structural interdependence of the seemingly unrelated coefficients.

Finally, the branching index will be of some interest to other theoretical approaches and may provide a useful reference. For example solubilities are related to molecular surface area.[21] Hermann developed a theoretical model in which a solute molecule is considered as a collection of spheres located at the nuclear centers, to which an envelope determined by the radius of the solvent is added.[22] The branching, cyclization, and positional isomerism are thus indirectly accounted for without the need to introduce additional terms. It is therefore of interest to see how the calculated surface area in this theoretical model depends explicitly on the branching index. The correlation based on a dozen available systems (hydrocarbons in water) is shown in Figure 5. The difference between the surface area based on the model of Hermann and derived from the correlation is less than 10 Å^2 which is less than the scatter in the correlation between the theoretical and experimental surface areas.[23] Thus the branching index can provide an alternative basis for the correlation of the solubility of hydrocarbons in water.

In concluding, we would like to emphasize the conceptual simplicity of the branching index here introduced and its importance as an expression based directly on molecular graphs. It appears that the application of graph theory which is concerned with a systematic study of connectivities may be a rewarding approach to illuminating some problems in chemistry, not so much by providing an accurate and precise scheme for predicting a particular property, but by revealing novel relationships among unsuspected quantities and by discerning the topological nature in others.

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The Importance of Nonbonded Attraction in the Stereochemistry of the SN2′ Reaction

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Abstract: The stereochemistry of the SN2′ reaction is controlled by nonbonded attraction and electrostatic factors. An orbital symmetry analysis is used to evaluate the one-electron factors for the SN2′ reaction involving representative neutral and charged nucleophiles. The results of ab initio (STO-4G) and semiempirical SCF-MO calculations are presented to support the conclusions reached by one-electron molecular-orbital theory.

The abnormal bimolecular substitution reaction (SN2′) has been a subject of controversy ever since the first authentic example was reported by Kepner, Winstein, and Young in 1949.[2a] Other examples were added in the following years.[2b] The mechanism first proposed involved simultaneous bond breaking at the α carbon and bond making at the γ carbon atom of an allyl system. Since then, the "concertedness" of the SN2′ reaction has been questioned and alternate mechanisms have been proposed.[3,4]

The stereochemistry of the SN2′ reaction was suggested by Stork and White[5] to be consistent with a nucleophilic attack on the same side from which the leaving group departs. That is, a syn as opposed to an anti attack on the allylic system. Qualitative theoretical interpretations of the stereoselectivity of the SN2′ reaction have appeared in the literature,[6-8] but quantitative quantum mechanical calculations have never been reported in support of the qualitative theoretical arguments. In 1973, we proposed that nonbonded at-

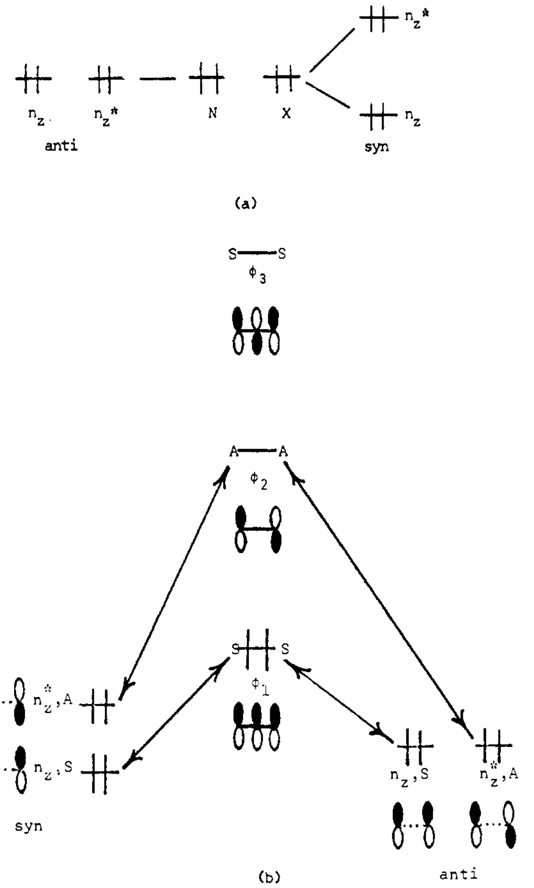
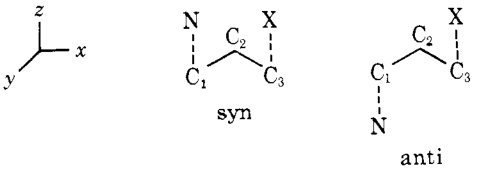


Figure 1. (a) Interaction between the $2p_z$ "lone pair" AO's of the attacking and leaving groups. The p_z AO's of N and X are assumed to be of equal energy. (b) Interaction diagram of the lone pair MO's and the π MO's of the allyl cation for the cases of syn and anti nucleophilic attack.

tractive interactions play a key role in determining the preferred geometry or conformation of molecules and transition states.[9-12] More recently, the recognition of overlap repulsion as a key factor in aromaticity[13] has paved the way toward a full understanding of the key electronic effects which determine stereochemical preferences. Thus, we decided to apply these concepts to the problem of the stereochemistry of the SN2′ reaction and test their validity with explicit calculations at various levels of sophistication. In this work, we report results of ab initio and semiempirical SCF-MO calculations supportive of the proposition that nonbonded attraction is an important factor in determining the stereochemical preferences of the SN2′ reaction. Furthermore, the theoretical analysis makes predictions about the dependence of the stereochemistry of the SN2′ reaction on the nature of the attacking nucleophile and suggests new experiments which can probe the mechanism of the reaction.

