The Periodic Table and the Intrinsic Barrier in S_N2 Reactions

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The identity S_N2 reactions on nitrogen (see eq 3) with nucleophiles having the general structure H_nX^- where X belongs to the group of nonmetallic elements which do not border the line separating them from the metallic elements (X = F, Cl, Br, I, O, S, Se, N, P, and C) were studied at the G2+ level. The results show that, similarly to the previously observed phenomenon for S_N2 reaction on carbon (*J. Am. Chem. Soc.* **1999**, *121*, 7724), the Periodic Table, through the valence of the element X, controls the intrinsic barrier for the reaction. The average intrinsic barriers obtained for nitrogen substrates were 20, 27, 39, and 57 kcal/mol for the mono-, di-, tri-, and tetravalent X's, respectively. It is also concluded that the intrinsic barriers are similar for N- and C-based substrates and dimethyl substitution on both raises the intrinsic barrier by ca. 10 kcal/mol.

Introduction

In Marcus theory,[1] the two factors contributing to the activation barrier height of a nonidentity chemical reaction are the intrinsic barrier and the exo-/endothermicity of the reaction.

In an exothermic reaction, there will be a thermodynamic driving force that will lower the transition state energy (within a structurally close family of reactions), whereas in endothermic reactions the thermodynamics will induce a higher activation energy. Thus, given the values of its two constituents, the Marcus theory enables the determination of the actual barrier in a chemical reaction. Over the years chemists have developed reasonably good intuition for the thermodynamics of reactions, being able to estimate the relative stabilities of the reactants and products by using models such as resonance, bond energies, charge delocalization, etc. However, similar intuitive tools for determining the heights of intrinsic barriers have not yet been acquired. We have recently discovered, much to our surprise, that the intrinsic barriers in S_N2 reactions involving nucleophilic attacks on carbon are controlled by the Periodic Table.[2] The activation energies were quantum mechanically computed at the G2+ level for a series of identity reactions shown in eq 1.

$$(Me_nH_m)X^- + Me - X(Me_nH_m) \longrightarrow (Me_nH_m)\,X - Me + X(Me_nH_m)^- \qquad (1)$$

The activation energy values are given in Table 1, which is arranged in accordance with the Periodic Table structure.

TABLE 1. G2+ Calculated Intrinsic Barriers for the Reactions of Eq 1

	C 44.7	N 29.3	O 19.5	F 11.6
	Si 45.8	P 29.8	S 21.9	Cl 13.2
	Ge 38.1	As 24.5	Se 17.8	Br 10.8
	Sn 30.6	Sb 19.7	Te 15.3	I 9.6
Average.[a]	**44.7**	**29.6**	**19.7**	**11.3**
Stdev		3.4	1.8	0.8

[a] Average and standard deviation values relate only to the groups of nonmetallic X's which do not border on the heavy line.

For X's which do not reside near the line separating the metallic from the nonmetallic elements, it is possible to predict, with a reasonable accuracy, the height of the intrinsic barrier according to eq 2.

$$\text{intrinsic barrier} \approx 10 \times \text{valence of X (kcal/mol)} \qquad (2)$$

Thus for example, the reaction of MeO^- with Me−O−Me (X = O) will have an activation energy of ca. 20 kcal/mol. This valence dependence holds only for the clearly defined nonmetallic elements.[2]

To determine the applicability range and the generality of the phenomenon we have extended our studies to the S_N2 reactions on nitrogen.

Results and Discussion

Method. The geometries and energies of the reactant (ion−dipole) complexes and transition sates were obtained, using Gaussian 98,[3] by a modified form of G2 theory, outlined by Glukhovtsev et al.,[4,5] called G2+, which was adapted from G2 to treat anions better by adding diffuse functions, and calculate heavy atom

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TABLE 2. G2+ Energies for the Species in Eq 3, Complexation Energies Needed To Form the Ion−Dipole Complex (ΔE_{IDC}), and Activation Energies

