from the reactant to the iminium ion (P2), r_1 is stretched and r_2 is contracted so that the system becomes more localized. A major factor contributing to the lower activation barriers for **I** than for **II** is the facility of bond cleavage due to a first-neighbor vicinal interaction[17] between the lone pair on N and $\sigma^*(r_3)$, $n_N \rightarrow \sigma^*(r_3)$, which is fairly large with second-order charge-transfer energies;

$$\Delta E^{(2)} = \frac{-2\langle n|\hat{F}|\sigma^*\rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_n} \tag{2}$$

ranging from 41.3 kcal mol^{-1} for Y = NH_2 to 28.8 kcal mol^{-1} for Y = H. This corresponds to a transfer of 0.05–0.06 unit of electron[17b] from N to the $\sigma^*(r_3)$ orbital. In this type of a strong first-neighbor vicinal interaction, a geminal bond (r_2) is formed while the vicinal σ^* bond (r_3) is broken. The corresponding second-order charge-transfer energies for **II**, σ (r_2) $\rightarrow$ $\sigma^*(r_3)$, are much lower with *ca* 5 kcal mol^{-1}, transfer of less than 0.01e to $\sigma^*(r_3)$. By comparison, for both systems the S_N2 processes are much more favored over the S_N1 processes in the gas phase.

Experimentally in water, the iminium ion was found to be highly unstable so that it has a short lifetime.[3] In the presence of a strong nucleophile, the iminium ion is reported to have an even shorter lifetime and there is no chemical barrier for reaction of a nucleophile with the iminium ion. This requires that the reaction of **I** with a nucleophile should proceed as a concerted bimolecular substitution (S_N2) reaction.[3,4] Our gas-phase results of

Table 5. Hammett ρ values estimated for various activation ($\Delta E^{\neq}$) and equilibrium (ΔE°) processes

	Activation		Equilibrium	
System	S_N1	S_N2	P1	P2
I	−1.3	−0.8	−14.0	−4.3
II	−8.0	≈0	−12.5	—

negative activation barriers, $\Delta E^{\neq} = -5$ to $-7\,\text{kcal mol}^{-1}$ (MP2) for the S_N2 processes in Table 4, are thus in good accord with the experimental findings in water;[3,4] since solvation/desolvation of such nucleophiles are not required in the gas phase the barrier will be much lower. Here again the cationic or more localized nature of the substrate, **I**, in the TS raises the correlated barrier heights,[16] by 2–4 kcal mol^{-1}. The stability of the phenonium ion is lower for **I** than **II** by *ca* 12–15 kcal mol^{-1}, which may be caused by the presence of a heteroatom N in the three-membered ring of **I** (P1) introducing some strain energies.

Even though we used only three substituents, Y = NH_2, H and NO_2, we attempted to estimate Hammett ρ values using Eqn. (3a) for the activation and Eqn. (3b) for the equilibrium processes as shown in Table 5:

$$-\frac{\Delta E^{\neq}}{2.3RT} = \rho\sigma \qquad (3a)$$

$$-\frac{\Delta E^{\circ}}{2.3RT} = \rho\sigma \qquad (3b)$$

The value of ρ for the formation of the iminium cation at equilibrium is *ca* -4.3, which is not much different from that found in water, $\rho^{-} = -3.3$.[3a] Since in water the back-reaction of the leaving group anion with the iminium ion is diffusion controlled, $\rho = 0$, $\rho^{-} = -3.3$ for the solvolysis reaction, for the activation process of the iminium ion-formation process and for the equilibrium process.[3a] However, in the present work, the forward reaction is the leaving group departure and the back-reaction is the reaction of the iminium cation with the neutral ammonia molecule, so that the ρ values for the forward reaction ($\rho = -1.3$) and equilibrium process ($\rho = -4.3$) are not the same; the ρ value for the back-reaction will be *ca* $+3.0$, which is reasonable since the back-reaction is a reaction between a delocalized cation, arylmethylene iminium ion, and a neutral molecule, NH_3. Since in the phenonium ion large positive charge delocalization occurs into the ring, the P1 processes have large negative ρ values (-14.0 and -12.5 for **I** and **II**, respectively). For the S_N2 process of **I** the ρ value is relatively low (-0.8) since the positive charge development in the TS is relatively small and since the reaction center is separated by an extra intervening group (a fall-off of *ca* 2.8 applies),[18] NH, from the substituent. For the corresponding reaction of **II**, ρ is nearly zero, indicating very low positive charge development at the reaction center, C-8; this is because the major part of positive charge is shared by the two NH_3 molecules (leaving group and nucleophile) in the TS.

In summary, the iminium ion-forming reactions are much more favorable than the corresponding 2-phenylethyl cation-forming reactions, mainly owing to a large amount of electron donation from the nitrogen atom to assist leaving group departure. The first-neighbor vicinal charge transfer from N to the cleaving bond (r_3), $n_N \rightarrow \sigma^*(r_3)$, corresponds to *ca*. 0.05–0.06 electron unit, which is over five times larger than the corresponding charge transfer, $\sigma(r_2) \rightarrow \sigma^*(r_3)$, in the 2-phenylethyl system. In the S_N1 TS, the bond contraction of r_2 (60%) is greater than the progress of reaction, *i.e.* bond cleavage (51%), and bond stretching of r_1 (51%). This sort of imbalance in the structural reorganization nevertheless provides a minimum energy pathway and is a universal phenomenon which is in accordance with the basic laws of nature. The Hammett ρ values for the rate-limiting step and at equilibrium are *ca* -1.3 and -4.3, respectively. For the S_N2 process, the ρ values are smaller, -0.8 and *ca* 0 for the iminium ion-and 2-phenylethyl cation-forming reactions, respectively.

Acknowledgements

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