Molecular Orbital Studies of Enzyme Activity. 2. Nucleophilic Attack on Carbonyl Systems with Comments on Orbital Steering

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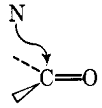
Abstract: Molecular orbital (MO) theory is applied to the study of several reactions involving nucleophilic attack at a carbonyl group. Nucleophile-carbonyl systems studied are $F^- + FCHO$, $OH^- + FCHO$, $CH_3O^- + H_2NCHO$, $NH_3 + HCHO$, $CH_3OH + HCOOH$, and $CH_3OH + HC(OH)_2^+$. The MO calculations are carried out at the minimum basis set level using the Partial Retention of Diatomic Differential Overlap (PRDDO) procedure. In order to assess the error associated with the minimum basis set, several calculations are repeated using an extended 4-31G basis set. The results are discussed with a critical eye toward the concept of "orbital steering".

Nucleophilic attack on a carbonyl system is often proposed as a step in many reaction mechanisms.[2-4] The carbonyl systems of aldehydes, ketones, esters, and amides are subject to nucleophilic attack because of a general electron deficiency at the carbonyl carbon. It is usually assumed that a nucleophile approaches the π system of a carbonyl group from above or below and from slightly to the rear of the carbon atom.[5]



Using approximate molecular orbital theory we have investigated the orientational requirements of several such reactions and have attempted to ascertain the potential importance of "orbital steering"[6] as a possible vehicle for accelerating nucleophilic attack on carbonyl systems. In addition, we have attempted to assess the role that solvent plays in damping the attraction that a nucleophile "feels" for the carbonyl carbon. These considerations lead to some insights concerning the action of certain enzymes whose mechanisms involve nucleophilic attack upon a carbonyl system.

Methods

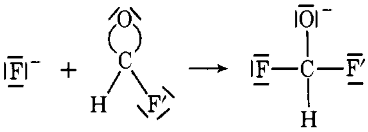
Unless otherwise noted, we have employed the partial retention of diatomic differential overlap (PRDDO)[38] approximation[7] in our calculations. The PRDDO method has been quite successful in simulating ab initio SCF calculations over a minimum basis set (MBS) of Slater orbitals. Details of the method[7] and comparisons with ab initio SCF and other approximate techniques[8] have been performed. Standard Slater exponents were used for all first row atoms and 1.2 for hydrogen in this study. We also report a limited number of calculations performed with the STO-3G and 4-31G bases of Pople et al.[9]

Localized molecular orbitals (LMO's) were generated from the canonical set of PRDDO MO's using a method described elsewhere[10] which is based upon the objective Boys criterion.[11] In most cases, the LMO's so obtained correspond very closely to familiar chemical concepts such as two-center bonds, lone pairs, and inner shells. Changes in LMO structure provide a convenient and intuitively satisfying way of describing changes in bonding which occur during the course of the reactions studied here.

Results

Formyl Fluoride + Fluoride Ion. The potential energy (PE) curve for the orthogonal approach[12] of a fluoride ion to the carbonyl carbon of formyl fluoride is given in Figure 1. The planar geometry of formyl fluoride was held rigid for this series of calculations. The calculated PE curve is attractive for all CF distances greater than the equilibrium value and suggests that no well-defined transition state (TS) separates reactants and product.

Using PRDDO optimized geometries, the energy change for formation of the "tetrahedral" F_2CHO^- from F^- and FCHO is −187 kcal/mol. The LMO picture for this reaction parallels the traditional valence bond description. The fluoride ion is described by four sp^3 hybridized lone-pair orbitals, formyl fluoride by CH and CF′ σ-bond orbitals, a pair of CO τ-bond orbitals, three lone pairs on F′, and two lone pair orbitals on O. The product F_2CHO^- ion is described by CF, CF′, CO, and CH σ-bond orbitals, and three lone-pair orbitals each on F, F′, and O:



The negative charge of the "tetrahedral" F_2CHO^- ion is largely localized on O as judged by its gross atomic population[13] (−0.54 e). Each fluorine atom in the product ion carried −0.21 e of charge.

Although many ion-molecule reactions in the gas phase are very efficient,[14] it does not necessarily follow that the analogous reactions will be essentially diffusion controlled in the condensed phase especially when strong solvent-solute interactions are expected. To probe the effect of water as a solvent, we have calculated the hydration energies for fluoride, formyl fluoride, and the "tetrahedral" intermediate. Figure 2 illustrates the presumed orientation of the water molecules about the reactants and product.

The partially optimized geometries for the hydrated species are summarized in Table I. The optimized geometries for FCHO and F_2CHO^- were retained in the hydrated species. One water molecule was included for each O or F lone pair in such a way that the HO—H- - -A (A = O or F) axis was colinear with the lone-pair LMO axis. The r_0 and R_0 distances were then optimized. The water molecules of $[F_2CHO(H_2O)_9]^-$ were first rotated about their respective CO and CF axes in order to minimize steric interactions before r_0 and R_0 were optimized. For all hydrated species the HOH angle and the uninvolved OH distance were left at their optimized values in the isolated water molecule.

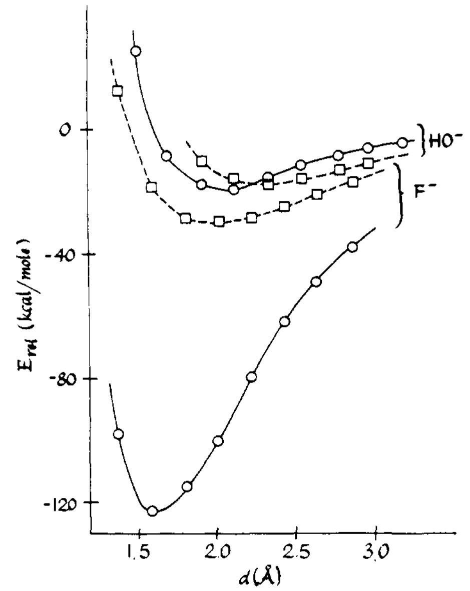


Figure 1. Plot of E_{rel} vs. d for F^- + FCHO and OH^- + FCHO. E_{rel} is the energy relative to the separated reactants and d is the distance of F^- or the O of OH^- from the carbonyl carbon. The formyl fluoride was constrained to the optimized planar geometry determined by PRDDO. Solid curves are PRDDO-MBS results and dashed curves are 4-31G results.