Theory

We shall illustrate our theoretical approach by reference to the two model transition states shown below.



Here, X is the leaving group, N is the attacking nucleophile, and the C_1- - -N and C_3- - -X bond distances are taken to be equal.

The π-type MO's of the transition-state complex can be constructed from the group MO's spanning the two p_z "lone pair" AO's of X and N and the π MO's of the allyl cation. First the X- - -N group orbitals are constructed for the two stereochemical modes of reaction as shown in Figure 1a. In the case of syn attack, the X and N p_z AO's overlap and their through space interaction lifts the degeneracy of the two "lone pair" MO's. In anti attack, overlap is nearly zero and the two "lone pair" MO's remain degenerate. The next step in the analysis is the interaction of the "lone pair" MO's with the π MO's of the allyl cation in order to derive the π-type MO's of the transition-state complex. This is shown in the interaction diagram of Figure 1b. We distinguish four types of interactions.

(a) A four-electron destabilizing interaction between the X and N lone pairs. The expression for this interaction is:

$$\Delta E_{\mathrm{XN}}{}^4 = (\epsilon_0 - k)\frac{4S_{\mathrm{XN}}{}^2}{1 - S_{\mathrm{XN}}{}^2} \qquad (1)$$

where ϵ_0 is the mean of the energies of the X and N p_z AO's before mixing,[14] S_{XN} is the overlap integral between the X and N lone pair AO's, and k is an energy constant. Equation 1 is derived by solving exactly the secular determinant for the two-orbital problem including overlap and making the usual approximation for the interaction matrix element, e.g., $H_{ij} = kS_{ij}$.[15] Since S_{XN} is nonzero in the syn but near zero in the anti transition state, the four-electron destabilization will be present in the syn case but absent in the anti.

(b) A four-electron destabilizing interaction between n_z and ϕ_1. The expression for this interaction is given by:

$$\Delta E_{n_z\phi_1}{}^4 = \frac{4S_{n_z\phi_1}{}^2}{1 - S_{n_z\phi_1}{}^2}(\epsilon_0 - k) \qquad (2)$$

where $S_{n_z\phi_1}$ is the overlap between the n_z and ϕ_1 of the allyl cation π MO's, and ϵ_0 is the mean of the energies of the n_z and ϕ_1 MO's before mixing. Equation 2 is derived in the same way as eq 1. The overlap integral $S_{n_z\phi_1}$ is larger in the case of anti attack since the normalization factor of the n_z group MO is greater in the anti case. This arises because the normalization factor of n_z has the form $(C_1{}^2 + C_2{}^2 + 2C_1C_2S_{\mathrm{XN}})^{-1/2}$, where C_1 and C_2 are the coefficients of the p_z AO of N and X, respectively, and will be smaller in the case of syn attack because $S_{\mathrm{XN}}(\mathrm{syn}) > S_{\mathrm{XN}}(\mathrm{anti})$. Furthermore, ϵ_0 is more negative for the syn transition state and leads to a smaller value for $(\epsilon_0 - k)$ in the case of syn attack. Hence, the four-electron destabilization energy will be *less* in the case of syn attack than for anti approach of the nucleophile.

(c) A two-electron stabilizing interaction between n_z* and ϕ_2. This interaction is described by the equation

$$\Delta E_{n_z*\phi_2}{}^2 = \frac{S_{n_z*\phi_2}{}^2\,(k - \epsilon_{n_z*})^2}{\epsilon_{n_z*} - \epsilon_{\phi_2}} \qquad (3)$$

where ϵ_{n_z*} and ϵ_{ϕ_2} are the energies of the n_z* lone pair MO and ϕ_2 of the allyl cation π MO's, respectively, and k is an energy constant. Equation 3 has been derived from the well-known perturbation expression for the two-electron stabilization upon interaction of a filled and unfilled MO (nondegenerate case) where the usual approximation for the interaction matrix element, $H_{ij} = kS_{ij}$, has been made. Since the normalization factor of the n_z* group orbital has the form $(C_1{}^2 + C_2{}^2 - 2C_1C_2S_{\mathrm{XN}})^{-1/2}$ and $S_{\mathrm{XN}}(\mathrm{syn}) > S_{\mathrm{XN}}(\mathrm{anti})$, the overlap integral, $S_{n_z*\phi_2}$, is larger in the case of syn compared to anti attack. Furthermore, inspection of Figure 1b reveals that $\epsilon_{n_z*} - \epsilon_{\phi_2}$ is smaller and $(k - \epsilon_{n_z*})^2$ is larger for the syn transition state and, hence, the two-electron stabilization will be greater for the syn than the anti case.

(d) A two-electron stabilizing interaction between n_z and ϕ_3. By going through the same arguments as before we conclude that this two-electron stabilization will favor anti attack. However, due to the large energy separation of the interacting orbitals we expect that the contribution of the n_z–ϕ_3 interaction to the total two-electron stabilization energy will be small.

