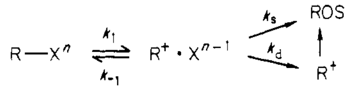
of the reaction occurs through clusters of solvent molecules with a low entropy.[21]

We conclude that, in the reverse direction, catalysis of alcohol expulsion by buffer acids disappears at approximately the point at which the carbocation reacts with the solvent or a leaving alcohol to a significant extent before diffusion occurs. For the hydrolysis of substituted benzaldehyde diethyl acetals this point is apparently reached with the 4-chlorobenzaldehyde derivative.[10]

As the stability of the cation decreases the reaction with solvent can occur either by a preassociation mechanism without diffusion, k_s in eq 4, or through rate-limiting diffusion away from the leaving group, k_d.



$$\begin{tikzcd} & & \mathrm{ROS} \\ \mathrm{R{-}X}^{n} \arrow[r, shift left, "k_1"] & \mathrm{R}^{+}\cdot\mathrm{X}^{n-1} \arrow[l, shift left, "k_{-1}"] \arrow[ur, "k_s"] \arrow[dr, "k_d"'] & \\ & & \mathrm{R}^{+} \arrow[uu] \end{tikzcd} \qquad (4)$$

General acid–base catalysis must disappear when diffusion is rate limiting in these reactions, because buffers do not accelerate diffusion.[2,19] The requirements for rate-limiting diffusional separation are stringent, so that it is not often observed. The requirements are that $k_{-1} > k_d > k_s$; i.e., the leaving group must be a good nucleophile and the solvent must react more slowly than diffusion occurs; the intermediate must also have a significant lifetime, with $k_{-1} < 10^{13}$ s^{-1}. This is consistent with the behavior of the pH-independent cleavage reactions of 2-(aryloxy)tetrahydropyrans[30] and benzaldehyde ethyl arylthiol acetals,[31] in which ArO^- and ArS^-, respectively, are the leaving groups. It is less likely to be of major significance when an alcohol is the leaving group in hydroxylic solvents, because of the requirement for a considerably larger value of k_{-1} compared with k_s. However, the increase in the α-secondary deuterium isotope effect for the hydrolysis of benzaldehyde dimethyl acetal in the presence of increasing concentrations of dioxane has been attributed to rate-limiting diffusional separation of methanol.[32] When the carbocation becomes less stable the intermediate $R^+\cdot X^{n-1}$ will cease to have a significant lifetime so that the initial product of a dissociative mechanism must have the leaving group in an unreactive position, such as a solvent-separated pair. The reverse, addition reaction can still be diffusion controlled in this situation.

When the carbocation becomes still less stable, so that substitution occurs through a concerted bimolecular displacement reaction with no intermediate, general acid–base catalysis is also not observed. This presumably reflects the small sensitivity of these reactions to the basicity of the nucleophile and the small advantage that can be expected from catalysis in an early transition state. If catalysis is not significiant for normal S_N2 displacement reactions it certainly will not be significant for concerted substitution reactions that proceed through an open, "exploded" transition state, which have even less positive charge development on the attacking reagent than ordinary displacement reactions. General base catalysis is observed in some intramolecular displacement reactions, presumably because of the smaller requirement for loss of entropy in the transition states of these intramolecular reactions.[33]

In all of these cases the disappearance of general acid–base catalysis corresponds to a change to a reaction mechanism in which the attack of ROH is not subject to catalysis and the cleavage of ROR′ in the reverse direction is subject to specific acid catalysis (eq 2). Thus, the mechanism of catalysis is determined to a significant extent by the lifetime of the carbocation intermediate.

Registry No. 1-(4-Methoxyphenyl)ethyl carbocation, 18207-33-5; 1-(3-bromo-4-methoxyphenyl)ethyl carbocation, 88510-80-9; 1-(3-nitro-4-methoxyphenyl)ethyl carbocation, 88510-81-0; trifluoroethanol, 75-89-8.

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[31] Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476-1488.

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Nucleophilic Substitution at Vinylic Carbon: The Importance of the HOMO–HOMO Interaction

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Abstract: A theoretical treatment of the stereochemical course of nucleophilic addition to alkenes is presented. On the basis of frontier molecular orbital theory and ab initio molecular orbital calculations, it is concluded that nucleophilic substitution with simple alkenes involves a concerted one-step mechanism. The developing anticarbanion rotates syn to the leaving group with the lowest lying σ^* orbital, with concomitant inversion of the carbanion at C_β and expulsion of the leaving group. This overall process results in retention of configuration of the alkene. With substituents at C_β capable of stabilizing the incipient carbanion, addition of the nucleophile affords a planar, freely rotating carbanion, resulting in stereoconvergence of the alkene being formed. Poor leaving groups may also result in alkene stereoconvergence as a consequence of a loss of rotational selectivity to the best leaving group in a late transition state. The importance of the four-electron interaction (HOMO–HOMO) in determining the energetics and the relative position of the transition state on the reaction coordinate is discussed by invoking a three molecular orbital, four-electron model. The net effect of the four-electron interaction in the presence of a third higher lying empty orbital is to lower the enthalpy of activation.

The addition–elimination reaction of a nucleophile (e.g., RS^-, Cl^-, NH_2R, etc.) involving a carbon–carbon double bond is an intriguing process because ostensibly it involves the interaction of two nucleophilic species. The reaction typically occurs with an alkene bearing a substituent with lone pairs of electrons that would tend to increase the apparent nucleophilicity of the double bond. Recent experimental studies on nucleophilic vinylic substitution[1] have addressed one of the most important mechanistic questions remaining: Is the overall substitution reaction a single-step or a multistep process? In general, vinyl halide substitution occurs with nearly complete retention of configuration[2a,b]

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[1] (a) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (b) Rappoport, Z.; Avramovitch, B. *J. Org. Chem.* **1982**, *47*, 1397.

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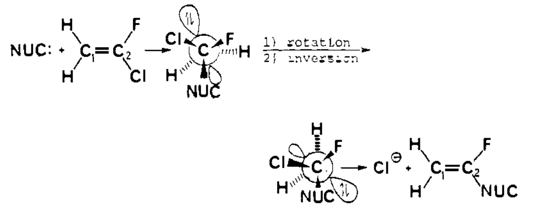
which has supported the contention that the reaction is concerted (eq 1).[2c–e] However, with activating substituents at C_β that can stabilize a long-lived carbanion by resonance, a loss of stereospecificity can result, and in some cases, complete stereoconvergence is noted. In the absence of a unique carbanionic intermediate, the initial reaction coordinate must involve a nucleophilic addition, while late along the reaction pathway, an elimination reaction is involved that requires the necessary molecular reorganization to place the developing carbanionic center antiperiplanar with the leaving group.



(1)

In an early account, Modena[2a] concluded that the nucleophile attacks C_α perpendicular to the nodal plane containing the leaving group. It was suggested that bond making was well advanced at the transition state but that relatively little C–X bond rupture has occurred. Significantly, he also recognized that the carbanion at C_β was either planar or rapidly inverting. More recently Rappoport[1] has presented convincing evidence in support of a variable transition state theory[3] analogous to that advanced for E_2 elimination reactions involving alkenes.[4] In this scheme, a multistep route was suggested for alkenes with poor nucleofuges (leaving groups) or with alkenes activated by strongly resonative electron withdrawing groups. However, in those cases where an intermediate carbanion cannot be sufficiently stabilized, a concerted process was postulated to be involved.