XH_n	Me_2NXH_n (au)	H_nX^- (au)	E_{IDC} (au)	ΔE_{IDC} (kcal)	E_{TS} (au)	E_a (kcal)
F	−233.9822	−99.7606	−333.7782	−22.2	−333.7459	20.3
Cl	−593.9996	−459.8090	−1053.8332	−15.5	−1053.7965	23.0
Br	−147.4168	−13.2293	−160.6639	−11.2	−160.6324	19.8
I	−145.6324	−11.4469	−157.0950	−9.9	−157.0674	17.4
OH	−209.9780	−75.7124	−285.7161	−16.2	−285.6752	25.7
SH	−532.6145	−398.3715	−931.0009	−9.3	−930.9518	30.8
SeH	−144.0896	−9.8587	−153.9612	−8.1	−153.9230	24.0
NH_2	−190.1224	−55.8171	−245.9600	−12.8	−245.8998	37.8
PH_2	−476.3902	−342.0948	−818.4975	−7.9	−818.4332	40.3
CH_3	−174.1042	−39.7476	−213.8625	−6.7	−213.7724	56.6

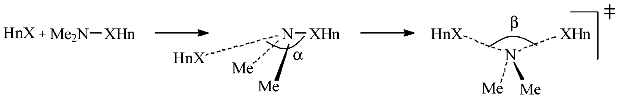
systems by using the Wadt−Hay[6] effective core potentials (ECP). All electron basis sets were used for all first- and second-row atoms, and the appropriately modified ECP basis sets[6] were used for the third- and fourth-row atoms.

Preliminary Considerations. It has been shown that in the ion−dipole complex formed upon encounter of a nucleophile (X) with H_2N-Cl, the nucleophile interacts mainly with the hydrogen on the nitrogen. In fact, computations have shown that a linear X- - -H−N array is formed[7] and that there is a barrier for shifting of the H bond to the other hydrogen.[8] This preassociation complex has, in the sense of Marcus theory, the right configuration for the proton abstraction reaction. Indeed, in the cases where the nucleophile's basicity was sufficiently high, the proton-transfer reaction was dominant.[9] To avoid this complication and to force the appropriate configuration suitable for the S_N2 reactions, we have replaced the two H's by two Me groups (eq 3). As can be seen from Table 3 below, even with this precaution, the X- - -N−X angle in the ion−dipole complex (IDC) was less than 180° with the nucleophile slightly bent toward the hydrogen atoms on the Me groups. As expected, the deviation from a collinear X- - -N−X arrangement was more pronounced for the small nucleophiles than for the larger ones (Table 3 below).

An additional deviation from the approach used in our previous study of nucleophilic reactions on C studies was that instead of using nucleophiles of the $Me(H_n)X^-$ structure we have used H_n-X^- as the nucleophile. The general reaction is shown in eq 3.

TABLE 3. Structural Parameters for the Species in Eq 3

	free reactants	IDC			TS	
XH_n	R_{N-X} (Å)	R_{X-N} (Å)	R_{N-X} (Å)	α	R_{X-N} (Å)	β
F	1.463	3.306	1.494	156.4	1.874	173.9
Cl	1.761	4.01	1.781	163.7	2.261	157.1
Br	1.933	4.24	1.952	164	2.394	151
I	2.111	4.544	2.128	164.7	2.541	141.1
OH	1.46	3.437	1.483	157.6	1.945	170.6
SH	1.742	4.196	1.74	167.6	2.28	149.4
SeH	1.897	4.426	1.897	170.5	2.383	142.5
NH_2	1.432	3.68	1.439	163.1	2.055	169.9
PH_2	1.733	4.378	1.718	174.5	2.242	134.2
CH_3	1.456	4.025	1.448	171.7	2.031	158.1



(3)

The computational results for X's which do not boarder on the line separating the metallic from the nonmetallic elements are given in Tables 2 and 3.

