

Theoretical studies of S_N2 transition states. Substituent effects

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Similar substituent and angular constraint effects are noted for pyramidal inversion at tricoordinate nitrogen and inversion at a carbon centre undergoing an S_N2 displacement reaction. The former process has been analyzed successfully by a quantitative PMO analysis which focuses on the frontier orbital interactions between X and NH_2 in the planar and pyramidal structures of $X-NH_2$ molecules having $X = F, CH_3, CHO$. Based on total energy calculations at the 6-311G*//4-31G level, the effects of X upon the rates of the gas phase S_N2 reactions $F^- + XCH_2F \rightarrow XCH_2F + F^-$ are found to be $CHO \gg H > F > CH_3 > OH$. Taking the treatment of nitrogen inversion as a precedent, the origin of this trend has been examined by a quantitative PMO analysis which focuses on the frontier orbital interactions between X and $CH_2F_2^-$ in the transition states, and between X and CH_2F in the reactants. This has revealed that the rate enhancement associated with an α -carbonyl substituent in these S_N2 reactions can be related to the presence of a stabilizing orbital interaction of a new type in the transition state, coupled to an exceptionally low destabilizing orbital interaction.

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On note des effets de substituants et des effets de contrainte angulaire similaire dans le cas de l'inversion pyramidale au niveau de l'azote tricoordonné et dans le cas de l'inversion au niveau du centre carboné subissant la réaction de déplacement S_N2 . On a analysé avec succès le premier processus en faisant appel à l'analyse quantitative des OMP qui porte sur les interactions d'orbitales frontières entre X et NH_2 dans les structures planes et pyramidales des molécules de $X-NH_2$ où $X = F, CH_3, CHO$. En se basant sur les calculs d'énergie totale au niveau 6-311G*//4-31G, on a trouvé que les effets de X, sur les vitesses des réactions S_N2 en phase gazeuse, sont dans l'ordre suivant: $CHO \gg H > F > CH_3 > OH$. En considérant le traitement de l'azote comme un précédent, on a étudié l'origine de cette tendance par l'analyse quantitative de OMP qui porte sur les interactions d'orbitales frontières entre X et $CH_2F_2^-$ dans les états de transition et entre X et CH_2F dans les réactifs. Cette étude révèle que le taux d'augmentation, associée au substituant en position α du carbonyle dans ces réactions S_N2 , peut être relié à la présence d'interactions d'orbitales stabilisantes d'un nouveau type dans l'état de transition, qui s'ajoutent à une interaction d'orbitale déstabilisante exceptionnellement faible.

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The deformation of a carbon atom from tetrahedral to trigonal-bipyramidal geometry makes a significant contribution to the energy barrier associated with an S_N2 displacement reaction (1). There is some analogy between such geometrical effects at an initially tetracoordinate centre and the geometrical changes associated with pyramidal inversion at a tricoordinate centre. It is, therefore, not surprising that the two seemingly different processes exhibit rather similar substituent and angular constraint effects. For example, α -halogen or α -alkyl substituents cause an increase in the barrier to pyramidal inversion at nitrogen (2), and a decrease in S_N2 reactivity at carbon (3, 4). Conversely, an α -carbonyl substituent causes a substantial decrease in the pyramidal inversion barrier (5), and a substantial increase in S_N2 reactivity (4, 6).

Table 1 compares ΔG^\ddagger for pyramidal inversion at nitrogen in a series of cyclic amines (2) with the S_N2 reactivities of the corresponding series of bromocycloalkanes upon reaction with lithium io-

TABLE 1. Effect of ring size upon pyramidal inversion at nitrogen in cyclic amines and upon S_N2 reactivities of bromocycloalkanes

Ring size	Nitrogen inversion ^a	S_N2 reactivity ^c
3	23.8 ^b	< 0.0001 ^d
4	13.4	0.0075
5	10.3	1.6
6	13.7	0.010
7	9.0	0.98

^aData from ref. 2.

^bRefers to ΔG^\ddagger in kcal/mol.

^cData from ref. 4.

^dRelative rates for reaction with lithium iodide in acetone at 25°C ($Me_2CHBr = 1.00$).

ide in acetone solvent (4). The same trends with ring size (i.e., angular constraint) are observed in both cases.