The results of the above discussion are summarized below:

$$\Delta E_{\mathrm{XN}}{}^4(\mathrm{syn}) > \Delta E_{\mathrm{XN}}{}^4(\mathrm{anti})$$

$$\Delta E_{n_z\phi_1}{}^4(\mathrm{anti}) > \Delta E_{n_z\phi_1}{}^4(\mathrm{syn})$$

$$\Delta E_{n_z*\phi_2}{}^2(\mathrm{syn}) < \Delta E_{n_z*\phi_2}{}^2(\mathrm{anti})$$

$$\Delta E_{n_z\phi_3}{}^2(\mathrm{anti}) < \Delta E_{n_z\phi_3}{}^2(\mathrm{syn})$$

In general, the overlap repulsion $\Delta E_{\mathrm{XN}}{}^4$ favoring an anti attack is counteracted by the overlap repulsion $\Delta E_{n_z\phi_1}{}^4$ which favors a syn attack. In fact, $(\Delta E_{\mathrm{XN}}{}^4 + \Delta E_{n_z\phi_1}{}^4)$ tends to favor a syn attack, in most cases. As a result, the stereochemical preference of SN2′ reactions depends primarily upon the stabilizing interactions $(\Delta E_{n_z*\phi_2}{}^2 + \Delta E_{n_z\phi_3}{}^2)$ which clearly favor syn attack.

Once we have determined the energetics of orbital interactions for the two stereochemical modes of nucleophilic attack in the SN2′ reaction, we can turn our attention to the bonding consequences of orbital interactions. Upon union of the p_z "lone pair" MO's and the π MO's of the allyl cation the transition state MO's for syn and anti attack are obtained. The unnormalized MO's have the following form

$$\psi_1 = (n_z + \lambda_1\phi_1 + \lambda_3\phi_3) \qquad (4)$$

$$\psi_2 = (n_z* + \lambda_2\phi_2) \qquad (5)$$

$$\psi_3 = (\phi_1 - \lambda_4 n_z) \qquad (6)$$

$$\psi_4 = (\phi_2 - \lambda_5 n_z*) \qquad (7)$$

$$\psi_5 = (\phi_3 - \lambda_6 n_z) \qquad (8)$$

where the mixing coefficients, when overlap is neglected, are given by the following equations

$$\lambda_1 = \lambda_4 = \frac{H_{n_z\phi_1}}{E_{n_z} - E_{\phi_1}} = \frac{kS_{n_z\phi_1}}{E_{n_z} - E_{\phi_1}} \qquad (9)$$

$$\lambda_2 = \lambda_5 = \frac{H_{n_z*\phi_2}}{E_{n_z*} - E_{\phi_2}} = \frac{kS_{n_z*\phi_2}}{E_{n_z*} - E_{\phi_2}} \qquad (10)$$

$$\lambda_3 = \lambda_6 = \frac{H_{n_z\phi_3}}{E_{n_z} - E_{\phi_3}} = \frac{kS_{n_z\phi_3}}{E_{n_z} - E_{\phi_3}} \qquad (11)$$

and the approximation $H_{ij} = kS_{ij}$ has been made. The above discussion is best understood by reference to Figure 2. By neglecting overlap the effects of four-electron repulsive interactions upon bonding will be automatically eliminated. However, since we have already attested to the fact that filled–filled orbital interactions are dominated by filled–vacant orbital interactions, one does not lose essential information by neglecting overlap in the "charge transfer approach". Consequently, we need only examine the effects upon bonding of the n_z*–ϕ_2 and n_z–ϕ_3 two-electron stabilizing interactions.

We will first examine the bonding consequences of the n_z*–ϕ_2 orbital interaction. The normalized perturbed MO's resulting from this interaction are

$$\psi_2 = \frac{1}{(1 + \lambda_2{}^2)^{1/2}}(n_z* + \lambda_2\phi_2) \qquad (12)$$

$$\psi_4 = \frac{1}{(1 + \lambda_5{}^2)^{1/2}}(\phi_2 - \lambda_5 n_z*) \qquad (13)$$

The results of this orbital interaction in terms of bonding can be stated as follows.

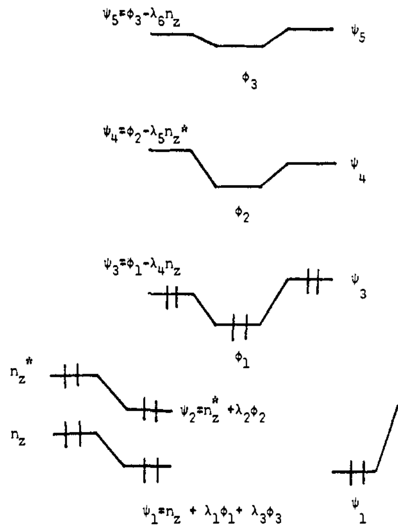


Figure 2. Construction of the transition state π MO's for syn and anti attack.