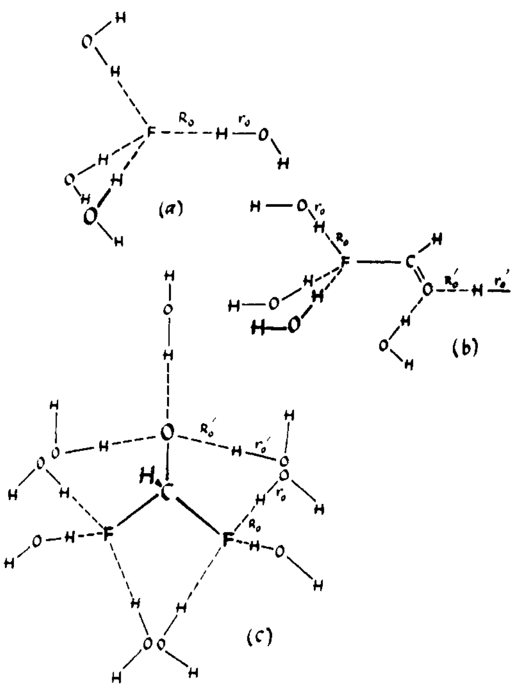


Figure 2. Hydrated fluoride ion (a), formyl fluoride (b), and tetrahedral intermediate (c).

The calculated ΔE for the formation of the hydrated "tetrahedral" intermediate from the hydrated reactants

$$\begin{tikzcd}
F^- \arrow[d, "-255"] & + & FCHO \arrow[rr, "-187"] \arrow[d, "-9"] & & F_2CHO^- \arrow[d, "-110"] \\
F(H_2O)_4^- & + & FCHO(H_2O)_5 \arrow[rr, "-33"] & & F_2CHO(H_2O)_9^-
\end{tikzcd}$$

is −33.4 kcal/mol and is to be compared to the calculated gas phase value of −187 kcal/mol. While the accuracy of the energy changes may be suspect, it is clear that specific solvent-solute interactions are extremely important. The rearrangement of water of hydration during the course of the nucleophilic attack may well introduce a barrier for this reaction in aqueous solution but a more detailed investigation of the "hydrated" PE surface was not pursued.

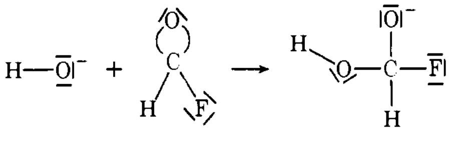
Table I. Geometrical Parameters for FCHO, F_2CHO^-, H_2O, $F(H_2O)_4^-$, $FCHO(H_2O)_5$, $[F_2CHO(H_2O)_9]^-$ [a]

Molecule	Bond distance (AB)	Bond angle (ABC)
FCHO (planar)	1.24 (CO)	124 (OCF)
	1.37 (CF)	124 (OCH)
	1.12 (CH)	
F_2CHO^-	1.31 (CO)	102 (FCF)
	1.44 (CF)	121 (OCH)
	1.19 (CH)	114 (OCF)
		101 (HCF)
H_2O	1.00 (OH)	99 (HOH)
$[F(H_2O)_4]^-$	1.03 (r_O)	
	1.32 (R_O)	
$FCHO(H_2O)_5$	1.00 (r_O)	
	1.79 (R_O)	
	1.00 (r_O')	
	1.83 (R_O')	
$[F_2CHO(H_2O)_9]^-$	1.00 (r_O)	
	1.51 (R_O)	
	1.02 (r_O')	
	1.49 (R_O')	

[a] All bond distances are in Å and all angles in deg. r_O, R_O, r_O', and R_O' are defined in Figure 2.

Also included in Figure 1 are the results of 4-31G calculations on the F^- + FCHO system. Clearly, the 4-31G procedure predicts a much smaller exothermicity (~28 kcal/mol) and an equilibrium value of d which is 0.5 Å larger than that predicted by PRDDO. However, the qualitative conclusions concerning the essential attractive potential of the reaction surface are unchanged. Tetrahedral adducts of negative halide ions and acyl halides have recently been identified by ion cyclotron resonance spectroscopy.[15] A more detailed discussion of the minimum basis set errors (MBSE) is deferred to a later section of this paper.

Formyl Fluoride + Hydroxide. In order to compare the nucleophilicity of fluoride ion with that of hydroxide ion and to determine the dependence of the MBSE on nucleophile charge density, calculations were performed on the OH^- + FCHO system. First, the OH distance in OH^- ion was PRDDO optimized to 1.12 Å. While maintaining the optimized geometries of both OH^- and FCHO the OH^- ion was allowed to approach the carbonyl carbon with the OH bond orthogonal to the plane of FCHO. The LMO description of the formation of the "tetrahedral" adduct once again parallels the usual qualitative valence bond description:



The PRDDO energy curve for the attack is presented in Figure 1 along with the corresponding 4-31G curve. The calculated well depths are 20 kcal/mol at d = 2.01 Å by PRDDO and 17 kcal/mol at d = 2.25 Å by 4-31G. Again we note the tendency of the PRDDO-MBS calculations to overestimate the well depth and underestimate the optimum nucleophile-carbonyl carbon distance. However, both PRDDO and 4-31G calculations suggest that F^- is a stronger nucleophile than OH^- in the gas phase.

Methoxide Ion + Formamide. The attack of methoxide ion on formamide to form a tetrahedral intermediate serves as a useful model for the action of serine proteinases (e.g., trypsin).