Geometries. One of the most interesting features of the transition state structure is the X- -N- -X angle β. The preferred geometry for an S_N2 transition state is a collinear arrangement. Coulombic interactions between the partly negatively charged X groups and the H's on the Me groups will tend to bend the X groups inward (see eq 3, $\alpha < 180°$). On the other hand, steric repulsion between the X and the Me groups will bend them outward (see eq 3, $\beta < 180°$). Since small atoms have only small steric repulsion and yet they benefit much from electrostatic interactions the small X's are not expected to drastically deviate from a collinear arrangement. On the other hand, large atoms are more sensitive to steric crowdedness, which will decrease β, and at the same time these atoms benefit much less from electrostatic interactions. As a result, large atoms will significantly deviate outward (small β). The net result is that variations in the X---N−N angle at the transition state are quite large, ranging from a small deviation from collinearity (ca. 6°) for F to more than 40° for P (Table 3).

Wolfe et al. have noted[10] from MP2/6-31+G* studies of identity and nonidentity methyl transfer with anionic nucleophiles that a looser transition state is associated with a higher activation energy. Recently, Williams et al.[11] have extended this study to neutral nucleophiles and

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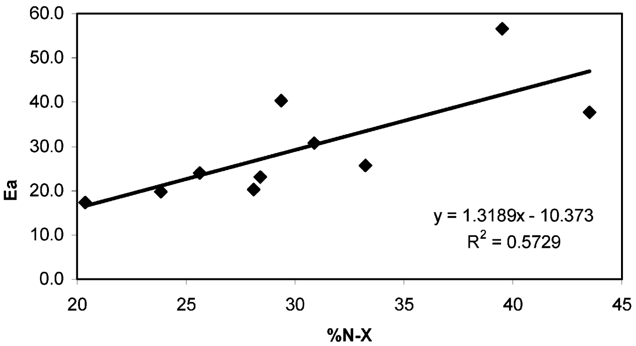

FIGURE 1. Intrinsic activation energies (kcal/mol) vs TS looseness.

TABLE 4. G2+ Calculated Intrinsic Barriers (kcal/mol) for the S_N2 Reaction of Eq 3.

	C 56.6	N 37.8	O 25.7	F 20.3
		P 40.3	S 30.8	Cl 23.0
			Se 24.0	Br 19.8
				I 17.4
average	**56.6**	**39.1**	**26.8**	**20.1**
stdev.		1.8	3.5	2.3

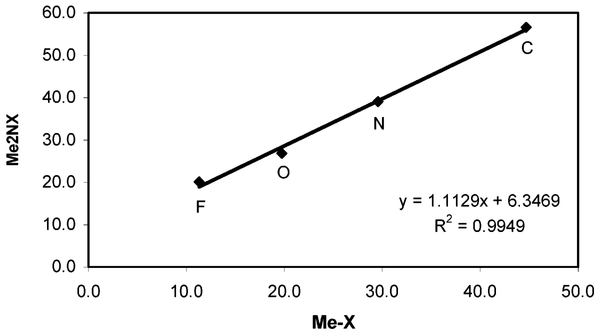

FIGURE 2. Column average intrinsic barriers (kcal/mol) for S_N2 on $Me_2N\text{-}XH_n$ vs the corresponding values for the analogous Me derivatives.

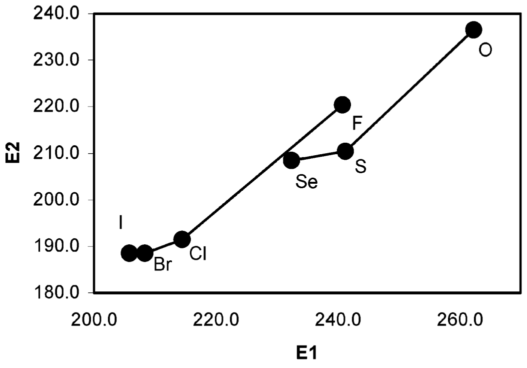

FIGURE 3. TS vs IDC energies relative to the $H_nX^- + Me_2N^+ + H_nX^-$ state. For notations see Scheme 1. Values in kcal/mol.

did not find a simple relationship between the looseness and the energy barriers. Using the looseness definition of Shaik, Shlegel, and Wolfe[12] ($\%\ NX^{\ddagger} = 100(d^{TS}_{NX} - d^{GS}_{NX})/d^{GS}_{NX}$), our results for nucleophilic attacks on nitrogen show an intermediate picture. When the activation energies are plotted vs the looseness of the N−X bond at the transition state (Figure 1), the general trend is that "*looseness is only loosely associated with the activation energy*". Namely, the derived *linear* correlation is rather poor (Figure 1, $r = 0.7569$).