An early theoretical analysis of the mechanism of the nucleophilic addition reaction by Stohrer suggested that a concerted pathway with a planar carbanion could explain the observed stereochemistry in a majority of cases.[2b] Previous work had assumed a stepwise mechanism.[2c] More recently, MO calculations by Texier[2d] and Rappoport[2e] led them to the conclusion that retention of the alkene stereochemistry should be observed for a concerted pathway with both nonplanar and planar carbanions. It was suggested that a multistep process could also proceed with retention. Additionally, the importance of hyperconjugation in stabilizing the developing carbanion with the σ^* orbital of the leaving group was recognized by these authors. By applying a hyperconjugative model to a series of calculated rotational barriers for planar β-substituted ethyl anions, it was concluded that hyperconjugation was the major factor that determines the stereochemistry of nucleophilic vinylic substitution. We now provide theoretical evidence based upon ab initio calculations for an entire spectrum of transition states that vary from substitution involving a long-lived carbanionic center, where a multistep process is required, to one where the nucleophile–C_α bond is not yet fully developed. We provide a rationale for (1) the activating influence of halogen substituents toward nucleophilic addition, (2) loss of stereospecificity with alkenes bearing resonating substituents, (3) substitution with retention of configuration with simple alkenes, (4) the origin and the relative position of the transition state on the reaction coordinate, and, most importantly, (5) the role of the four-electron interactions and the principle of atomic orbital cancellation in these nucleophilic substitution reactions. We mainly wish to stress the importance of these theoretical concepts and emphasize that we have chosen this particular nucleophilic addition reaction because it best serves to exemplify the significance of HOMO–HOMO interactions in such reactions. Many of our mechanistic conclusions are based upon earlier experimental and theoretical observations that are cited in the present study.

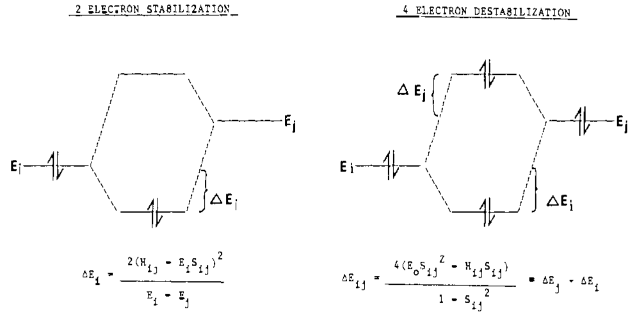


Figure 1.

Theory and Method of Calculation

Perturbation theory allows one to construct the molecular orbitals of complex molecules from those of simpler subsystems. In a similar fashion, the molecular orbitals of a transition state can in principle be approximated from the orbitals of the reactants. There are two basic types of orbital interactions that will affect the energetics of orbital mixing (Figure 1). In a two-electron interaction the filled orbital is stabilized (ΔE_i) while its empty antibonding complement, although elevated in energy, is without effect upon the energetics of the system. A four-electron interaction is destabilizing as a consequence of the filled antibonding combination being increased (ΔE_j) in energy to a greater extent than the lower bonding combination is stabilized ($\Delta E_j > \Delta E_i$). The destabilization energy (ΔE_{ij}) is the difference in the orbital changes relative to the energy of the unperturbed levels. This basic equation for ΔE_{ij} may be derived by solving exactly the secular determinant for a simple two-orbital problem (e.g., H_2^+ or C_2H_4)[5] including overlap.[6] That the in-phase bonding combination has been lowered in energy less than the out-of-phase orbital has been elevated has not been proven absolutely but is based upon a convincing plausibility argument.[7]

Frontier molecular orbital (FMO) theory normally ignores the four-electron interaction, using only the HOMO–LUMO interaction to explain features of differential reactivity. This has been considered to be a reasonable assumption since the four-electron destabilization (ΔE_{ij}) is small relative to the overall magnitude of the orbital splitting (Figure 1). It has been generally assumed that the destabilization energy becomes larger with increasing S_{ij} but is independent of $E_i - E_j$.[6d] We emphasize that the *magnitude of the orbital splitting is proportional to the energy difference* between the interacting levels, E_i and E_j, just as in the case for a two-electron interaction. Four-electron splittings are consistently larger in absolute magnitude than two-electron stabilization energies since the former interactions are usually between orbitals of comparable energy while the latter involves one filled and one empty orbital, which are normally well separated in energy. Consequently, when the energy levels of the HOMO's of two approaching reactants are close in energy, the four-electron interaction will have a significant effect upon the overall energetics of the reaction. This interaction can be responsible for a large portion of the activation energy and is fundamental to understanding the derivation of the resultant MO's in the transition state.

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[5] For a derivation of the secular equations for a simple Hückel treatment involving two nuclei, see: Roberts, J. D. "Molecular Orbital Calculations"; W. A. Benjamin, Inc.: New York, 1962; p 28.

[6] (a) Epiotis, N. D.; Yates, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 461. (b) Baird, N. C.; West, R. M. *Ibid.* **1971**, *93*, 4427. (c) Muller, K. *Helv. Chim. Acta* **1970**, *53*, 1112. (d) The destabilization is proportional to the mean of E_i and E_j. For a discussion, see: Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yales, R. L.; Bernardi, F. "Topics in Current Chemistry"; Springer-Verlag: New York, 1977; p 7. Houk, K. N. *Top. Curr. Chem.* **1979**, *79*, 1.

[7] Libit, L.; Hoffmann, R. *J. Am. Chem. Soc.*, **1974**, *96*, 1370, see Appendix I.

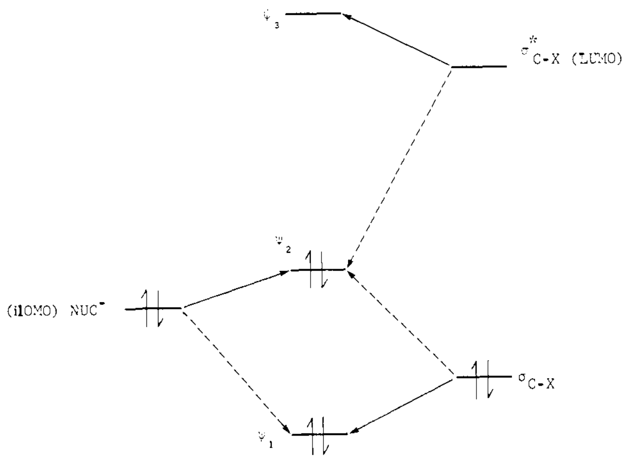

Figure 2. Orbital interactions in nucleophilic displacements.

The significance of the four-electron interaction has been recognized in rotational barriers of hydrazines and peroxides where electron repulsion of lone pairs is involved. We advocate that such interactions are also important in a variety of reactions and use the simple S_N2 displacement at saturated carbon to illustrate this point. The HOMO of ammonia (−0.327 au) is calculated (STO-3G) to be much closer in energy to the filled σ level of methyl iodide (σ_{C-I} = −0.395 au) than to the σ^* level (LUMO = +0.309 au) of the C−I bond. The combined orbital interactions (Figure 2) serve to elevate the energy of a filled MO closer to the σ^* (LUMO) level. One of the basic tenets of PMO theory is that the HOMO–LUMO gap must narrow along the reaction coordinate. This has been referred to as the principle of frontier orbital narrowing.[8] The energy required to raise the antibonding combination of the four-electron interaction, the "effective HOMO" (ψ_2), is largely compensated for by the stabilization of the lower lying bonding MO (ψ_1). As one proceeds along the reaction coordinate, this repulsive interaction between two filled levels induces a C−X bond elongation, which is, in principle, attended by a lowering of the σ^*_{C-X} level. However, this narrowing of orbital energies imparts stabilization to ψ_2 as a result of its developing two-electron interaction with the LUMO (σ^*_{C-X}). This two-electron interaction will result in an increase in the energy of the empty σ^*_{C-X} orbital. In practice, the resultant energy of the σ^*_{C-X} level will depend upon the extent of C−X bond stretching and the magnitude of the two-electron interaction as one proceeds along the reaction coordinate (vida infra). Thus, the four-electron interaction is responsible for the elevation of HOMO and may also be accompanied by a lowering of LUMO along the reaction coordinate. In this manner, we can understand how reactions where the reactants have a large initial HOMO–LUMO energy gap (>100 kcal/mol) can proceed at ambient temperature with comparatively low activation energies. This argument suggests that it is beneficial to extend the commonly used FMO treatment of two MO's to include a three MO model containing four electrons (Figure 2) where the effect of the four-electron interaction, *in the presence of a higher lying empty orbital of the correct symmetry*, can be net stabilizing at the expense of an empty orbital that is increased in energy.