(1) An amount of electron density which equals $2\lambda_2{}^2/(1 + \lambda_2{}^2)$ is transferred from n_z* to ϕ_2. This can be determined from examination of the probability densities of the unperturbed and perturbed doubly occupied orbitals:

$$n_z*^2 = \frac{1 + \lambda_2{}^2}{1 + \lambda_2{}^2} n_z*^2 \quad (\text{"before" interaction}) \qquad (14)$$

$$\psi_2{}^2 = \frac{1}{1 + \lambda_2{}^2} n_z*^2 + \frac{\lambda_2{}^2}{1 + \lambda_2{}^2}\phi_2{}^2 \quad (\text{"after" interaction}) \qquad (15)$$

(2) The contribution to the total pσ bond order between C and N and C_3 and X will be given by

$$P_{C_1N} = \frac{C_1}{(C_1{}^2 + C_2{}^2)^{1/2}(1 + \lambda_2{}^2)^{1/2}} \frac{\lambda_2}{2^{1/2}(1 + \lambda_2{}^2)^{1/2}} = \frac{C_1\lambda_2}{(2C_1{}^2 + 2C_2{}^2)^{1/2}(1 + \lambda_2{}^2)} \qquad (16)$$

$$P_{C_3X} = \frac{C_2}{(C_1{}^2 + C_2{}^2)^{1/2}(1 + \lambda_2{}^2)^{1/2}} \frac{\lambda_2}{2^{1/2}(1 + \lambda_2{}^2)^{1/2}} = \frac{C_2\lambda_2}{(2C_1{}^2 + 2C_2{}^2)^{1/2}(1 + \lambda_2{}^2)} \qquad (17)$$

If

$$C_1/(2C_1{}^2 + 2C_2{}^2)^{1/2} = R \qquad (18)$$

and

$$C_2/(2C_1{}^2 + 2C_2{}^2)^{1/2} = R' \qquad (19)$$

We obtain the following simplified expressions for the contributions to the total pσ bond orders:

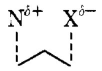
$$P_{C_1N} = R\lambda_2/(1 + \lambda_2{}^2) \qquad (1 > \lambda > 0) \qquad (20)$$

$$P_{C_3X} = R'\lambda_2/(1 + \lambda_2{}^2) \qquad (1 > \lambda > 0) \qquad (21)$$

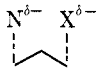
From an inspection of eq 10 and Figure 1, we see that the mixing coefficient λ_2 will be larger in the case of syn than anti attack because of a smaller energy difference between the interacting orbitals and a larger MO overlap integral. Therefore, on the basis of eq 14 and 15, a larger amount of electron density is transferred from n_z* to ϕ_2 for the syn transition state than for the corresponding anti case. Also, we can see from eq 10, 20, and 21 that the pσ bond orders C_1- - -N and C_3- - -X will be greater for syn than anti attack. In summary, it can be seen from the nodal properties of the n_z^* and ϕ_2 MO's that the $n_z^*-\phi_2$ stabilizing interaction will be responsible for the following bonding changes accompanying the transformation anti → syn: (a) an increase in the N- - -X pπ bond order, (b) a decrease in the C_1–C_3 pπ bond order, (c) no change in the C_1–C_2 and C_2–C_3 pπ bond orders, and (d) an increase in the pσ bond orders C_1- - -N and C_3- - -X.

The bonding consequences of the $n_z-\phi_3$ two-electron stabilizing interaction, which favors the anti transition state, can be treated in a similar way and the pertinent bond orders in the transformation anti → syn vary in the following ways: (a) a decrease in the pσ bond orders C_1- - -N and C_3- - -X, (b) a decrease in the C_1–C_3 pπ bond order, and (c) an increase in the C_1–C_2 and C_2–C_3 pπ bond orders. However, we expect that the $n_z^*-\phi_2$ orbital interaction will dominate the $n_z-\phi_3$ interaction since the energy difference between the unperturbed levels is much less in the former case than in the latter case and also $S_{n_z^*\phi_2} > S_{n_z^*\phi_3}$. Hence, the bonding trends in the transformation anti to syn will be determined primarily by the $n_z^*-\phi_2$ stabilizing interaction. However, since the $n_z^*-\phi_2$ interaction does not affect the bonding in all of the atom pairs, e.g., C_1–C_2 and C_2–C_3, the effects of the $n_z-\phi_3$ interaction should also be considered in formulating our bonding predictions. Predictions recognizing the bonding consequences of both stabilizing interactions are shown in Table I.

We now differentiate between two classes of nucleophiles, (a) neutral and (b) charged. One expects that the charge distributions in the transition state complex will differ depending on the nature of the nucleophile. These expected differences are illustrated below for the case of syn attack, assuming that X is more electronegative than N.



neutral nucleophile



charged nucleophile

In the case of an attacking neutral nucleophile, the N and X groups are expected to be oppositely charged at the transition state and the resulting electrostatic interaction will tend to stabilize the syn more than the anti geometry of attack due to the greater proximity of the two oppositely charged groups in the former case. On the other hand, in the case of an attacking charged nucleophile, the N and X groups are expected to be both negatively charged at the transition state and the resulting electrostatic interaction will tend to destabilize the anti less than the syn geometry due to a greater distance of the two negatively charged centers in the former case.