Other than the expected (reasonable) linear correlation between complexation energies and the charges on the nitrogen (graphs not shown), no other meaningful correlation was obtained between any geometric or electronic related feature and activation energies (NPA charges are given in Table S1).

Intrinsic Barriers. Presented in Table 1 are the activation energies for the identity S_N2 reactions on Me−X. A similar presentation, arranged according to the order of the Periodic Table, is given in Table 4 for nucleophilic attacks on Me_2N-X. As can be seen from this table, the phenomenon of intrinsic barriers depending on the valence of the nucleophilic atom repeats itself in this case as well, although not as tightly as for the Me−X substrate; the difference is mainly due to the oxygen column that does not exhibit the homogeneity which is displayed by the analogous reactions with the Me-based substrates.

A plot of the average intrinsic barriers for the F, O, N, and C groups in the reactions with Me_2N-X vs the corresponding averages for the reactions with Me−X yields a linear correlation with a correlation coefficient of 0.9974 (Figure 2), showing that the Periodic Table indeed also controls the intrinsic barriers in the S_N2 reaction on the N-based substrates.

It should be pointed out that the constancy of the activation energies in the halogen series was previously reported by Glukhovtsev, Pross, and Radom.[8] These researchers reported activation energies for identity reactions with H_2N-X rather than with the dimethyl derivative. The values they obtained at the G2+ level were 14, 13.9, 11.2, and 9.4 kcal/mol for F, Cl, Br, and I, respectively (average value: 12.1 ± 2.2 kcal/mol compared to 20.1 ± 2.3 kcal/mol for the dimethyl system of the present work).

It is highly likely that the aforementioned Periodic Table dependence stems from two causes which largely cancel out each other's effects. The first possibility that comes to mind is that variations in the complexation energy (to form the ion−dipole complex) largely resemble in magnitude and direction the variations in the transition state energy. Since the appropriate choice of a reference state is of crucial importance in such an analysis, we have examined two different reference states. The first one was the free reactants and the second one, following Uggerud suggestion,[13] the dissociated reactants, namely $X^- + Me^+ + X^-$. It is clear from Figures 3 and 4 that in both cases there is no linear correlation between the complexation energy and E_a.

An interesting explanation was suggested by Arnout[14] for the Periodic Table control over the intrinsic barriers.

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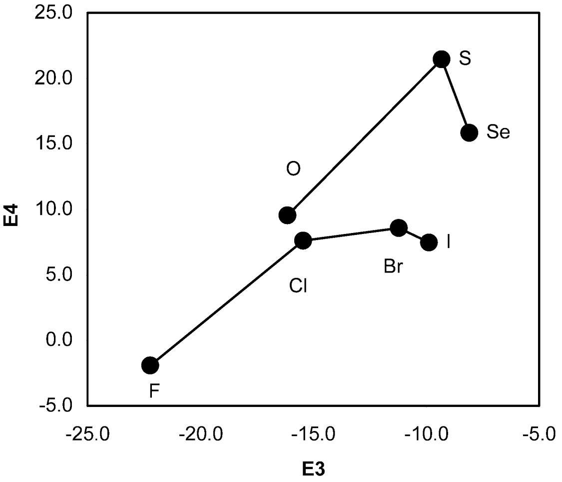
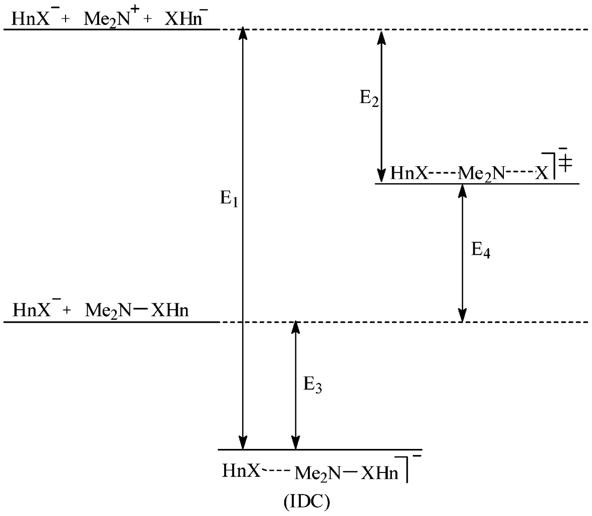


FIGURE 4. TS vs IDC energies relative to the $H_nX^- + Me_2N\text{-}XH_n$ state. For the notations see Scheme 1. Values in kcal/mol.