If the orbital interactions shown in Figure 2 have any merit, then the phasing or the sign and relative magnitudes of the atomic orbital coefficients of HOMO should reflect this orbital mixing. For example, the HOMO of a simple S_N2 reaction (Figure 2) should be comprised of the antibonding combination of the four-electron interaction (ψ_2) mixed in a bonding fashion with the σ^*_{C-X} orbital. For a reversible reaction which has a symmetric transition state, such as chloride ion reacting with methyl chloride, the two chlorine atom atomic coefficients of the wave function (in the LCAO approximation) will reflect the molecular symmetry (Figure 3). This set of molecular orbitals describing the atomic interactions along the principal axis of reaction may be derived by FMO theory by using the fragment orbitals and orbital mixing given graphically in Figure 2. Contrary to what is typically assumed, the HOMO (ψ_{22}) for this transition state has no contribution from the carbon atomic p orbital on the axis of the reaction. Similarly, the next lowest occupied MO consisting of σ_{C-Cl} orbitals (ψ_{17}) can have no contribution from a carbon s orbital as a consequence of orbital symmetry. To generate these molecular orbitals at the transition state, the net two- and four-electron interactions must achieve atomic orbital cancellation (s and p) on the central atom as a result of enforced combinations of the σ and σ^* orbitals of the carbon-leaving group bond. This principle of orbital cancellation provides a criterion in addition to the total energy to recognize when the transition state has been achieved. Initially, the incoming nucleophile is antibonding to the substrate. At that null point where the attacking nucleophile switches from antibonding to bonding with respect to the central carbon, and the net overlap of the leaving group and the nucleophile to the carbon are the same, a symmetric transition state (Figure 3) will be attained. For an asymmetric transition structure (e.g., F^- + CH_3Cl) located with an extended basis set,[9] the carbon 2p coefficient on the principal axis of reaction is not zero but is still largely diminished by orbital cancellation. For example, the F, C, and Cl p coefficients in HOMO are +0.86, −0.32, and −0.45, respectively, when using this transition-state geometry and an STO-3G basis set. The extent of orbital cancellation in the frontier MO's can also be used to estimate the relative magnitude of two- and four-electron interactions along the reaction coordinate as demonstrated below.

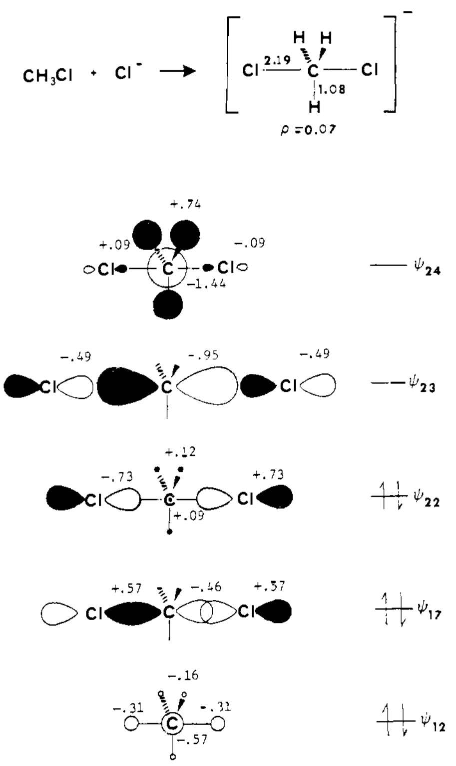

Figure 3. The symmetrical transition state for S_N2 displacement on methyl chloride by chloride ion (STO-3G).

The calculations were performed with the GAUSSIAN 80 series of programs with standard MO theory.[10] Both minimal STO-3G and extended 4-31G basis sets were used. The reactants and products were fully minimized by using energy gradients[10b] employing either a 4-31G or an STO-3G basis set. In some cases the structures were optimized by STO-3G and the energies were compared by using a 4-31G basis on that geometry (4-31G//

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[8] (a) Fukui, K. *Top. Curr. Chem.* **1970**, *15*, 26. (b) Fukui, K. "Theory of Orientation and Stereoselection"; Springer-Verlag: New York, 1975; p 106.

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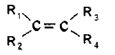
[10] (a) Binkley, J. F.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE* **1981**, *13*, 406. (b) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214.

Table I. Optimized Geometry of Substituted Ethylenes



				bond lengths, Å					bond angles, deg				
R_1	R_2	R_3	R_4	C=C	R_1–C	R_2–C	R_3–C	R_4–C	R_1–C=C	R_2–C=C	R_3–C=C	R_4–C=C	E_{tot}(4-31G), au
H	H	H	H	1.316	1.073	1.073	1.073	1.073	121.99	121.99	121.99	121.99	−77.92216[g]
H	H	H	F	1.305	1.069	1.071	1.066	1.372	119.80	119.00	129.20	120.80	−176.65105[h]
H	H	H	CN[a]	1.320	1.071	1.071	1.072	1.428	120.85	122.17	121.31	123.14	−169.51592[g]
H	H	H	Cl	1.307	1.083	1.082	1.085	1.778	120.18	122.83	124.59	122.64	−536.32590[f]
H	H	F	OH[b]	1.303	1.066	1.066	1.368	1.347	120.40	119.96	122.23	126.71	−251.40521[g]
H	H	F	F	1.299	1.066	1.066	1.342	1.342	120.24	120.24	125.30	125.30	−275.38131[g]
H	H	F	CN[c]	1.309	1.069	1.068	1.368	1.424	120.38	120.92	120.92	126.14	−268.23504[g]
H	H	F	Cl	1.300	1.069	1.066	1.351	1.793	119.80	121.18	123.57	125.15	−635.04625[g]
H	H	F	$^+NH_3$[d]	1.310	1.086	1.084	1.341	1.529	119.21	122.91	129.56	121.43	−231.92955[f]
CN	H	H	F[e]	1.313	1.421	1.070	1.066	1.357	121.74	120.48	127.06	120.20	−268.24058[g]

[a] r_{C-N} = 1.143 Å. [b] r_{O-H} = 0.952 Å, ∠(C-O-H) = 114.94°. [c] r_{C-N} = 1.141 Å. [d] r_{N-H_a}(in plane, syn) = 1.042 Å, r_{N-H_b}(out of plane) = 1.045 Å, ∠(C-N-H_a) = 111.34°, ∠(C-N-H_b) = 107.93°, ∠(H_a-N-H_b) = 107.91°. [e] r_{C-N} = 1.143 Å. [f] 4-31G//STO-3G. [g] 4-31G. [h] Kato, S.; Morokuma, K. *J. Chem. Phys.* 1980, *72*, 206.

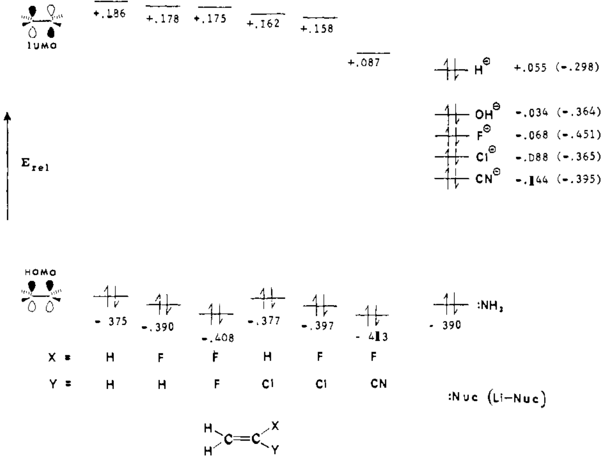


Figure 4. Relative energy levels (minimized, 4-31G (au)) for substituted alkenes and nucleophiles.