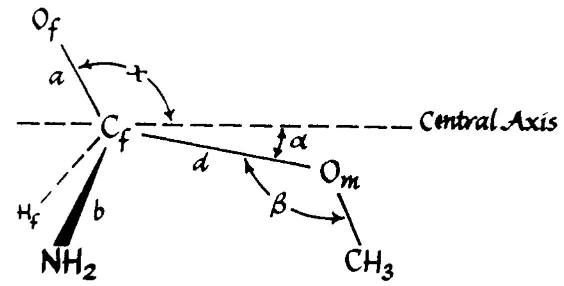


Figure 3. Geometry of the $CH_3O^- + HCONH_2$ complex. The angles that H_f and NH_2 make with the central axis are also equal to χ. The carbon atom of the methyl group and O_m are in the plane defined by the central axis and O_f.

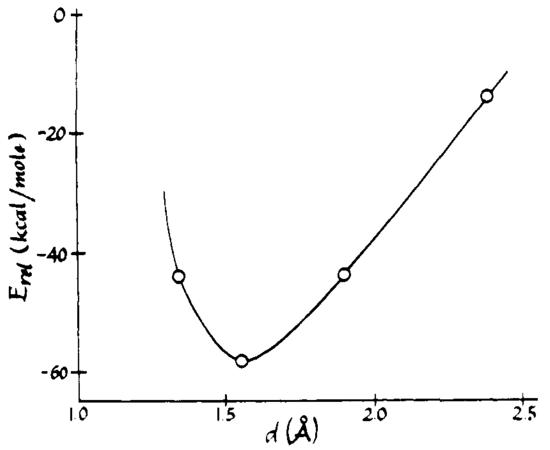


Figure 4. Energy profile of the methoxide anion and formamide system.

The initial geometry of methoxide was fully optimized subject to the constraint of C_{3v} symmetry (optimized internal coordinates: $d_{CO} = 1.49$ Å, $d_{CH} = 1.12$ Å, $\angle OCH = 116.2°$). The initial geometry of formamide was obtained by optimizing the microwave geometry[16] with respect to the C_fO_f and C_fN distances (the subscript f refers to formamide).

The geometrical parameters which were varied during the attack are shown in Figure 3 and the optimized values of these parameters at several values of the reaction coordinate, *d* (*d* is the C_f–O_m distance), are presented in Table II. Puckering of formamide was effected by having the H_f, O_f, and NH_2 groups of formamide bend synchronously through equal angles χ toward the central axis[12] and away from the approaching methoxide. A value of $\chi = 90°$ corresponds to a planar carbonyl group and a value of 109.5° to a tetrahedral arrangement. At $d = 1.55$ Å the O_f atom was given the freedom to bend independently of H_f and the NH_2 group, but preferred to pucker through the same angle χ as the other two substituents.

Taking the ground state of the methoxide-formamide system at infinite separation as the reference state, we find that as the anion approaches the carbonyl carbon from infinity, the energy of the system steadily decreases until the bottom of a well having a depth of some 60 kcal/mol is reached. From the PE profile (Figure 4) it appears that a stable tetrahedral intermediate is formed from the reactants at $d = 1.55$ Å without an intervening energy barrier.[17]

Table IIIA shows the expected charge transfer from the methoxide anion to formamide as the reaction takes place. Most of the transferred charge seems to be associated with the carbonyl oxygen of the intermediate. Table IIIB illustrates the expected trends in atomic overlap populations as a C_fO_m bond is formed with a simultaneous weakening of the C_fO_f and C_fN bonds.

Table II. Optimized Internal Coordinates[a] and Relative Energies for the Methoxide-Formamide System at Several Values of the Reaction Coordinate, *d*

d, Å	χ, deg	*a*, Å	*b*, Å	α, deg	β, deg	E_{rel}, kcal/mol
∞	90.0	1.24	1.41			0
2.38	93.0	1.24	1.41	6.1	115.4	−14.1
1.90	101.1	1.27	1.48	5.4	111.3	−42.8
1.55	105.3	1.30	1.51	5.4	111.3	−57.7
1.34	108.3	1.34	1.55	2.7	116.9	−43.3

[a] Defined in Figure 3.

Table III. Population Analyses[a] for the Methoxide-Formamide System at Several Values of the Reaction Coordinate, *d*

(A) Atomic charges for

d, Å	$(NH_2)^b$	O_f	H_f	C_f	O_m	$(CH_3)^b$
∞	+0.009	−0.185	0.106	0.070	−0.540	−0.460
2.38	−0.057	−0.290	0.072	0.112	−0.439	−0.398
1.90	−0.161	−0.418	0.001	0.106	−0.275	−0.253
1.55	−0.227	−0.517	−0.032	0.124	−0.198	−0.149

(B) Mulliken overlap populations by atoms

d, Å	C_f–O_m	C_f–O_f	C_f–N
∞		0.854	0.729
2.38	0.065	0.833	0.697
1.90	0.211	0.759	0.614
1.55	0.364	0.689	0.559

(C) Atomic populations in two-center LMO's

d, Å	N–C_f		O_f–C_f		O_f–C_f		O_m–C_f	
∞	1.21	0.83	1.10	0.90	1.11	0.90		
2.38	1.23	0.81	1.14	0.87	1.17	0.83		
1.90	1.26	0.78	1.22	0.79	1.25	0.74	1.50	0.47
1.55	1.29	0.75	1.10	0.92	1.53	0.45	1.33	0.69

[a] Reference 13. [b] Group charge is calculated as the sum of atomic charges for atoms in the group.