In summary, there are two principal factors which determine the stereochemistry of an S$_N$2′ reaction: (a) a nonbonded interaction factor and (b) an electrostatic interaction factor. For convenience, we tabulate the direction of these factors for the two classes of nucleophiles below:

	Neutral Nucleophile	Charged Nucleophile
Nonbonded interaction	syn > anti	syn > anti
Electrostatic interaction	syn > anti	anti > syn

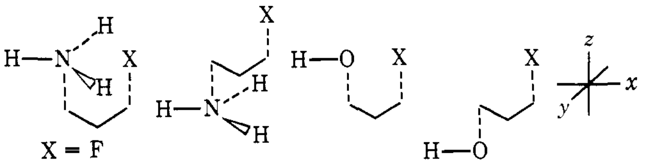
Ab Initio Computations

The model transition states consisted of the nucleophile and leaving group situated above the plane of an unsubstituted allyl framework for syn attack and on opposite sides of the plane defined by the allyl framework in the case of anti attack.

Table I. Overlap Populations of Syn and Anti Attack of a Neutral Nucleophile, NH_3 (STO-4G)

Atom pair	Predicted bonding changes in the transformation anti → syn	Overlap population Syn	Overlap population Anti	Δ (syn − anti)
C_1–C_2	+	0.13257	0.14045	−0.00788
C_1–C_3	−	−0.00026	−0.00052	0.00026
C_2–C_3	+	0.05254	0.04248	0.01006
C_1–X	−	−0.00088	−0.00090	0.00002
C_3–N	−	−0.00079	−0.00044	−0.00035
C_2–N	+	−0.03186	−0.03225	0.00039
C_3–X	+	0.13954	0.14493	−0.00539
C_2–X	+	−0.01200	−0.01114	−0.00086
N–X	+	0.00104	−0.00001	0.00105
N–C_1	+	0.08774	0.07622	0.01152

The C_1- - -N and C_3- - -X distances were set at a 20% extension of the corresponding standard covalent bond length and the assumed geometries for attack of a neutral (NH_3) and charged (^-OH) nucleophile in a syn and anti mode are shown below:



The N–H and O–H bond lengths were assumed to be standard and the NH_3 group was taken to be planar with ∠HNH angles of 120°. The geometry of the allyl framework was optimized at the STO-4G level.[16] Computations on the model transition states were performed using the Gaussian 70 series of computer programs[17] and utilized a STO-4G basis set.

The results of the ab initio calculations are shown in Table II. The total overlap population, P_T, is taken as the sum of all pπ and pσ overlap populations between the five p_z AO's which comprise the AO basis set for the syn and anti transition states. Considering the case of attack by a neutral nucleophile (planar NH_3) first, we see from Table II that the syn transition state is energetically preferred over the anti transition state by 6.88 kcal/mol, a result paralleled by the total overlap population, P_T, which is larger for syn than anti attack. That is, the lower energy of the syn transition state is directly attributable to the through space interaction of the attacking nucleophile and leaving group which results into greater overall bonding in the syn relative to the anti transition state where this interaction does not obtain. The changes in the total overlap population, ΔP_T, and the long range π overlap population between attacking nucleophile and leaving group, $\Delta P_{NX}{}^{\pi}$, are both positive indicating that syn is favored over anti due to an increase in nonbonded attraction which is reflected in the positive sign of $\Delta P_{NX}{}^{\pi}$. Here, we would like to stress that the change in a long-range overlap population can serve as a reliable index of "attractive" or "repulsive" nonbonded interactions if it parallels the change in the total overlap population.

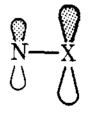
We now turn to the comparison of the predicted bonding changes arrived at by one-electron MO (OEMO) theory and those calculated at the STO-4G level for the case of attack by a neutral nucleophile. As can be seen in Table I the agreement is very good. The quantity Δ(syn − anti) is the overlap population difference between atom pairs in two distinct geometries and can be directly compared to the predicted bonding changes. Furthermore, the only prediction in significant disagreement with the ab initio results concerns

Table II. Overlap Populations for the SN2′ Reaction of Neutral and Charged Nucleophiles (STO-4G)

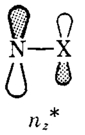
	π overlap population			
Atom pair	N = NH$_3$ Syn	X = F Anti	N = $^-$OH Syn	X = F Anti
C_1–C_2	0.13257	0.14045	0.07641	0.07616
C_1–C_3	−0.00026	−0.00052	−0.00128	−0.00035
C_2–C_3	0.05254	0.04248	0.07199	0.07284
C_1–X	−0.00088	−0.00090	−0.00052	−0.00050
C_3–N	−0.00079	−0.00044	−0.00073	−0.00071
C_2–N	−0.03186	−0.03225	−0.02265	−0.02250
C_3–X	0.13954	0.14493	0.13179	0.13012
C_2–X	−0.01200	−0.01114	−0.01730	−0.01727
N–X	0.00104	−0.00001	0.00065	0.00000
N–C_1	0.08774	0.07622	0.13918	0.13837
P_T	0.36762	0.35880	0.37753	0.37614
ΔP_T	0.00880		0.00140	
$\Delta P_{NX}{}^{\pi}$	0.00103		0.00065	
E_T(rel), kcal/mol	0.0	6.88	4.73	0.0

the π bonding in the C_3–X atom pair. We will discuss this point in detail in order to show that "apparent anomalies" in the ab initio results make perfectly good sense in terms of OEMO theory.