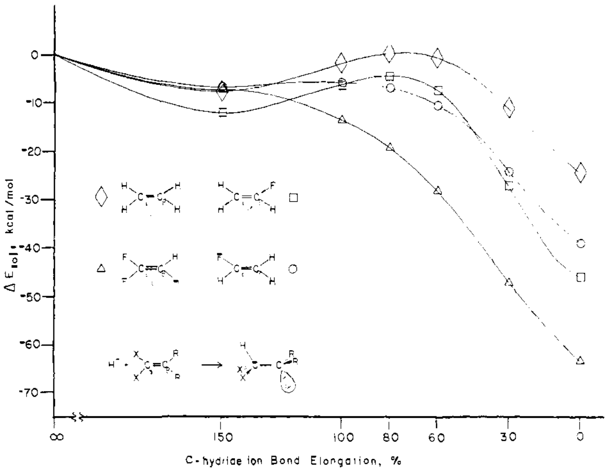


Figure 5. Activation barriers (4-31G) for hydride additions to alkenes at C_α affording an antiperiplanar carbanion.

Table II. Bond Distance (Å) and Energies (kcal/mol, 4-31G) for Ethyl Anions

alkene	r_{C-H}[b]	ΔE[c]	ΔE[d]
$H-CH_2\bar{C}H_2$, 4	1.117	−23.0	−6.2 (2.79)[e]
$H-CHF-\bar{C}H_2$, 5	1.084	−39.2	−7.1 (2.77)[e]
$H-CF_2-\bar{C}H_2$, 6	1.087	−63.6	−7.6 (2.72)[e]
$H-CFCl-\bar{C}H_2$,[a] 7	1.117	−65.7	
$H-CH_2-\bar{C}HF$, 8	1.101	−46.0	−11.9 (2.75)[e]
$H-CH_2-\bar{C}FCl$,[a] 9	1.089	−92.2	

[a] 4-31G//STO-3G basis set. All other anions fully optimized by 4-31G. [b] Optimized C-hydride bond distance for the antiperiplanar carbanion. [c] Calculated ΔH for addition of H^- to the alkene. [d] Exothermicity of H^- addition to alkenes constrained to a C-hydride bond distance 150% of r_{C-H} (see above Figure 5). [e] 150% elongation of r_{C-H} given in angstroms.

STO-3G). For a description of the reaction pathway, the nucleophile–carbon distance (r_1) was chosen as the independent variable, and the entire molecule was initially minimized with the C_β carbanion constrained to a geometry antiperiplanar to the incoming nucleophile. The Nuc–C_α bond length was then elongated by 30, 60, 80, 100, and 150%, affording a preliminary scan of the potential energy surface. All other variables were fully minimized. The barrier to C_α–C_β bond rotation with concomitant inversion decreases as r_1 is decreased. At the point where this barrier falls to zero and rotation is exothermic, the reaction has shifted from an addition to an elimination mechanism. We have defined the last stable calculated geometry prior to exothermic bond rotation as the "transition point" between an addition and elimination pathway, as there are often no true transition states for these highly exothermic gas-phase reactions. We did calculate a transition state for chloride ion displacing chloride ion (Figure 8).

Effect of Substituents on Nucleophilic Addition

The addition of a nucleophilic species to a carbon–carbon double bond is typically a difficult reaction and requires activation of the double bond by a π-bonding substituent (e.g., C=O, C≡N) or by a σ-electron-withdrawing group such as a halide. In the former case, a resonance-stabilized intermediate may result in charge delocalization. The electronic factors involved in alkene activation by a halide substituent are less obvious, and this poses one of the questions we now address.

We first considered the addition of hydride ion to alkenes **1**–**3** (Figure 5) to assess the role of a fluoro substituent in activating nucleophilic addition and in stabilizing the resultant anion. The optimized geometries for a series of alkenes are given in Table I. We examined the possible effect of the energy levels of the frontier MO's since the principal interaction early along the reaction coordinate is that of the relatively high lying hydride (HOMO) anion with the π* orbital (LUMO) of the alkene. From the series of calculated FMO energies in Figure 4, it is immediately obvious that increasing the number of fluoro substituents has only a modest effect upon the energy of the LUMO. As anticipated, a cyano substituent markedly lowers the LUMO, which is reflected in its reactivity in the Michael reaction.

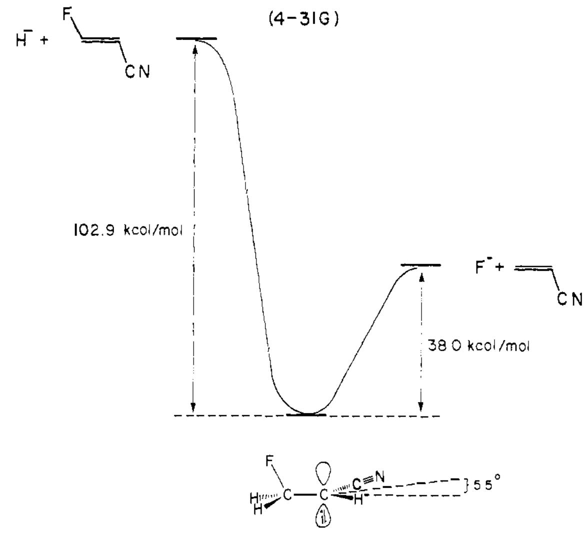
We next examined the possibility that the increased reactivity of a vinyl halide toward a hydride addition may be attributed to the relative stability of the resulting anion (Table II). We note that highly exothermic gas-phase reactions of this nature typically proceed without activation. In each case the approaching hydride ion was initially stabilized as it interacts with the alkene. We arbitrarily chose a point on the reaction trajectory (Figure 5) where the C_α–hydride bond length was 150% greater than that in the minimized antiperiplanar carbanion. At an r_{C-H} of 2.75 Å a β-fluoro substituent increases the stability of the aggregate by only 5.7 kcal/mol relative to the comparable structure with ethylene, with a negligible energetic effect of α-fluoro substituents early on the reaction coordinate (Table II).

The α-halo substituents do exert a marked effect upon the early trajectory for nucleophilic addition. It has been reported that hydride[11] and borohydride[12] addition to formaldehyde show a tendency for the $H^-\cdots C{=}O$ angle to approach 110° and 115°, respectively, as the carbon atom becomes tetrahedrally coordinated. The angle of approach of fluoride ion to ethylene has been reported to be 119°.[13] We note an angle of approach of hydride to **1**–**3** at a C_α–H bond distance of approximately 2.75 Å (150% r_{C-H} bond elongation) of 109°, 137°, and 165°, respectively. All three reactions converge to a hydride trajectory of about 120° as the C_α–H bond distance is shortened to 60% r_{C-H} bond elongation.

The addition of hydride ion to ethylene has been reported by Houk[14] to afford an antiperiplanar anion with an activation barrier of 1.9 (4-31G) and 16.6 (4-31G + CI) kcal/mol. The preferred trans bending of the ethylene moiety was attributed to a favorable mixing between the π^*_{CC} and σ^*_{CH} bonds. We find an approximate barrier (relative to the structure at 150% r_{C-H}) of 7.8 and 1.2 kcal/mol (4-31G) for hydride addition to **1** and **2**, while reaction with **3** occurs without activation. Hydride addition to **2′** affording α-fluoro anion **8** has a barrier of 7.4 kcal/mol, comparable with that of addition to ethylene. It is also evident (Figure 5) that the transition state for hydride addition comes earlier on the reaction coordinate as the number of α-fluorine substituents is increased.