As the anion approached the formamide along the optimum path, Boys' localizations of the resulting wave functions were performed at several values of *d*. At infinite separation, the methoxide anion LMO description is the conventional one with O_m having three lone pairs. Formamide is described by four bonds to carbon: two to oxygen, and one each to nitrogen and H_f. Oxygen has two lone pairs, nitrogen one, and carbon none. The two C_fO_f bond orbitals are a pair of equivalent τ-bond orbitals. Qualitatively, the localized bond description is that of the separated molecules for all *d* greater than 1.90 Å. At $d = 1.90$ Å one lone-pair orbital on O_m is replaced by a C_fO_m bond orbital leading to a description of the adduct in which C_f is formally pentavalent.[18] This description persists in the optimized intermediate although one of the C_fO_f bond orbitals is so highly polarized that it might best be described as an O_f lone pair:[19]

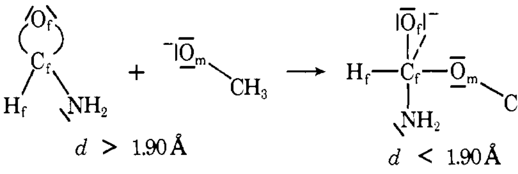


Table IIIC presents the atomic populations of the atoms in each of the two-center orbitals. The two nonequivalent C_fO_f

Table IV. Spherical Polar Coordinates of O_m on the Null Isoenergy Surface[a]

	$\phi =$					
d, Å	0°	60°	120°	180°	240°	300°
2.38	27	35	22	44	48	46
1.90	30	38	28	45	45	43
1.55	31	37	31	43	44	40

[a] Values in the table are θ_{null} angles, deg.

Table V. Optimized Internal Coordinates and Relative Energies for the Ammonia-Formaldehyde System at Several Values of the Reaction Coordinate, d

d, Å	χ, deg	r(CO), Å	E_{rel}, kcal/mol
∞	90	1.24	0
5.29	90	1.24	−0.8
3.18	90	1.24	−2.6
2.62	91	1.24	−4.4
2.12	93	1.24	+10.8
1.85	103	1.28	+26.8
1.59	104	1.33	+52.9

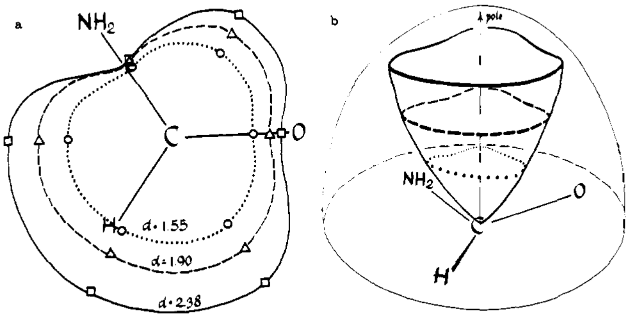


Figure 5. (a) Projections of null isoenergy curves onto the equatorial plane. (b) Reaction funnel showing cross-sections at three values of d.

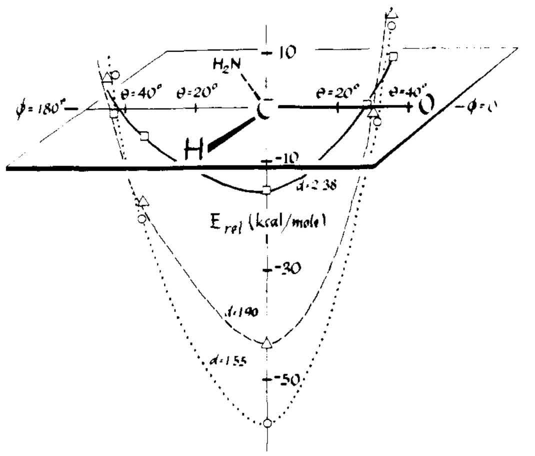


Figure 6. CH_3O^- + $HCONH_2$ energy as a function of the misdirection angle θ for ϕ = 0, 180°.

bond orbitals are shown separately. At d = 1.55 Å there is a near indeterminacy in the localization involving the two C_fO_f bond orbitals.[20] The increasing polarity of one of these bond orbitals as the adduct is formed is evident.

In order to describe the orientational requirements of this reaction, we have defined a spherical polar coordinate system for each value of the reaction coordinate d: C_f defines the origin, the *optimized* positions of C_f and O_m define the pole, and the angle ϕ is measured from the projection of O_f into the equatorial plane. The orientation of the methoxide ion is then described by the spherical polar coordinates of O_m. For each value of d and ϕ listed in Table IV, we misdirected the methoxide ion from its optimum orientation on the pole through angles θ while maintaining the optimum formamide geometry for that d and optimizing the methyl group position with respect to rotation about the C_fO_m axis. The calculated values of E_{rel} (energy relative to the separated molecules) were then used to estimate[21] those values of θ (for each value of d and ϕ) where E_{rel} = 0. The values for the spherical polar coordinates of the methoxide ion which were thus determined to lie on the null (E_{rel} = 0) energy surface are recorded in Table IV and the contours are plotted in Figure 5.

The curves in Figure 5 may be interpreted as cross-sections through a "reaction funnel". As long as the methoxide anion remains within the funnel (i.e., the oxygen atom within the funnel with the methyl group optimally oriented) the system is energetically more stable than the two separated species. This funnel is rather wide (θ_{null} = 48° at d = 2.38 Å and ϕ = 240°) and the anion is thus not very restricted in its path of approach. Taking an average of 37° for θ_{null} over all ϕ values, the reactive funnel subtends about 20% of the hemispherical surface centered at C_f and lying above the plane of the carbonyl.

Figure 6 illustrates the θ dependence of E_{rel} for several values of d and ϕ = 0 and 180°. At ϕ = 180° and at the equilibrium value of d = 1.55 Å, the force constant for misdirecting was calculated from the parabola in Figure 6 to be 0.062 (kcal/mol)/deg^2. This compares favorably with the experimental bending force constants[22] of 0.048 (kcal/mol)/deg^2 reported for C-C-O(R) angles. At larger d values where a transition state might be presumed to occur, the potential wells are even less steep (e.g., k = 0.014 (kcal/mol)/deg^2 at d = 2.38 Å and ϕ = 180°).