In our calculated model transition states the attacking and leaving groups differ in electronegativity and, consequently, the AO coefficients of the n_z and n_z* group MO's will differ qualitatively as shown below,



n_z



n_z*

where X is more electronegative than N. The bonding consequences of having X more electronegative than N can be approached in the same manner as before. Considering the n_z^*–ϕ_2 stabilizing interaction first we make the following points:

(1) Charge transfer from n_z* to ϕ_2 is larger for the case of syn than anti attack.

(2) From eq 20 and 21 we see that the contribution to the pσ bond order $P_{C_1N}{}^{\sigma}$ and $P_{C_3X}{}^{\sigma}$ will be greater for syn than anti attack since λ_2(syn) > λ_2(anti).

(3) The contribution to $P_{C_1N}{}^{\sigma}$ will be greater than to $P_{C_3X}{}^{\sigma}$ in the syn transition state since the p_z AO coefficient of N, C_1, is larger than the p_z AO coefficient of X, C_2.

We conclude from the above that: (a) $P_{C_1N}{}^{\sigma}$(syn) > $P_{C_1N}{}^{\sigma}$(anti), (b) $P_{C_3X}{}^{\sigma}$(syn) > $P_{C_3X}{}^{\sigma}$(anti), and (c) $P_{C_1N}{}^{\sigma}$(syn) > $P_{C_3X}{}^{\sigma}$(syn). Now, the important points to consider in the n_z–ϕ_3 stabilizing interaction are: (1) charge transfer from n_z to ϕ_3 is larger for the case of anti than syn attack; (2) the contribution to $P_{C_1N}{}^{\sigma}$ and $P_{C_3X}{}^{\sigma}$ will be greater for anti than syn attack since λ_3(anti) > λ_3(syn); (3) the contribution to $P_{C_3X}{}^{\sigma}$ will be larger than that to $P_{C_1N}{}^{\sigma}$ since, in this case, $C_1 < C_2$.

Hence, the n_z–ϕ_3 interaction will have the following results: (a) $P_{C_1N}{}^{\sigma}$(anti) > $P_{C_1N}{}^{\sigma}$(syn), (b) $P_{C_3X}{}^{\sigma}$(anti) > $P_{C_3X}{}^{\sigma}$(syn), and (c) $P_{C_3X}{}^{\sigma}$(anti) > $P_{C_1N}{}^{\sigma}$(anti).

From the above discussions we conclude that in the transformation anti → syn, the overall C_1- - -N pσ bond order will be greater in syn than anti attack because the n_z^*–ϕ_2 interaction results in a large positive $P_{C_1N}{}^{\sigma}$, since C_1 is large in n_z*, which favors syn attack but only a small positive P_{C_1N} due to the n_z–ϕ_3 stabilizing interaction which favors anti attack because C_1 is small in the n_z MO. However, even though the n_z^*–ϕ_2 stabilizing interaction dominates the n_z–ϕ_3 stabilizing interaction, the total C_3- - -X pσ bond order resulting from a superposition of these two interactions may be greater in anti than syn attack simply because the X_{p_z} AO coefficient is much greater in the n_z than the n_z* MO and hence C_3- - -X bonding may be greater in anti than syn. This is indeed the situation found in the ab initio results as can be seen in Table I where Δ(syn − anti) is negative for the C_3- - -X pσ overlap population (−0.00539) but is a larger positive number for the C_1- - -N pσ overlap population (0.01152). Other minor discrepancies, most notably the C_1–C_2 pπ overlap population, are probably due to the differential inductive effects of N and X which are not recognized in our theoretical treatment. In addition to the stabilization of the syn transition state by "nonbonded attraction", the calculated group charges for syn and anti attack shown in Figure 3 show that the syn transition state is favored by electrostatic interactions to a greater degree in syn than is the case in anti attack.

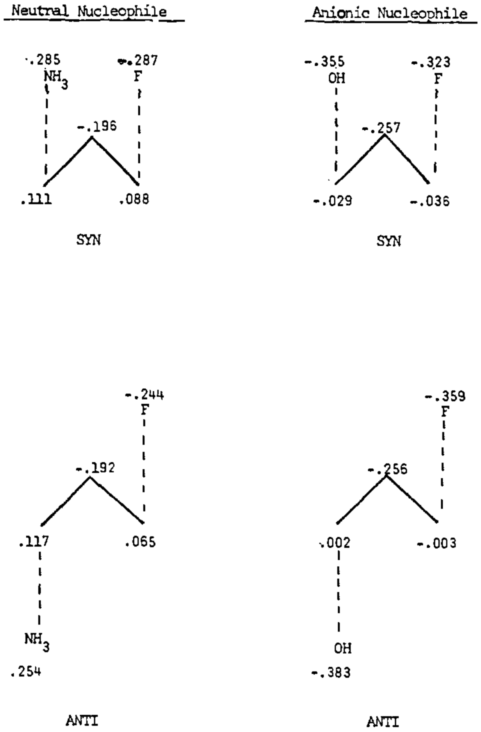


Figure 3. Ab initio (STO-4G) group charges for syn and anti attack of a neutral and anionic nucleophile.