We note that although the barrier for addition to vinyl fluoride at C_α, affording **5**, is lower than addition at C_β, affording **8**, the thermodynamic stability of α-halo anions is greater than that of β-halo anions (Table II). The greatest stabilizing influence in this series of ethyl anions is due to an α-chloro substituent. Thus, the α-dihalo anion **9** is considerably more stable than either **4** or the α-fluoro anion **8** relative to reactants despite the fact that the carbanion is gauche to the stabilizing halogen atoms in **5**–**7**; polarization[15a] or hyperconjugation[2b,e,15b] effects are expected to be small in these constrained β-halo anions. The increased reactivity of a vinyl halide toward nucleophilic addition[1,2] may thus be attributed to the relative stability of the resultant anions. If the constrained β-fluoro tetrahedral anion **5** is allowed to rotate so that the electron pair is either syn- or antiperiplanar to the fluorine, elimination of F^- is exothermic by 19.6 and 14.3 kcal/mol (4-31G), respectively.[13] This synperiplanar carbanion was shown to undergo inversion of configuration at C_β to form the anti anion without energy of activation.

We next sought to examine the effect of a π-bonding substituent on the stability of a β-fluoro anion. Houk has examined the addition of ammonia to cyanoacetylene affording a stable β carbanion.[16] We found that addition of hydride ion to 2-cyano-1-fluoroethylene afforded the *stable carbanion* **10** in which the developing anionic center has rotated antiperiplanar to the fluorine leaving group (Figure 6). This anion, which is only 5.5° from planarity, has an activation barrier of 38.0 kcal/mol for expulsion of F^-. A planar anionic center in **10** exhibited an increase in energy of only 0.26 kcal/mol (4-31G). A stable syn anion could not be found. These data suggest that a substituent which can stabilize a β-halo anion by resonance will afford a sufficiently long-lived anion to allow free rotation about the C–C bond. This is consistent with experimental observations where such substitution has resulted in either partial or complete stereoconvergence.[1,2]



10

Bond Length, Å	Bond Angles, deg.	
$r\ C_1{-}C_2 = 1.434$	$> FC_1C_2 = 117.2$	$> H_1C_1C_2F = 117.2$
$r\ C_1{-}F = 1.524$	$> H_1C_1C_2 = 113.8$	$> H_2C_1C_2F = 115.6$
$r\ C_1{-}H_1 = 1.080$	$> H_2C_1C_2 = 113.4$	$> H_3C_2C_1F = 80.8$
$r\ C_1{-}H_2 = 1.081$	$> H_3C_2C_1 = 119.0$	$> C_3C_2C_1F = 88.2$
$r\ C_2{-}H_3 = 1.074$	$> C_3C_2C_1 = 122.6$	
$r\ C_2{-}C_3 = 1.385$	$> NC_3C_2 = 180.0$	
$r\ C_3{-}N = 1.164$		

Figure 6. Geometry and relative energy of the 3-fluoropropionitrile anion (4-31G).

The Effect of the Nucleophile on the HOMO–HOMO Interaction

The addition of a nucleophile to an alkene must involve both attractive and repulsive interactions. Those reactions where the HOMO of the nucleophile lies closer in energy to the alkene LUMO (π*) should be exothermic and have an early transition state in accordance with the Hammond postulate.[17] However, the addition of ammonia, which has a calculated HOMO at −0.391 au, to 1-chloro-1-fluoroethylene (**11**) with a HOMO at −0.397 au (Figure 4) should be repulsive in nature and exhibit a very late transition state. As the reaction proceeds, the filled antibonding combination ($NH_3 - \pi$) or ψ_2 (Figure 2) must be elevated in energy sufficiently to mix with the π* (LUMO) orbital. We reiterate that much of the enthalpy of activation for the repulsive interaction is energetically compensated for by the stabilization energy (ΔE_i) of ψ_1, the bonding combination ($NH_3 + \pi$) that decreases in energy. The dominant four-electron interaction early along the reaction coordinate can contribute to the endothermicity of such a reaction in addition to the increase in enthalpy resulting from extensive bond breaking. The initial HOMO–LUMO interaction for this nucleophilic addition will be minimal since the energy gap between the frontier orbitals of the reactants is calculated to be 345 kcal/mol (0.548 au, Figure 4). In contrast, exothermic reactions will experience a net stabilizing two-electron (HOMO–LUMO) orbital splitting early on the reaction coordinate as the high lying nucleophile is stabilized by interaction with LUMO. We recognize that the calculated energies of these virtual orbitals are too high in energy, but we stress the relative changes in energies. The most striking feature of the FMO energies given in Figure 4 is that the relative changes in frontier orbital energies of the alkenes are small relative to the energy differences of the HOMO's of the nucleophiles. Consequently, we should be able

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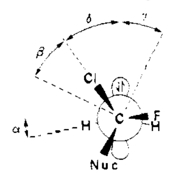
Table III. Optimized Geometries (STO-3G) and Energetics (ΔH_{TP}, kcal/mol) for the Transition Point for Nucleophilic Substitution with 1-Chloro-1-fluoroethylene and Reaction Energies (4-31G) at Infinite Separation (ΔH, kcal/mol)



	:NH_3	Cl^-	CN^-	F^-	OH^-	H^-
r_{C-Nuc}, Å	1.725	2.125	1.950	1.786 (1.745)[a]	2.148	1.830 (2.011)[a]
% elongation[b]	13	19	32	33 (30)	59	72 (89)
r_{C-Cl}, Å	1.90	1.88	1.93	2.30 (1.96)	1.92	2.50 (2.00)
% elongation	6	5	8	28 (9)	7	40 (12)
α, deg	0.08	9.79	7.76	−6.54 (4.53)	5.22	−4.8 (5.64)
β, deg	18.55	25.09	22.30	15.20 (20.56)	21.58	13.6 (22.5)
γ, deg	10.19	2.24	13.22	64.24 (11.27)	12.08	70.9 (6.68)
δ, deg	61.27	62.67	54.48	10.57 (58.17)	56.34	5.5 (60.82)
ΔH_{TP}	+44.24	+2.74	−12.43	−130.84 (−27.49)	−55.32	−88.24 (−16.64)
ΔH	+123.09	0.0	−49.95	−71.83	−98.15	−131.52

[a] Fully minimized, 4-31G. [b] Relative to the product alkene, Table I.

to predict both the position of the transition state and the relative enthalpy of nucleophilic addition for this series of nucleophiles. Inclusion of the lithium cation results in a lowering of the frontier orbital of the nucleophile (Figure 4), which would tend to decrease the two-electron HOMO–LUMO interaction. The position of the transition state on the reaction coordinate will also obviously be influenced by solvent effects.

Employing 1-chloro-1-fluoroethylene (**11**), which is an experimentally viable alkene in this reaction as our "electrophile", we observe the anticipated reactivity trend for nucleophilic addition (Figure 7). Addition of hydride ion to **11** is exothermic while reaction of **11** with NH_3 is endothermic. The "transition point", where the reaction surface changes from addition to elimination, for the former is early on the reaction coordinate, occurring without activation with a C–hydride bond distance of 1.83 Å (72% r_{C-H} elongation, Table III). In contrast, addition of NH_3 had a $\Delta H^{*} = 44.2$ kcal/mol with the C–N bond being almost completely formed ($r_{C-N} = 13\%$ elongation) with the anion at C_β being essentially planar ($\alpha = 0.08°$) in this highly endothermic reaction.

Cyanide ion has a HOMO orbital energy approximately half-way between that of the HOMO and LUMO of **11** (Figure 4). Because the two- and four-electron contributions are of comparable magnitude, the relative energy of the HOMO of CN^- does not change very much as one proceeds along the reaction coordinate until after the transition point. Consequently, addition of CN^- to **11** is only mildly exothermic ($\Delta H_{TP} = 12.4$ kcal/mol) and has a fairly late transition point (C_α–CN bond elongation 32%). In general, we noted that the HOMO of the nucleophile (Figure 4) changes to approach in the limit an energy approximately equidistant between the HOMO and LUMO of alkene **11** as the nucleophilic addition progresses.