Formaldehyde and Ammonia. A fifth reaction studied was the nucleophilic attack by ammonia upon the carbonyl carbon of formaldehyde. An experimental geometry was used for ammonia[23] and an idealized C_{2v} geometry for formaldehyde (∠HCO = ∠HCH = 120°, r(CH) = 1.09 Å). Ammonia approached formaldehyde along the central axis.[12] During the attack ammonia was maintained in a rigid and staggered conformation relative to formaldehyde, and formaldehyde was given the freedom to pucker in a manner analogous to that described for formamide in the previous section. The pucker angle χ and r(CO) were optimized for each value of the reaction coordinate, d = r(CN). The results are presented in Table V and the PE curve for the orthogonal approach is depicted in Figure 7.

Although a very shallow well appears at d = 2.62 Å, there is no indication from the localization that a chemical bond is being formed. In fact, the localized MO's for this system do not include a two-center CN bond orbital[19] until d is less than 1.9 Å, a point well up on the repulsive part of the potential. As a check, several calculations were repeated for geometries along the optimized PRDDO path but using the ab initio SCF program written by R. M. Stevens.[24] The ab initio energy curve was found to be nearly parallel to, but higher than, the PRDDO curve (by about 8 kcal/mol). We thus conclude that only a very weak bond is formed between ammonia and formaldehyde.[25]

Methanol and Formic Acid. The reaction of methanol and formic acid has been used as a model system for the study of the effects of orbital steering in esterification. Dafforn and Koshland[6c] have proposed a TS for this reaction with the idealized geometry shown in Figure 8. It was our hope to follow this reaction energetically and thus obtain a more accurate description of the TS.

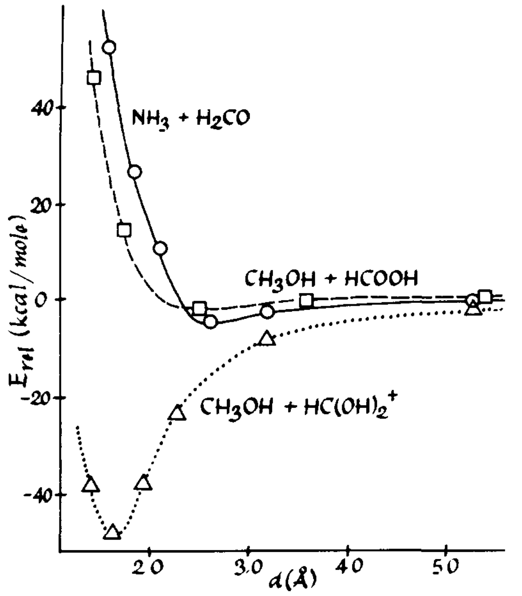


Figure 7. Energy profiles for three reactions involving nucleophilic attack on a carbonyl or protonated carbonyl system.

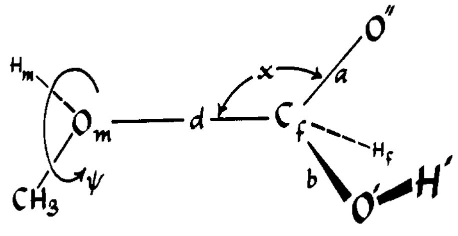


Figure 8. Geometrical parameters for methanol plus formic acid reaction. Dafforn and Koshland's[6c] idealized geometry for the "tight" transition state has tetrahedral angles and "normal" bond lengths except that $a = d = 1.43$ Å. Our normal bond lengths were taken as r(CH) = 1.093 Å, r(OH) = 0.96 Å, and r(CO) = 1.43 Å. The conformation depicted here (i.e., C of CH_3 in the same plane as O_m, C_f, and O'') has $\psi = 0°$. $\chi = \angle O_m\text{-}C_f\text{-}O'' = \angle O_m\text{-}C_f\text{-}O' = \angle O_m\text{-}C_f\text{-}H_f$.

Table VI. Optimized Value of χ (Figure 8) and Energies for $CH_3OH\text{-}HCOOH$ at Several Values of the Reaction Coordinate, d

d, Å	χ, deg	E_{rel}, kcal/mol
∞	90	0
5.40	90	−0.3
3.55	90	−0.8
2.51[a]	92.6	−2.2
1.75	98	+14.4
1.43	98	+46.4

[a] The geometry at d = 2.51 Å was calculated in the greatest detail. For other points, χ was only allowed to equal 90, 98, or 109°.

Table VII. Optimized Geometric Parameters χ, a, and b (see Figure 8) and Energies for $CH_3OH\text{-}HC(OH)_2^+$ at Several Values of the Reaction Coordinate, d

d, Å	χ, deg	a, Å	b, Å	E_{rel}, kcal/mol
∞	90	1.32	1.30	0
5.29	90	1.32	1.30	−2.5
3.18	90	1.33	1.30	−8.1
2.28	93.0	1.33	1.30	−23.9
1.92	98.7	1.35	1.32	−38.1
1.62	102.9	1.37	1.35	−47.9
1.41	106.7	1.39	1.38	−38.6

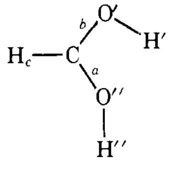
We maintained the idealized bond distances and bond angles of Dafforn and Koshland but optimized the dihedral angle ψ at d = 1.43 Å before proceeding with d variations. We found that the most stable configuration is a staggered one with H_m between O'' and O'H' (i.e., ψ = 120°). Unfortunately, upon subsequent variation of d, we found only a very shallow well (about 3 kcal/mol) at d = 2.28 Å and no energy barrier separating reactants from products.

It was thought that perhaps keeping both a and b equal to 1.43 Å was a bit too restrictive since the C_fO'' bond is expected to have more double bond character than the C_fO' bond. Using a = 1.22 Å and b = 1.34 Å the PE curve was translated to lower energy but there was little change in its essential shape.

In order to outline better the energy profile for this reaction methanol was allowed to approach formic acid along the central axis as before but the acid was given the freedom to pucker. Even with additional freedom, only a very shallow well is obtained and no energy barrier is discerned (Figure 7 and Table VI).