SCHEME 1



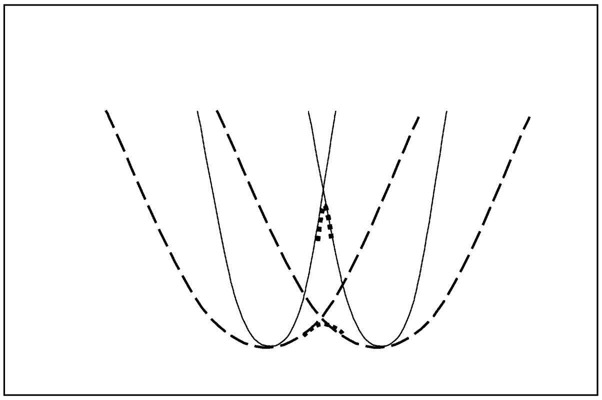


FIGURE 5. Different TS (crossing point) height as a function of parabola curvature for equally separated parabolas.

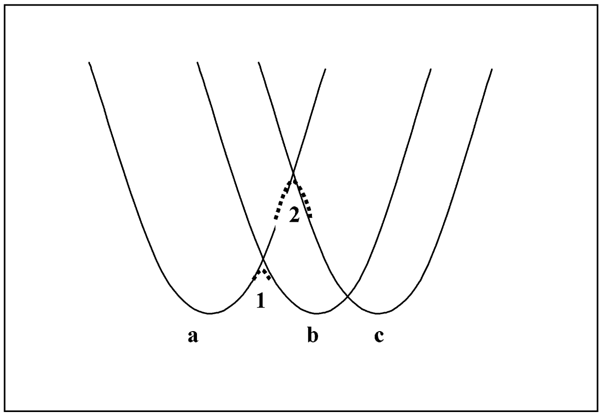


FIGURE 6. Short interatomic distance: parabolas **a** and **b** crossing at TS**1**. Long interatomic distance: parabolas **a** and **c** crossing at TS**2**.

This explanation, which because of its simplicity we find very attractive, is based on the classical curve crossing concept whereby the transition state is achieved around the crossing point of the Morse curves of the reactants and products. According to this, as we descend down a column and the X−N bond force constants become smaller, the parabolas (representing the Morse curves) will become flatter. For a given distance between two such parabolas, the crossing point and therefore the transition state will be achieved at a lower energy (see Figure 5).

On the other hand, as we go down the same column, the atoms become larger and therefore the distance between the centers of the two parabolas will increase. An increased separation between two parabolas will induce an increase in the transition state energy (Figure 6). Thus, going down the column, the intrinsic barrier remains approximately constant because the increase in the size of the atom, and therefore in the internuclear distance, will vary together with the decrease of the force constant and hence with the curvature of the potential surface. Since these two features move in opposite directions, they largely cancel each other, resulting in a near constant barrier.

The beauty of this explanation lies undoubtedly in its straightforwardness and simplicity. However, more evolved and less straightforward arguments will be needed to explain why the phenomenon stops near the borderline separating the metallic from the nonmetallic elements. Also, it is not immediately clear why reactions with some other elements give an “ate” complex, namely, an addition elimination mechanism rather than a maximum (TS) along the reaction coordinate. Unfortunately, the inclusion of the quantitative aspects necessary to provide the explanation for these points into the suggested model will, most probably, clutter its simplicity.