Since most of the reactions with **11** (Table III) proceeded without activation energy, we selected a "transition point" on the reaction surface where the addition merged into an elimination reaction. We minimized the initial carbanion formed by nucleophilic addition with C_α–C_β bond rotation constrained to prevent elimination of Cl^- (or F^-) as described above. We then allowed the carbon–nucleophile bond distance to vary with removal of the rotational constraint. Early on the reaction coordinate, C_α–C_β bond rotation is endothermic. As the nucleophile approaches, the barrier diminishes to zero and the reaction sequence then becomes exothermic. The last calculated stable structure prior to rotation is defined as the "transition point" (solid points, Figure 7). The geometric and energetic parameters for this series of reactions is compared in Table III (STO-3G). Hydride and fluoride nucleophiles, both of which are poorly represented by the STO-3G basis set, are clearly out of line. Recalculation of hydride and fluoride addition using a 4-31G basis set showed that the position of the "transition points" changed only slightly, while providing a more acceptable geometry. The "transition points" for NH_3 and Cl^- exhibit an energy barrier to addition and should be close in energy to the actual transition states. The addition of Cl^- to **11** involves a degenerate reaction and should proceed through a symmetrical transition state. The calculated transition state for Cl^- addition afforded C–Cl bond distances of 2.13 Å and an energy barrier of 22.5 kcal/mol (4-31G, Figure 8; 6.2 kcal/mol by STO-3G). In general, the relative position of the transition points and their exothermicities parallel the energy of the nucleophile. Thus, the higher the energy of the attacking nucleophile, the more exothermic the reaction (Figure 7, Table III).

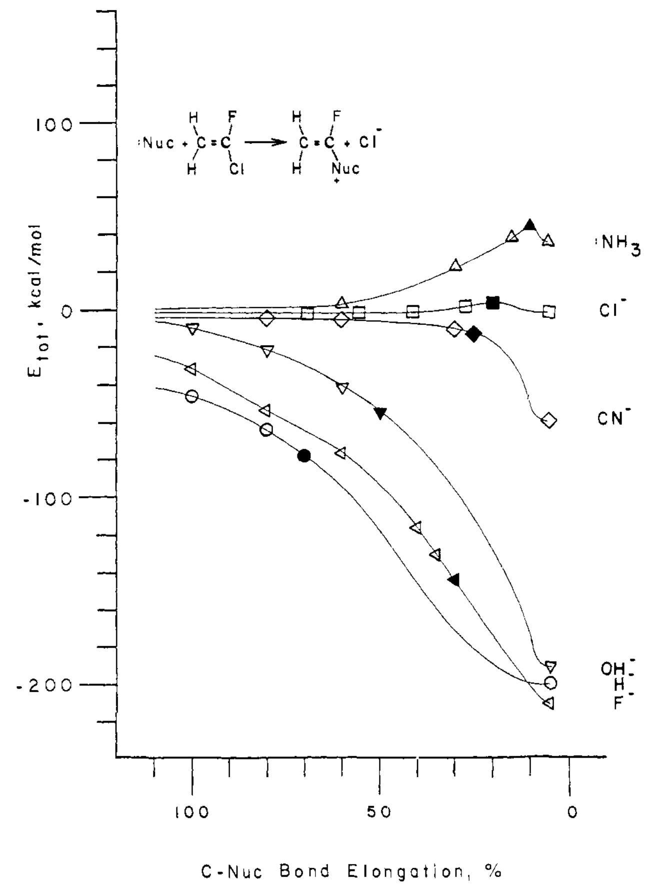
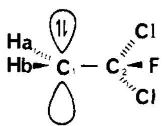
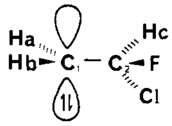


Figure 7. Energetics of nucleophilic addition to 1-chloro-1-fluoroethylene with transition points (solid) including formation of a product cluster (STO-3G).

The relative amounts of two- and four-electron interactions can also be assessed by examining the orbital cancellation of the pertinent FMO's as noted in the exercise above for a simple S_N2



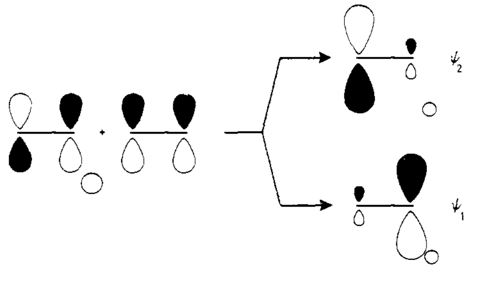
Bond Lengths, Å			Bond Angles, deg.		
r C_1-C_2	=	1.327	>FC_2C_1	=	119.8
r C_2-F	=	1.359	>ClC_2C_1	=	117.5
r C_2-Cl	=	2.133	>HaC_1C_2	=	118.6
r C_1-Ha	=	1.071	>HbC_1C_2	=	121.1
r C_1-Hb	=	1.065	>FC_2C_1Cl	=	124.5



Bond Lengths, Å			Bond Angles, deg.			Bond Angles, deg.		
r C_1-C_2	=	1.339	>C_1C_2Hc	=	122.0	>HcC_2C_1F	=	115.0
r C_2-F	=	1.375	>C_1C_2F	=	118.6	>HcC C Cl	=	¯112.5
r C_2-Cl	=	1.955	>C_1C_2Cl	=	115.7	>HcC_2C_1Ha	=	-91.0
r C_2-Hc	=	2.0113*	>C_2ClHa	=	118.7	>HcC_2C_1Hb	=	77.7
r C_1-Ha	=	1.071	>C_2C_1H	=	120.8			
r C_1-Hb	=	1.066						

Figure 8. Geometry and energy (4-31G) for the hydride transition point and chloride transition state in nucleophilic addition to chlorofluoroethylene.

displacement. The phase and magnitude of the atomic orbital coefficient of the "electrophilic carbon center" involved in bonding to the nucleophile will depend upon the mixing of the π and π^* orbitals with the HOMO of the nucleophile. These initially orthogonal subsystem wave functions will being to mix with each other primarily in second-order perturbation theory.[7] To illustrate this point, we examine the transition point for hydride addition to ethylene. The calculated HOMO (Figure 9) that corresponds to ψ_2 in Figure 2 has a contribution from hydride and the carbanion at C_β. Significantly, there is *no contribution from the atomic p orbital coefficient at* C_α, the "electrophilic center" bonding to the nucleophile. This FMO can be derived by using the orbital coefficient cancellation arguments presented above. Early along the reaction coordinate the hydride ion mixes with the π^* orbital in a bonding way affording the (π^* + Nuc) combination (Figure 10) by a two-electron interaction. As that orbital decreases in energy, and the π orbital is elevated along the reaction coordinate due to the C-C bond stretch, mixing of the π orbital into (π^* + Nuc) in an antibonding way will cause the atomic p orbital coefficient at C_α in ψ_2 (HOMO) to diminish as illustrated in eq 2. Consequently, at the transition point for H^- addition (Figure 9), we see in this case an exact cancellation of the p atomic orbital in the antibonding combination derived from the orbital mixing in eq 2.



(2)

The repulsive interaction of a "poor nucleophile" (low lying HOMO) will afford the (π − Nuc) combination (Figure 10) in an analogous manner. This is demonstrated (Figure 11) by the orbital interactions along the reaction coordinate for nucleophilic addition of ammonia to **11**, where the resultant symmetry in HOMO at the transition point is (π − Nuc). This is a late "transition point" where the two-electron component of orbital mixing (HOMO–LUMO) is reduced in magnitude and orbital cancellation is incomplete. Nonetheless, the dominant HOMO–HOMO interaction is clearly reflected in the orbital phasing of HOMO in agreement with our analysis above based upon energy considerations. Interestingly, even though Cl^- is closer to LUMO in **11** than to HOMO (Figure 4), the four-electron interaction, based upon orbital cancellation considerations, surpasses the classical HOMO–LUMO orbital mixing (Figure 12) in the addition of Cl^- to **11** (i.e., π − Nuc symmetry).