These observations suggested that the effects of substituents upon S_N2 displacement reactions might be rationalized by an appeal to interpretations that have been proposed (7) to account for substituent effects upon pyramidal inversion barriers. One such interpretation is based on the perturbational molecular orbital (PMO) approach, and focuses (8)

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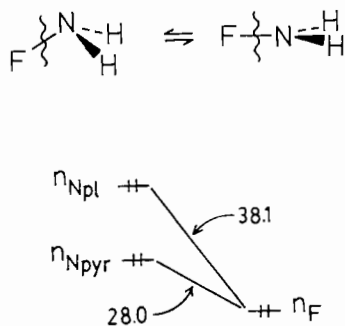


FIG. 1. Frontier orbital interaction between n_F , a fluorine lone pair and $n_{N_{\text{pyr}}}$ or $n_{N_{\text{pl}}}$, the nitrogen lone pairs of the pyramidal and planar forms, respectively, of F-NH_2 . The numbers shown refer to the magnitude of this interaction in kcal/mol based on 4-31G level computations on the fully optimized pyramidal and planar structures. See ref. 9, eq. [64], and ref. 10.

on the frontier orbital interactions both in the pyramidal ground state and in the planar transition state for the inversion process. The application of this procedure to pyramidal inversion in fluoramine is illustrated in Fig. 1. Replacement of one hydrogen of ammonia by fluorine introduces a two-orbital, four-electron destabilizing interaction between the nitrogen lone pair and a fluorine lone pair. The geometrical change affects principally the orbital energy and overlap associated with the nitrogen lone pair, and leads to a 10.1 kcal/mol difference between the destabilizing interactions in the two structures. This difference compares favorably with the 9.4 kcal/mol difference between the computed pyramidal inversion barriers of ammonia (0.4 kcal/mol) and fluoramine (9.8 kcal/mol).

Although the 4-31G basis set employed to obtain these data is known (11) to be deficient for the quantitative calculation of specific inversion barriers, it should be adequate for the determination of trends associated with substituents. Table 2 summarizes the total energy changes and PMO interaction energy changes associated with NH_2 bending in fluoramine, methylamine, and formamide, and appears to validate a frontier orbital analysis of substituent effects upon pyramidal inversion barriers.

For the $\text{S}_{\text{N}}2$ displacement reaction $\text{F}^- + \text{XCH}_2\text{F} \rightleftharpoons \text{XCH}_2\text{F} + \text{F}^-$, the corresponding frontier orbital analysis refers to the fragmentation $\text{X}\cdots\text{CH}_2\text{F}$ in the reactant, and $\text{X}\cdots\text{CH}_2\text{F}_2^-$ in the transition state. For several reasons the problem is simplified considerably by restriction to a thermoneutral or degenerate process: (i) the rates of gas phase $\text{S}_{\text{N}}2$ reactions and the geometries of the transition states depend upon the heat of reaction (12, 13); (ii) for a degenerate reaction, trends in substituent effects are revealed by a comparison between the energies

TABLE 2. Calculated total energy differences^a (ΔE_{T}) and PMO interaction energies^a (ΔE_{PMO}) associated with NH_2 bending in NH_2X molecules

X	PMO interaction energy ^b	ΔE_{PMO}	ΔE_{T} ^c	
F	Pyramidal $n_{\text{N}}-n_{\text{F}}$	28.0	10.1	9.4
	Planar $n_{\text{N}}-n_{\text{F}}$	38.1		
CH_3	Pyramidal $n_{\text{N}}-\pi_{\text{CH}_3}$	39.4	4.7	1.1
	Planar $n_{\text{N}}-\pi_{\text{CH}_3}^*$	-1.8		
CHO	Pyramidal ^d $n_{\text{N}}-\pi_{\text{CO}}$	37.8	-1.6	-4.0
	Planar $n_{\text{N}}-\pi_{\text{CO}}^*$	-23.1		
	Pyramidal $n_{\text{N}}-\pi_{\text{CO}}$	38.9		
	Planar $n_{\text{N}}-\pi_{\text{CO}}^*$	-25.8		

^aIn kcal/mol.

^bCalculated by the procedure of refs. 9 and 10.

^cAt the fully optimized 4-31G geometries.

^dThe NH_2 group was constrained to the geometry of pyramidal CH_3NH_2 . All other parameters retained the values found for planar formamide.

TABLE 3. Calculated energy difference between $\text{F}^- + \text{XCH}_2\text{F}$ and XCH_2F_2^- transition structures (6-311G**/4-31G)

X	$\Delta E_{\text{F,F}}^{a,b}$
H	-3.3 ^c
F	-2.1 ^c
OH	+1.0 ^d
CH_3	-1.9 ^c
CHO	-17.4 ^{c,c}

^aIn kcal/mol.

^bSee Fig. 1 of ref. 13.

^cThe transition state lies below the reactants.

^dThe transition state lies above the reactants.

^eThe 6-311G* computation of $\text{HCO-CH}_2\text{F}_2^-$ was performed by J. M. Lefour, Orléans, France, whose assistance is gratefully acknowledged.

of the separated reactants and the transition state (13); (iii) the principal effect of a transfer of gas phase data to solution is associated with the different heats of solvation of the entering and leaving groups (14). Restriction to a thermoneutral process should, therefore, allow comparison between the calculated trends and experimental data in solution (4). Unfortunately, direct comparison with experimental gas phase results is not possible, because the latter are complicated by competing reaction channels.²

Figure 2 shows the C—F bond lengths (Å) and FCX bond angles (deg) in the series of transition states XCH_2F_2^- , in which X = H, F, OH, CH_3 ,

²Personal communications from Professors J. I. Brauman and W. E. Farneth.