It should be pointed out that the recurrence of the phenomenon in nucleophilic attacks on nitrogen[8] is even more surprising since, for some nucleophiles, the deviation from the optimal collinear arrangement of the X−N−X array is very significant (Table 3). Interestingly, in the reactions with $H_2N{-}Cl$ the deviation occurs in the opposite direction. In other words, because of the electrostatic interaction, the X groups are bent toward the hydrogens with F having the largest deviation (16°) and I the smallest (1°). In the case of $Me_2N{-}X$, the bending is to the other side and away from the Me groups. Yet,

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despite that, the two series present practically a constant activation barrier.

Other Energetic Trends. Two issues will be addressed in this section. The first one is the variation of the activation energies along a row and the other is the comparison between the intrinsic barrier for the S_N2 reactions on carbon and nitrogen. In the case of nucleophilic attack on carbon, the incremental increase in the activation barrier going along a row from F to C was very ordered and followed eq 2 above. The analogous reactions on nitrogen as the central atom do not vary in such an orderly manner. Using the value of 14.5 kcal/mol instead of 10 in eq 1 gives poor results for the average intrinsic barrier for the reactions with Me_2N-X. This is reflected also in the large standard deviation for the average values given in Tables 1 and 4. It should be pointed out that for nucleophilic attacks on methyl derivatives, the variations in the intrinsic barrier moving along a row were predicted by Shaik et al. based on his curve crossing model.[15]

It is interesting to compare the intrinsic barriers for the reactions on C with those on N. Experimental results in the gas phase showed that the reaction of Cl^- with H_2N-Cl is 700-fold faster than that with Me−Cl.[16] On the other hand, G2+ computations by Radom et al.[8] showed that the barrier height are not greatly affected by the identity of the central atom, C or N. Comparison of the column average intrinsic barrier values given in Tables 1 and 4 shows that the intrinsic barrier for attack on N is larger by 9 ± 2 kcal/mol than that on C. However, unlike the C-centered substrates, the central nitrogen in the present study is substituted by two Me groups which increase the steric hindrance at the transition state. Surprisingly, it was experimentally found that the rate constant for the reaction $Cl^- + H_2N-Cl$ in solution (6.6×10^{-5} M^{-1} s^{-1}) is nearly the same as that for the dimethyl derivative Me_2N-Cl (6.3×10^{-5} M^{-1} s^{-1}).[13] In the gas phase, the two methyl groups, as found computationally by Schafer, increase the activation energy by ca. 10 kcal/mol.[7] Similar substitution on carbon increased the activation energy by ca. 9 kcal/mol.[17] For the sake of comparison we have performed a few G2+ computations on the isopropyl system for X = F, Cl, and OH. The results are given in Table 5. Comparison with the data in Table 1 shows that the steric effect of the two methyl groups causes an increase of ca. 10 kcal/mol in the activation energy for these nucleophiles. The outcome of these results, which is in line with previous reports in the literature,[8] is that for the same nucleophile and substrate substitution, the intrinsic barriers are essentially the same regardless of the identity of the central atom, be it C or N.

TABLE 5. G2+ Calculated Energies for the Identity S_N2 Reactions $X^- + i\text{-Pr}\ X$

X	IDC (au)	TS (au)	E_a (kcal)
F	−317.80823	−317.7764	19.98
Cl	−1037.8435	−1037.813	19.01
HO	−269.73298	−269.684	30.7

Summary and Conclusions

We have found that the Periodic Table also controls the intrinsic barrier in S_N2 reactions on nitrogen, just as was found previously for S_N2 reactions on carbon. The pattern is clear although the results are not as tight as we have previously found for nucleophilic attack on carbon because of a greater spread in barrier energies for the oxygen column nucleophiles. The explanation for the Periodic Table column dependence with the carbon substrates offered by Arnout is intuitively very appealing, although at the level of simplicity that it is presented, it cannot provide a complete explanation of all the observations.

We have also shown that the proclivity of nitrogen to undergo S_N2 reaction is very similar to that of carbon, and that dimethyl substitution raises the intrinsic barrier for both elements by ca. 10 kcal/mol.

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Supporting Information Available: NPA charges and archive files of the MP2 optimized ground states, ion−dipole complexes, and transition states structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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