The esterification reaction often proceeds via the mediation of an acid catalyst. Thus, nucleophilic attack by an alcohol on a protonated acid may be a more likely step in the esterification mechanism. We, therefore, decided to study the nucleophilic attack of methanol on protonated formic acid in order to see if this reaction had a more well-defined TS and more stringent orientational requirements than the attack on the neutral acid.

We first partially optimized the geometry of $HC(OH)_2^+$. The following bond distances and angles were assumed: r(CH) = 1.09 Å, r(OH) = 0.96 Å, ∠C-O-H = 109.5°, and ∠X-C-Y = 120°. When the acid was given the freedom to pucker and the hydroxyl hydrogens given the freedom to rotate about their respective CO bond axes, the planar conformation



was found to be most stable. Methanol approached the protonated acid along the central axis[12] and in the relative orientation shown in Figure 8 (i.e., ψ = 0°). The geometry of the adduct was optimized with respect to the parameters a, b, and χ for the various values of d shown in Table VII. Figure 7 depicts the energy profile along the optimum path and shows no evidence for an energy barrier separating the reactants from the stable intermediate whose stabilization energy is 48 kcal/mol.

In order to obtain the reaction "funnel" cross-sections at d = 1.62 Å and d = 2.28 Å, the methanol, as a rigid body, was rocked away from the central axis by an angle of θ = 35° in the $O_mC_fH_f$ plane, and then rotated rigidly about the new O_mC_f axis to minimize the energy. During this operation, the acid was maintained in its optimized geometry for that value of d. The same quadratic approximation used above for the methoxide-formamide system was used here to find the θ_{null} values for which $E_{rel} = 0$ (see Figure 9). Once again the funnel is quite wide (θ_{null} = 50° at d = 2.28 Å). However, in this case the funnel widens more quickly as d increases, widening by over 10° as d increases from 1.62 to 2.28 Å. If we assume θ_{null} to be roughly independent of φ and take θ_{null} equal to 35° at d = 1.62 Å and 48° at d = 2.28 Å, we find that the fractions of the hemisphere subtended by the funnel are 18 and 33%, respectively. We also note that at 1.62 Å the calculated force constant for misdirecting the methanol is ~0.078 (kcal/mol)/deg^2, while at d = 2.28 Å it has dropped to ~0.020 (kcal/mol)/deg^2.

Errors. The use of a minimum basis set for the calculations described above introduces a significant but largely systematic

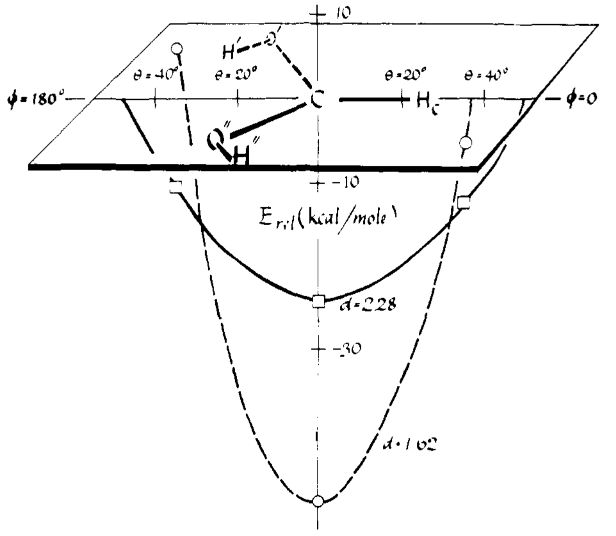


Figure 9. Energy as a function of the misdirection angle θ for the $CH_3OH + HC(OH)_2^+$ system.

Table VIII. Energetics for Several Ion-Molecule Reactions Calculated at Several Levels of Approximation

	F^-	+	H_2O	→	$F(H_2O)^-$	ΔE
PRDDO	−61 816.7		−47 493.6		−109 443.5	−133.2
Ab initio[a]	−61 816.7		−47 505.9		−109 452.6	−130.0
STO-3G	−61 252.3		−47 041.0		−108 402.4	−109.1
4-31G	−62 278.0		−47 628.2		−109 947.2	−41.0

	F^-	+	FCHO	→	$[F_2CHO]^-$	
PRDDO	−61 816.7		−132 971.3		−194 975.0	−187.0
STO-3G	−61 252.3		−131 667.5		−193 079.5	−159.7
4-31G	−62 278.0		−133 304.5		−195 643.6	−61.1

	CH_3O^-	+	H_2NCHO	→	$[CH_3O\text{-}\underset{\displaystyle NH_2}{\underset{\vert}{C}}HO]^-$	
PRDDO	−71 437.5		−105 652.9		−177 148.1	−57.7
STO-3G	−70 726.8		−104 607.6		−175 382.7	−48.3
4-31G	−71 690.4		−105 878.8		−177 578.2	−9.0

[a] Ab initio MBS calculations using Stevens' program (ref 24).

error into the computed energy changes. Calculations at the MBS level are less accurate for species with highly concentrated negative charge[27] so that an MBS treatment of a negative ion-molecule reaction exaggerates the energy changes associated with the dispersal of charge in the product ion.

Three examples of this disturbing feature are provided in Table VIII. For each ion-molecule reaction presented we have carried out calculations at both the MBS and the 4-31G level. The MBS calculations systematically predict energy changes in significant excess of those calculated with the 4-31G basis set. The PRDDO calculation for the fluoride-H_2O reaction predicts a hydrogen bond strength which is greater than that of many full-strength covalent bonds.[28] The PRDDO energy changes for the fluoride-formyl fluoride and methoxide-formamide reactions overestimate the corresponding 4-31G values by 126 and 49 kcal/mol, respectively.