For the attack of a charged nucleophile ($^-$OH) the calculations show that the anti transition state is lower in energy than the syn transition state (Table II). From our OEMO approach we expect that nonbonded interactions should favor the syn transition state. This is confirmed by the total overlap population shown in Table II where P_T is larger for syn than anti attack. Also, we see that both ΔP_T and $\Delta P_{NX}{}^{\pi}$ are positive indicating that π interactions are stronger in the syn than the anti transition state. Since P_T does not parallel the relative E_T in the SN2′ attack of a charged nucleophile we conclude that nonbonded attraction, *although present*, is not the primary factor in determining the preferred stereochemistry in this case. On the other hand, we expect that electrostatic repulsion should be greater for the syn than the anti mode of nucleophilic attack. It is clear from the charge distribution shown in Figure 3, for the case of an anionic nucleophile, that electrostatic repulsion is less for the anti transition state. Consequently, these results indicate that even though "nonbonded attraction" favors syn attack, the dominant factor for determining the stereochemistry of a SN2′ reaction in which the

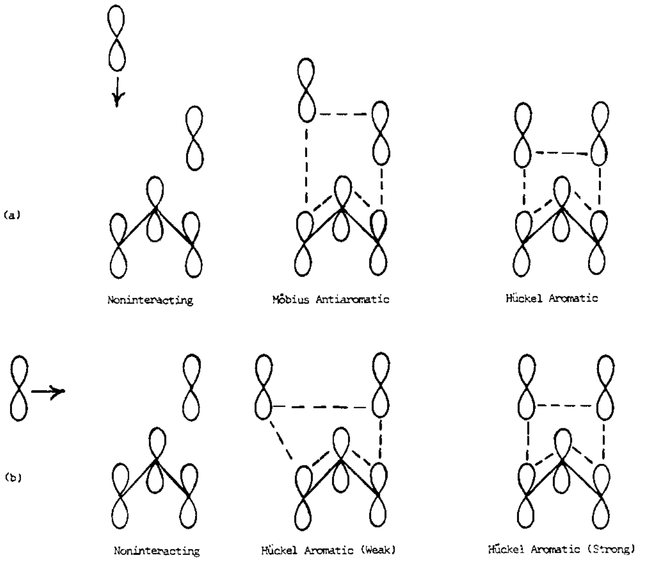
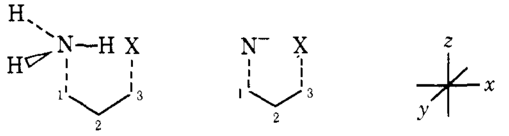


Figure 4. (a) Nucleophilic attack perpendicular to the plane of the allyl group. This mode of approach passes through a high-energy Möbius antiaromatic configuration. (b) Nucleophilic attack parallel to the plane of the allyl group. This approach involves continuous enhancement of Hückel aromaticity.

nucleophile is charged is the electrostatic interaction factor.[18]

CNDO/2 Computations[19]

The model transition states geometries for neutral and anionic SN2′ nucleophilic attack are shown below for the case of syn attack:



X = F

N = X = F

The $C_1 \cdots N$, $C_1 \cdots F$, and $C_3 \cdots F$ distances were set at a 20% extension of the corresponding standard covalent bond length. Standard bond lengths and angles were used in all cases and the NH_3 group was assumed to be planar with $\angle HNH$ angles of 120°.

The results of the CNDO/2 calculations are shown in Table III. For the case of the attack of a neutral nucleophile we see that the syn transition state is calculated to be 10.47 kcal/mol lower in energy than the anti transition state. As in the ab initio calculations, the total overlap population is largest for the lower energy syn transition state and ΔP_T is paralleled by $\Delta P_{NX}{}^{\pi}$ indicating that nonbonded attraction is the major factor influencing the preferred syn attack of neutral nucleophiles. A close inspection of Tables II and III reveals that the bonding trends are nearly the same in both the ab initio and CNDO/2 calculations. The reason for this agreement is directly related to the already attested to fact that filled-filled orbital interactions may well favor syn attack. Specifically, in calculations performed within the ZDO approximation the bonding consequences of four-electron-two-orbital interactions are zero. However, these filled-filled orbital interactions have an effect upon bonding in ab initio methods where overlap is explicitly included. Therefore, ZDO and ab initio computations will agree in those instances when four-electron overlap repulsions in two geometrical arrangements of atoms tend to cancel, a situation which clearly obtains in any comparison between an "aromatic" and a "nonaromatic" system as we have discussed before.

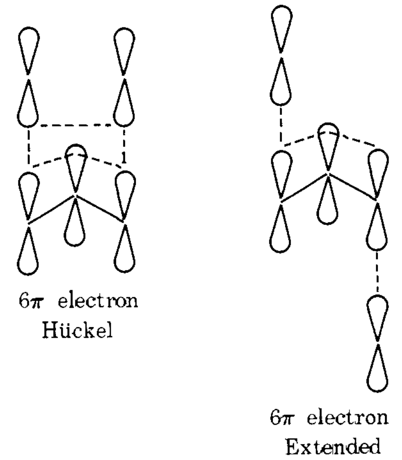
Table III. Overlap Populations for the SN2′ Reaction of Neutral and Charged Nucleophiles (CNDO/2)