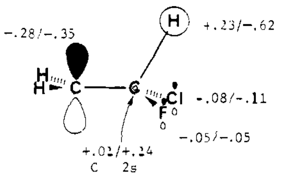


Figure 9. HOMO for the calculated transition point (4-31G) for hydride addition of chlorofluoroethylene with orbital coefficient (inner/outer).

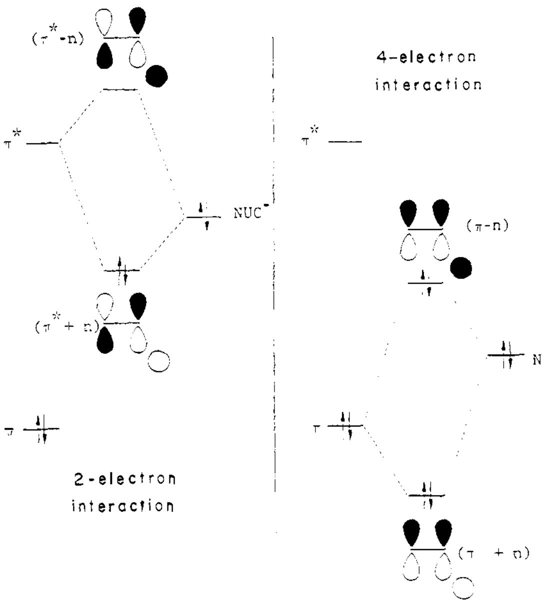


Figure 10. Frontier molecular orbital interactions involved in hydride addition to ethylene.

The overall concept of frontier orbital narrowing[8] should also be addressed at this point. In principle, the energy of the donor (HOMO) should rise as one proceeds along the reaction coordinate while the energy of the acceptor (LUMO) becomes lower in the event of transfer of charge. In this approximation bond weakening will be followed by a "serious narrowing of inter-.rontier energy level separation".[8] However, this oversimplified theory now requires modification when viewed within the context of the three molecular orbital, four-electron model (Figure 2 or 14). When the reaction coordinate is dominated by an early two-electron stabilizing influence, such as that involved in H^- addition to **11**, the HOMO ψ_2 (π^* + H^-) has decreased in energy by 63 kcal/mol (4-31G) while LUMO (ψ_3, π^* − H^-) has increased in energy by 94 kcal/mol, resulting in a *widening of the HOMO–LUMO energy gap* of 157 kcal/mol. When the energy of the nucleophile (HOMO) is intermediate between the HOMO–LUMO energy gap of **11**, such as Cl^- or CN^-, then the magnitude of the two- and four-electron interactions should be comparable and the energy of Cl^- should only experience a modest change in energy (17 kcal/mol) while ψ_3 should increase (67 kcal/mol) and ψ_1 decrease (59 kcal/mol) substantially at the transition state (Figure 12) due to orbital splitting (Figure 14). Ironically, it is when a large HOMO–HOMO interaction is involved that one should expect a narrowing of the HOMO–LUMO energy gap. For example, when NH_3 adds to **11**, ψ_1 (π + NH_3) is stabilized by 60 kcal/mol,

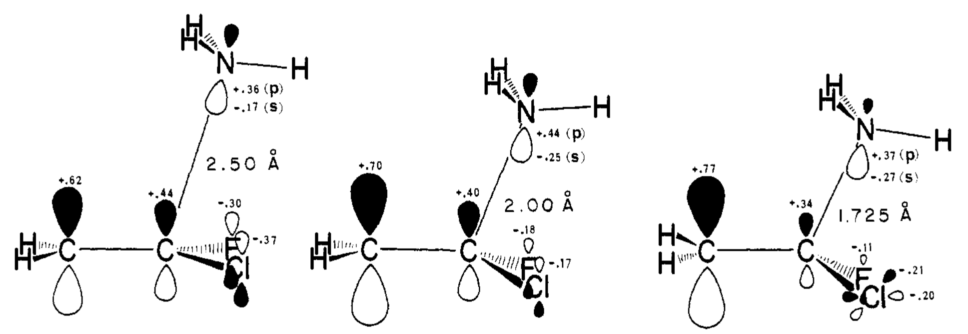


Figure 11. Development of HOMO along the reaction coordinate for nucleophilic addition of ammonia to the vinylic carbon.

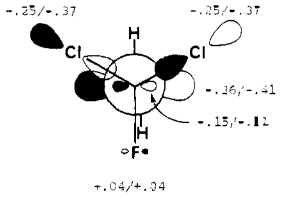


Figure 12. HOMO for the calculated transition state (4-31G) for chloride addition to chlorofluoroethylene with orbital coefficients (inner/outer).

ψ_2 ($NH_3 - \pi$, Figure 11) is increased in energy 69 kcal/mol, while ψ_3 ($\pi^* - NH_3$) has been elevated by only 13 kcal/mol. Thus, the two-electron contribution to the composition of ψ_2 Figure 14) is considerably less than the HOMO–HOMO interaction. The net frontier orbital narrowing is calculated to be 56 kcal/mol at the transition point. The initial HOMO–LUMO gap for this reaction is 381 kcal/mol (Figure 4). Significantly, highly exothermic reactions with an early transition state involving a dominant two-electron interaction need not experience orbital narrowing on the reaction pathway. It is the energetics involved in the requisite orbital interactions resulting in formation of the central orbital, ψ_2, that is vital to our understanding of the mechanism of organic reactions.

One must keep in mind, however, that these calculations simulate gas-phase reactions, and consequetnly, the energy of the nucleophilic anions would be "artificially high" if one were to extrapolate these results to solution conditions. The effect of solvation on these charged nucleophiles would obviously result in a drastic decrease in the HOMO energies as evidenced by the lithiated species (Figure 4). This stabilization would bring the nucleophile HOMO closer to the HOMO level of the alkene, increasing the four-electron contribution to the overall reaction energetics and imparting a decrease in the HOMO–LUMO energy gap.

The Mechanism of Nucleophilic Substitution at a Double Bond

Our detailed analysis of the orbital interactions involved in nucleophilic addition reactions allows us to refine the existing mechanism.[1,2] We suggest that the developing nonplanar carbanion is formed anti to the incoming nucleophile and that the incipient anion is initially stabilized by a long-range two-electron interaction with the σ^* *oribtal of the developing carbon–nucleophile bond*. Using the principle of microscopic reversibility, when a σ bond is stretched to a point where it has a relatively long carbon–nucleophile bond distance, the σ bond is high in energy and its σ^* component is correspondingly relatively low in energy.[18] In a variable transition state theory *this developing carbanion is the point of divergence* between a concerted single step and a multistep addition mode (Figure 13). This study provides the first evidence that a short-lived carbanion is not a requirement for a concerted vinylic elimination. The smooth transition from a nucleophilic addition to an elimination surface that embodies a C_1–C_2 bond rotation involves a continuous path that is set into motion long before an anion, that exists as a discrete energy minimum, is even starting to develop.

In the concerted mechanism (path a) the partially formed β carbanion rotates (30°) *syn toward the best leaving group* (i.e., the bond with the lowest lying σ^* orbital) affording **13**, where X and Z are eclipsed ((Figure 13), with concomitant inversion of configuration at C_β.[13] Elongation of the C-leaving group σ bond, in concert with rotation, lowers the level of σ^* resulting in increasing stabilization of the carbanion along the reaction coordinate. The relative stability of this entity on the reaction pathway will depend on *both* the leaving group and the nucleophile since the essentially *planar anion* in transition-state **13** is interacting with the σ^* orbital of both the C–Y and the C–Nuc bonds. The orbital cancellation in HOMO is demonstrated pictorally in Figure 12 for the symmetrical transition state of Cl^- reacting with **11**. Completion of the 60° C_α–C_β bond rotation with attendant inversion at C_β affords **14a**, where the carbanionic center is anti to the leaving group, affording the most energetically favorable electronic alignment for an elimination reaction.[13] The anti β anion need not be completely tetrahedral, and we noted expulsion of the leaving group when the angel α (Table III) deviated from planarity by 5–10°. Elimination of Y is exothermic and without an activation barrier (to form the gas-phase cluster). We suggest that this sequence of events proceeds without a discrete intermediate and that the C_α–C_β bond rotation, and the ensuing elimination reaction, is initiated at varying positions along the reaction coordinate to maximize stabilization of the developing carbanion. The calculated percent elongation of the C–Nuc bond at this "transition point" varied from 72 to 13% for hydride ion and ammonia, respectively (Table III). This overall pathway must result in retention of configuration.