A comparison of calculated energies along the reaction coordinate reveals that the PRDDO-MBS and 4-31G curves for the $F^- + FCHO$ reaction are much less similar than the corresponding curves for the $OH^- + FCHO$ reaction (see Figure 1). The energy curves for both reactions are calculated for an orthogonal attack by the nucleophile on the carbonyl carbon of the formyl fluoride which is artificially restrained to a planar geometry. For both reactions, 4-31G and PRDDO predict attractive potentials up to the minimum at d_{min} in the PE curve. However, the 4-31G curves show larger d_{min} values and shallower wells than the corresponding PRDDO curves. While the PRDDO calculations for the $F^- + FCHO$ reaction predict a well depth which is ~93 kcal/mol greater than that predicted by 4-31G and a d_{min} value ~0.5 Å less than the 4-31G value, the corresponding PRDDO values for the $OH^- + FCHO$ reaction differ from the 4-31G values by only 2 kcal/mol and −0.2 Å, respectively. Evidently, the more concentrated charge is responsible for the larger MBS error when F^- is the nucleophile, and we expect that of all the ion-molecule reactions studied here the results for $F^- + FCHO$ are least reliable. In general, we predict that an MBS treatment will overestimate the well depth and underestimate the optimum bond distance, d_{min}, for the nucleophilic attack on a carbonyl system by a negatively charged ion. These errors will be greatest for ions with highly concentrated negative charge and should be least for neutral nucleophiles (e.g., $NH_3 + HCHO$).

Discussion

The negative ion-molecule reactions studied here exhibit attractive potentials for a wide range of approach angles of the negative ion to the electrophilic center of the target molecule. At large distances the interaction of an ion (e.g., F^-) with a planar molecule (e.g., formyl fluoride) which it is approaching orthogonally is dominated by the ion-induced dipole term:[31a,b]

$$V(d) = -e^2\alpha_\perp/2d^4 \qquad (1)$$

Approximating $\alpha_\perp$ as a sum of transverse bond polarizabilities[32] we obtain

$$V(d) = -3.37 \times 10^2\ \text{kcal/mol}/d^4 \qquad (2)$$

for the interaction of F^- with FCHO (d in Å). The essential attractive nature of the ion-molecule potential surfaces at large distances can thus be attributed to the ion-induced dipole interaction. At intermediate distances where the point dipole approximation is no longer valid, there is an additional attractive interaction if the negative ion approaches the positive end of the dipole (e.g., the carbonyl carbon of formyl fluoride). Our molecular orbital calculations for the $F^- + FCHO$ system are, thus, consistent with predictions based upon electrostatic considerations. Stable adducts with similar attractive potentials for their formation are also expected on the basis of electrostatic arguments for the methanol-protonated formic acid and methoxide-formamide systems. There is now some experimental evidence for the stability of alkoxide-amide adducts analogous to the methoxide-formamide system. In low dielectric solvents, Fraenkel and Watson[33] have observed NMR evidence for the existence of a stable adduct between *N,N*-dimethyltrifluoroacetamide and *tert*-amyloxide ion. Other molecular orbital studies[5b] have also supported the general conclusions reached here for nucleophilic attack on carbonyl systems by negative ions.

When the C_3 axis of ammonia is orthogonal to the molecular plane of formaldehyde, intermolecular dipole-dipole interactions vanish for large d so that the intermolecular potential should be dominated by weakly attractive dipole-induced dipole interactions. This result is consistent with the slight attraction exhibited in Figure 7 for large values of d. At the minimum in the PRDDO PE curve (d = 2.6 Å, E_{rel} = −4 kcal/mol) the stabilization energy for the dipole-induced dipole interaction is only on the order of 1 kcal/mol.[34] The somewhat larger stabilization predicted by PRDDO is consistent with the formation of a weak bond whose properties are similar to those of a hydrogen bond. Here the slightly positive carbon atom takes the place of hydrogen in a largely electrostatic interaction with a slightly negative nitrogen atom of ammonia. A similar weak bond is evidently formed between the carbonyl carbon of formic acid and the oxygen of methanol. In another molecular orbital study[35] of the electron donor-acceptor complex between water and carbonyl cyanide, electrostatic terms were found to dominate the stabilization. The stabilization energy for the carbonyl cyanide-water system was computed to be in the range of 3.5–8.0 kcal/mol at $d = 2.7$ Å,[35] a result remarkably similar to our own for the ammonia-formaldehyde system.

The methanol-formic acid reaction was used by Dafforn and Koshland[6c] as a model reaction in their application of the transition state theory in support of the orbital steering concept. The steric factor p for formation of the adduct was calculated from partition functions for an assumed TS. A steric factor much less than one implied that orbital steering would be effective in accelerating the reaction. Our calculations suggest that the orientational requirements for this reaction are minimal (i.e., $p \sim 1$). In any case Dafforn and Koshland's application of the TS theory seems rather tenuous. The geometrical parameters chosen for the supposed TS are clearly inconsistent with our PE curve. They assumed[6c] $d = 1.80$ Å in their "loose" TS, a value well up on the repulsive wall of our calculated PE surface. If d is increased from 1.80 to a more reasonable value of 3.5 Å the rotational partition functions, $q_{\mathrm{AB^+}\,(\mathrm{rot})}$ and $q_{\mathrm{AB}\,(\mathrm{rot})}$, will both increase but by approximately the same factor so that p (eq 1, ref 6c) should not be greatly affected. However, this large separation will surely result in a TS which is considerably looser than any of those considered by Dafforn and Koshland. At $d = 3.5$ Å the four low-frequency modes which correspond to rocking methanol and formic acid relative to the central axis are predicted by our calculations to be very low frequency ($\nu < 100$ cm^{-1}). Rocking methanol away from its preferred direction of approach (at $d = 3.5$ Å) by 20° changes the energy of the TS by less than 1 kcal/mol. Assuming a quadratic potential for this mode, the force constant is then estimated to be less than 2×10^{-13} erg/rad^2 and the corresponding frequency less than 30 cm^{-1}. If a value of 30 cm^{-1} is taken for the frequencies of these rocking modes rather than the 100-cm^{-1} frequency chosen for the loose TS by Dafforn and Koshland and if the effect of the increased moment of inertia on the ratio of the rotational partition functions is ignored, then a steric factor of 0.3 is obtained. Hence, orbital steering is not expected to have a large effect in accelerating the rate of this reaction. Furthermore, none of the reactions studied here are expected to have very stringent steric requirements. This important conclusion is best illustrated by the very wide reaction funnels obtained for the methoxide-formamide and methanol-protonated formic acid reactions.