TABLE 4. PMO analyses of $X\cdots\text{CH}_2\text{F}_2^-$ and $X\cdots\text{CH}_2\text{F}$ (9, 10)

System	X	Interacting orbital on X	Interaction energy ^{a,b}			
			A	B	C	Total
XCH_2F_2^-	F	n_{F}	17.0	-7.1	3.6	13.5
	OH	n_{O}	23.4	-11.0	3.5	15.9
	CH ₃	π_{CH_3}	13.3	-0.4	5.7	18.1
		$\pi_{\text{CH}_3}^*$	-0.5		-0.0	
	CHO	π_{CO}	8.4	-0.0	6.3	5.4
	π_{CO}^*	-1.8		-7.5		

System	X	Interacting orbital on X	Interaction energy			Total
			σ_{CF}	σ_{CF}^*	n_{F}	
XCH_2F^c	F	n_{F}	14.6	-5.0	0.0	9.6
	OH	n_{O}	20.9	-6.1	0.0	14.8
	CH ₃	π_{CH_3}	11.2	-0.5	0.1	10.4
		$\pi_{\text{CH}_3}^*$	-0.3		-0.1	
	CHO	π_{CO}	7.8	-0.0	0.1	6.3
	π_{CO}^*	-1.3		-0.3		

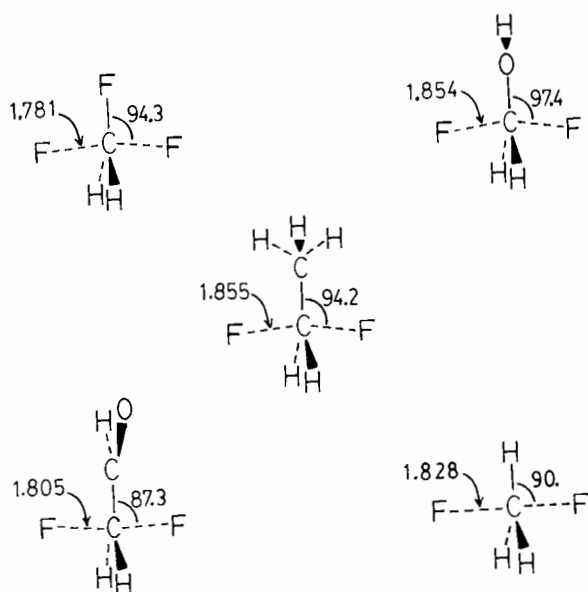
^aIn kcal/mol.^b4-31G computations.^cAt the conformation in which the interacting orbital of X lies in the symmetry plane of CH_2F .

FIG. 2. The C—F bond lengths (Å) and FCX bond angles (deg) in the series of transition states XCH_2F_2^- in which X = H, F, OH, CH₃, and CHO. These data are taken from the fully optimized structures at 4-31G.

CHO, from the fully optimized 4-31G level wavefunctions. The total energy data summarized in Table 3 were obtained at the 6-311G* level (15) using the 4-31G geometries of the reactants and transition states. Based on these data, the effects of these substituents on $\text{S}_{\text{N}}2$ reactivity at carbon are $\text{CHO} \gg \text{H} > \text{F} > \text{CH}_3 > \text{OH}$. The position of the α -oxygen substituent in this sequence strongly suggests that the rate enhancement observed for

this substituent in solution (4) is associated with an $\text{S}_{\text{N}}1$ process (16). The rate-enhancing effect of an α -carbonyl substituent and rate-retarding effects of α -fluoro and α -methyl substituents are reproduced by the calculations.

For the fragmentation $\text{X}\cdots\text{CH}_2\text{F}_2^-$ in the transition states, the orbital interactions forming the HOMOs were found to be A, B, and C; interactions possibly corresponding to A or B have often been proposed in the literature (4, 17) to account for the α -carbonyl rate enhancement, but without specification of their stabilizing or destabilizing nature. Interaction C has not been considered previously.

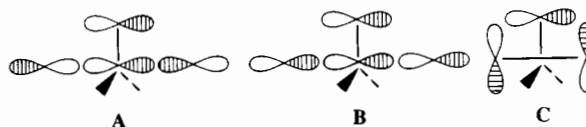


Table 4 summarizes the PMO results and allows the following *qualitative* interpretation of the trends in substituent effects: (1) with X = F or OH, interactions A and C are entirely destabilizing and B is stabilizing; (2) the availability of acceptor orbitals on CH₃ and CHO introduces a stabilizing contribution to A and C; (3) the difference between CHO and F, OH, or CH₃ is the result of a small destabilizing interaction of type A coupled with a large stabilizing interaction of type C; (4) correction of the transition state PMOs for the $\text{X}\cdots\text{CH}_2\text{F}$ orbital interactions in the reactants places α -carbonyl more reactive than α -hydrogen, as observed in the total energy calculations.

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