Stereoconvergence can result when a relatively poor leaving group (e.g., F^-) is involved, and the developing carbanion exhibits little selectivity in aligning with either Y or X in **12**. Since the σ^* levels of such nucleofuges are characteristically high, there is little stereoselection and diastereomeric alkenes may result. This important point was recognized by Apeloig and Rappoport[2c] in their theoretical study using calculated rotational barriers for a series of β-substituted ethyl anions. They were able to provide a quantitative measure for the hyperconjugative ability of various leaving groups, thereby ascertaining the preferred direction of rotation of the carbanionic intermediate. These authors, however, still advocate a short-lived carbanionic intermediate in a concerted rearrangement. In such cases, the carbanion is likely to be more highly developed. Such a stereoconvergent process, however, could still be concerted when X = H. A 120° bond rotation is required in order to eliminate Y with inversion of alkene configuration. A qualitative MO analysis by Texier[2d] showed that the 60° rotation is preferred over the 120° rotation in both single step and multistep pathways.

In a multistep mode, the β-carbanion **12** is a long-lived intermediate allowing thermodynamic equilibration of **14a** and **14b**. The product distribution would then be subject to the constraints of the Curtin–Hammett principle.[19] We point out that formation of **14a** requires inversion at C_β, whereas **14b** involves only C_α–C_β rotation. Potentially, a nonplanar stabilized carbanion (e.g.,

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[18] Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

[19] Lambert, J. B. "Physical Organic Chemistry"; Holden-Day, Inc.: San Francisco, 1978, p 90.

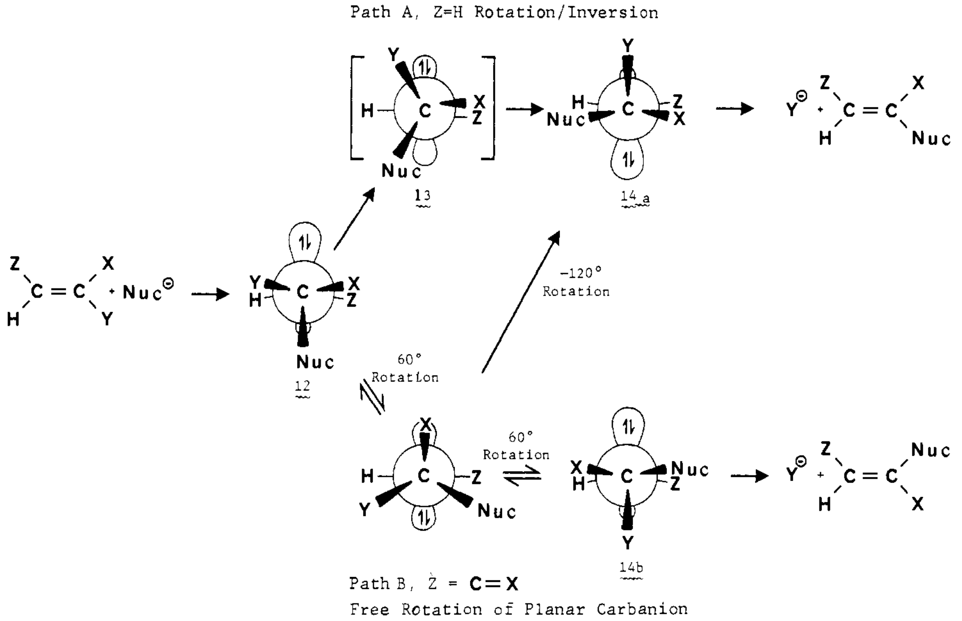

Figure 13. An overall mechanism for nucleophilic displacement at vinylic carbon.

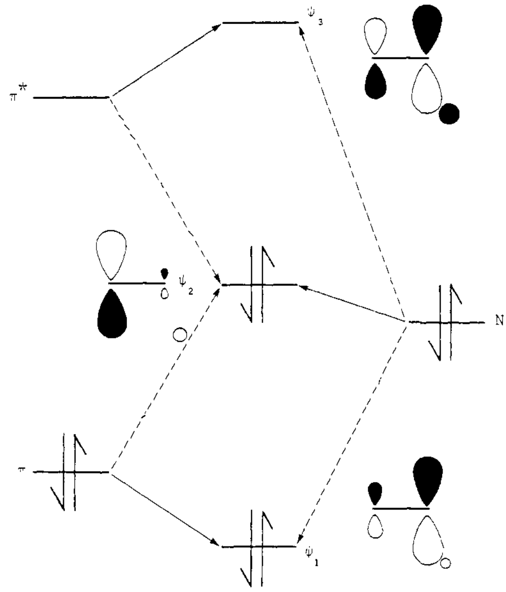

Figure 14. Three molecular orbital, four-electron model for nucleophilic addition to alkenes.

$-CF_2^-$) with a comparedly high inversion barrier relative to that for C_α–C_β rotation could result in preferential elimination from **14b**, affording alkene with formal inversion of stereochemistry.

Conclusion

Our theoretical analysis has provided a viable pathway for a concerted nucleophilic substitution at a vinylic carbon that proceeds with retention of configuration. The transition state for simple alkenes involves inversion of the β carbanion with concomitant C_α–C_β bond rotation toward the best leaving group. Stereoconvergence may either be a consequence of loss of selectivity in the formation of a late transition state when a poor leaving group is involved or the formation of a freely rotating stabilized carbanionic intermediate. The position of the transition state along the reaction coordinate is determined by a delicate balance in magnitude of the two- and four-electron interactions. The four-electron orbital splitting elevates the energy of the "effective HOMO" (ψ_2, Figure 14) on the reaction coordinate with an energy-compensating stabilization of ψ_1. This net interaction serves to lower the $\Delta H^{\ddagger}$ when an empty orbital is present (ψ_3). This orbital may initially increase in energy early on the reaction coordinate of a two-electron dominant reaction and then fall quickly as the extent of bond elongation is heightened as you approach the transition state. The three molecular orbital four-electron model (Figure 14) provides information about the energetics of organic reactions that compliments the classical FMO analysis of HOMO–LUMO interactions. The principle of orbital cancellation allows the qualitative prediction of the relative magnitude of atomic orbital coefficients in the HOMO of the transition state for a variety of reactions. Finally, a correlary to the Hammond postulate is that a HOMO–LUMO dominant reaction, where the major interaction on the reaction coordinate is between a high lying HOMO with a relatively low energy LUMO, should have an early transition state and, in general, be an exothermic reaction. A HOMO–HOMO dominant reaction, where extensive molecular reorganization accompanies the elevation of ψ_2 in energy, should have a late transition state and be an endothermic process. Although HOMO–HOMO dominant reactions are associated with an activation energy, the height of this barrier would typically be prohibitive in the absence of the stabilization of ψ_1. The net change in electronic energy of the four electrons in ψ_1 and ψ_2 is small relative to the increase in potential energy of the overall system that accompanies the bonding changes resulting from collision of the reactants.

The above discussion suggests that it may be advantageous to take HOMO–HOMO interactions into consideration, particularly when discussing reactions between two nucleophilic species. We have previously stressed the importance of such interactions in providing an analysis of the orbital composition and rotational barriers in amides,[20] the reactivity and thermodynamic stability of methyl-substituted alkenes,[21] and the transfer of oxygen in epoxidation reactions.[22]

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