In addition to arguments centered around the steric factor, Dafforn and Koshland[6c] argue that in an intramolecular reaction a slight missteering of reactant groups which possess orbital asymmetry will result in a considerable increase in activation energy relative to a reaction in which the reactants are ideally oriented. This argument again depends upon a rather tight TS for the bimolecular reaction so that a steered misorientation in the analogous intramolecular reaction will be very costly energetically. If the deformation is dominated by bending of the incipient bond between reactants, then misorientation will raise the energy of the TS by an amount $V^* = k^*\theta^2/2$ (θ is the deformation angle and k^* the force constant) and reduce the rate constant by a factor of $\exp(-k^*\theta^2/2kT)$. Thus, an angle deformation of 10° is expected to decrease the rate by a factor of 0.025 for a force constant of 10^{-11} erg/rad^2 but only by a factor of 0.5 for a force constant of 0.2×10^{-11} erg/rad^2. Our calculations suggest that even the latter force constant is high by about an order of magnitude for the rocking modes which deform the TS for the methanol-formic acid reaction. Thus, little effect on the exponential term is to be expected for small misorientations of reactants in the ground state.

Similar arguments can be brought to bear on all of the reactions studied here. None have very well-defined transition states, and the transition regions of the PE surface are very flat in those directions corresponding to deformations of the incipient bond. Thus, a very loose TS is suggested for these reactions so that the TS theory predicts steric factors near unity, and an exponential term which is quite insensitive to deformations of the incipient bond. However, in elucidating their theory of orbital steering, Dafforn and Koshland[6c] have included other effects, such as nonbonded interactions, which may be important in determining the orientational requirements of these reactions.

One could argue that solvent effects will introduce a considerable change in the PE surface for the reactions studied here. Indeed, the very significant effect of specific solvent interactions is quite remarkable for our theoretical treatment of the $\mathrm{F^-} + \mathrm{FCHO}$ reaction. Although no claims will be made for the quantitative accuracy of these calculations, they do give the clear impression that solvent effects are of great importance. Indeed, it is possible that all or most of the reactions studied here will have well-defined transition states and positive activation energies in hydroxylic solvents such as water. Certainly the presence of a high dielectric medium will damp the electrostatic effects which appear to dominate the ion-molecule reactions. Conversely, we should note that the elimination of solvent in passing from solution to the isolated environment within a molecular superstructure may accelerate nucleophilic addition. Thus, a negatively charged ethoxide side chain of Ser-195 in a trypsin-substrate complex will be a very strong nucleophile since water is apparently denied access to the contact area between substrate and enzyme.[36] The reaction of methoxide ion with formamide studied here serves as a model demonstrating the ease of nucleophilic attack by Ser-195 on a peptide linkage in the absence of solvent. A more detailed molecular orbital study of the action of the serine proteinases done in this laboratory[37] confirmed the absence of an energy barrier in the course of the attack. However, a transition state was observed in the formation of the tetrahedral intermediate. This transition state involved the proton transfer responsible for the charging of the Ser-195 residue. This would seem to account in part for the experimental observation of a deuterium isotope effect in acylation.[37] The transition states of other steps of the trypsin mechanism are associated with breakdowns of intermediates. The PRDDO method may thus be expected to detect transition states although it may overestimate the magnitude of the activation energy.

We should also note that the lack of any significant orientational effect on the essential attractive nature of the PE surface for the methoxide-formamide reaction also serves to diminish the suggestion that orbital steering may be the dominant effect in catalysis by serine proteinases. If it does play an important role, the contributions would have to arise from nonbonded interactions and nonproductive complexing in model systems.[6c] No one explanation works for any single enzyme, much less all enzymes. Orientational effects may play a part in enzyme catalysis, but for these model reactions their importance appears to be minimal.

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(20) This indeterminacy is indicated by a value of −0.07 for the highest eigenvalue of the second derivative matrix (ref 10).

(21) For each value of d and ϕ, θ_{null} (i.e., that value of θ for which $E_{\text{rel}} = 0$) was estimated by assuming a quadratic dependence of E_{rel} upon θ. The energy at $\theta = 35°$ was first calculated and together with the energy at the assumed minimum at $\theta = 0°$ determined the quadratic dependence of E_{rel} on θ (i.e., $(E_{\text{rel}}^{\theta} - E_{\text{rel}}^{\theta=0}) = \frac{1}{2}k\theta^2$). When this approach was tested by further calculations near the predicted value of θ_{null}, it was generally found to be accurate to within one or two degrees. For those d and ϕ values where the estimated value of θ_{null} differed significantly from 35°, further calculations were performed to better locate it.

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$$V(d) = -(2\mu^2_{NH_3}\alpha^{\perp}_{H_2CO}/d^6) - (\mu^2_{H_2CO}\alpha_{NH_3}/2d^6)$$

with $\mu_{NH_3} = 1.47$ D, $\mu_{H_2CO} = 2.34$ D, $\alpha^{\perp}_{H_2CO} = 20 \times 10^{-25}$ cm^3, and $\alpha_{NH_3} = 24 \times 10^{-25}$ cm^3. The dipole moment for ammonia was obtained from D. K. Coles, W. E. Good, J. K. Bragg, and A. H. Sharbaugh, *Phys. Rev.*, **82**, 877 (1951), and that of formaldehyde from J. N. Shoolery and A. H. Sharbaugh, *ibid.*, 95L (1951). The polarizability of ammonia was taken from ref 31a, p 950, and that of formaldehyde was estimated using the bond polarizabilities from ref 32. The expression for $V(d)$ was obtained from the standard formula (ref 31a), p 984, for the interaction of a dipole with a polarizable molecule, $V = -\mu^2\alpha(3\cos^2\theta + 1)/d^6$ where θ is the angle formed between the dipole and the vector connecting the two charge distributions.

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