	Overlap population			
Atom pair	$N = NH_3$ Syn	X = F Anti	$N = F^-$ Syn	X = F Anti
C_1–N	0.19674	0.19037	0.14683	0.14380
C_3–X	0.15521	0.16066	0.14683	0.14380
C_1–C_2	0.10199	0.10750	0.11040	0.11150
C_3–C_2	0.09289	0.08497	0.11040	0.11150
C_1–C_3	0.00081	0.00093	0.00153	0.00210
C_2–N	−0.01258	−0.01289	−0.00873	−0.00869
C_2–X	−0.00744	−0.00712	−0.00873	−0.00869
C_3–N	−0.00043	−0.00035	−0.00032	−0.00031
C_1–X	−0.00028	−0.00030	−0.00032	−0.00031
N–X	0.00027	−0.00001	0.00010	0.00000
P_T	0.52718	0.52376	0.49790	0.49470
ΔP_T	0.00342		0.0033	
$\Delta P_{NX}{}^{\pi}$	0.00028		0.0001	
E_T(rel), kcal/mol	0.0	10.47	6.908	0.0

When the nucleophile is charged, the results shown in Table II indicate that even though the syn transition state is favored by nonbonded attraction, as revealed by the signs of ΔP_T and $\Delta P_{NX}{}^{\pi}$, the anti transition state is predicted to be the most stable. This agrees with the results obtained in the ab initio computation. The calculated dipole moments provide some measure of the magnitudes of the electrostatic repulsions present in the syn and anti transition states. Specifically, the dipole moment *increases* by 5.343 D in going from an anti to a syn transition state in the case of a charged nucleophile (F^-) but *decreases* by 3.007 D in the transformation anti → syn when the nucleophile is neutral (NH_3). This agrees with the suggestion that electrostatic interactions will favor the syn transition state in the case of an attack by a neutral nucleophile but disfavor the syn relative to the anti if the nucleophile is charged.

Conclusion

The analysis we have provided leads to a very clear understanding of the key factors which may dictate syn nucleophilic attack in SN2′ reactions. In fact, one can condense the theoretical treatment into the statement: the allyl framework plus the nucleophile and the leaving group constitute a 6π electron system which will be more stable in a cis geometry (Hückel aromatic system) than in a trans geometry (extended nonaromatic system). The connection between aromaticity and nonbonded attraction has been made in one of our earlier papers.[10]



These ideas lead directly to some interesting speculations regarding the preferred trajectory of the incoming nucleophile. In one mode of approach the nucleophile may attack following a path perpendicular to the plane of the allyl group as shown in Figure 4a. This is predicted to be a high-energy approach since the nucleophile has to go through a Möbius antiaromatic configuration. In the second mode of approach, the nucleophile may attack following a path parallel to the plane of the allyl group as shown in Figure 4b. This is predicted to be a low-energy approach since it involves a continuous enhancement of Hückel aromaticity. Of course, nucleophilic attack parallel to the plane of the allyl group will be more sensitive to steric interactions than if the nucleophile followed a path perpendicular to the plane of the allyl group. Consequently, appropriate substitution at the γ carbon, or bulky nucleophiles, may result in a dominance of "steric effects" over the one-electron factors discussed in this paper and substitution anti to the leaving group may occur.

The results of this work can be summarized as follows.

(a) The stereochemical preferences of reagents in the SN2′ reaction are controlled by one-electron factors provided that severe "steric" repulsions do not obtain in the transition states. The direction of these one-electron factors can be easily predicted by the orbital symmetry approach used in this paper or by considering the aromatic, nonaromatic, or antiaromatic nature of the transition state.

(b) A dichotomy between neutral and charged nucleophiles, as revealed by our theoretical analysis and quantitative calculations, as well as the suggestion that nucleophilic attack parallel to the plane of the allyl group is favored, suggests new experiments which can probe more deeply the dependence of the stereochemistry of the SN2′ reaction upon the electronic and steric natures of the nucleophiles and allylic substrates. Specifically, the stereochemistry of the SN2′ reaction may be controllable by designing appropriate systems in ways suggested by the results of this paper.

Finally, it should be pointed out that the theoretical analysis in this paper does not differentiate between a classical SN2′ reaction vs. nucleophilic attack on a allylic ion pair. Clearly, a distinction of the two mechanisms would necessitate calculations of the potential surfaces for the following transformations:

$$\mathrm{R{-}X} \rightarrow \mathrm{R^{+}X^{-}} \xrightarrow{\mathrm{N:}} \mathrm{R{-}N} + \mathrm{X^{-}} \qquad \text{(ion pair mechanism)}$$

$$\mathrm{R{-}X} \xrightarrow{\mathrm{N:}} \mathrm{R{-}N} + \mathrm{X^{-}} \qquad \text{(classical S}_{\text{N}}\text{2 mechanism)}$$

Such calculations are not possible at the ab initio level at the present time since cost is prohibitive. However, the distinction between the two mechanisms is not the issue which this paper addresses itself to. The important point to comprehend is that regardless of which mechanism is preferred the stereochemical analysis provided in this paper holds. This arises because although overlap of N- - -X and allyl MO's will be different depending upon the distance between R and X (long for the ion pair mechanism and short for the classical SN2′ mechanism) the relative one-electron stabilization and destabilization of the syn and anti geometries will always vary in the manner discussed above. The only effect of the overlap variation would be to change the magnitude of the stereochemical preference. Finally, while theory seems to be "too expensive" to resolve this issue, it should be pointed out that the experimental distinction between the two mechanisms is a topic of considerable controversy.[20]

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