Anionic Substitution at Carbonyl Carbon. Implications for the Chemistry of Ions in Solution

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AM1 calculations are reported for the reactions of seven anions (HO^-, MeO^-, EtO^-, NH_2^-, $MeNH^-$, $OCHNH^-$, H^-) with eight carboxylic derivatives (formic acid, the methyl esters of formic, acetic, fluoroacetic, difluoroacetic, and trifluoroacetic acids, formamide, and *N*-methylformamide) and formaldehyde. All were predicted to involve exothermic addition to the carbonyl group without activation, to form tetrahedral adducts, in agreement with our earlier work and recent *ab initio* calculations. The barriers to such reactions in solution are thus due entirely to the energy needed to desolvate the anion in order that the other reactant can approach. The nature and role of such *desolvation barriers* are discussed, with special reference to the hard–soft-acid–base theory and the mechanisms of enzyme reactions.

According to the traditional view, activation barriers are due to the changes in bonding that take place during reactions, bonds that break having to be weakened before new bonds can begin to form. This forms the basis of the familiar Evans–Polanyi formalism (Figure 1) in which curves are plotted depicting (A) the increase in energy of the reactants as the old bonds progressively break and (B) the corresponding decrease in energy as new bonds form, the progress of the reaction being indicated by the value of an appropriate reaction co-ordinate. The crossing point (C) of A and B corresponds to the transition state (TS).

In this traditional picture, the solvent is assumed to play a secondary role, at least in reactions where charges are neither formed nor destroyed, because the difference in solvation energy between the reactants and the TS is expected to be relatively small. Large solvent effects are expected, and observed, in reactions where ions are formed or destroyed because the solvation energies of ions are much greater than those of neutral molecules. In reactions where ionic charges are conserved, *i.e.* in reactions of neutral molecules or of ions with neutral molecules, changes in the solvent usually have a relatively small effect on the rate.

This view was challenged by Dougherty[1] some years ago in the case of the S_N2 reaction. Several typical S_N2 reactions had been reported[2] to take place without activation in the gas phase and Dougherty *et al.*[1b] had found that, in the gas phase, halide ions combine very exothermically ($-\Delta H$, 40–80 kJ mol^{-1}) with alkyl halides to form unspecified adducts. He suggested that the adducts are the trigonal bipyramidal intermediates [*e.g.* (**1**)] normally regarded as the transition states (TS) in the corresponding S_N2 reactions. If so, the barriers in solution must be due entirely to solvation. However, subsequent experimental[3] and theoretical[4,5] studies showed this rather startling suggestion to be incorrect. Dougherty's adducts are charge–dipole (CD) complexes, *e.g.* (**2**). The trigonal bipyramidal species are TSs, in agreement with the conventional interpretation. Since formation of such a CD complex is very exothermic and since the corresponding energy cannot be rapidly dissipated in the gas phase, the S_N2 reaction may take place without activation by the 'hot molecule' mechanism indicated by the dotted line in Figure 2. In a condensed phase, where hot-molecule processes cannot occur, the CD–TS barrier has to be overcome.

While conventional ideas concerning the S_N2 reaction were thus saved, we recently found[6] a genuine example of the situation envisaged by Dougherty. AM1[7] calculations indicated that in the formally analogous $B_{AC}2$ reaction between an anionic nucleophile and a carboxylic acid derivative, the attacking anion adds very exothermically ($-\Delta H$, *ca.* 120 kJ mol^{-1}) to the carbonyl group of the ester or amide, without any intervening barrier or intermediate. The resulting tetrahedral adduct, while at most a high-energy intermediate in solution, is thus predicted to form exothermically and without activation in the gas phase. While earlier calculations[8,*] had suggested that

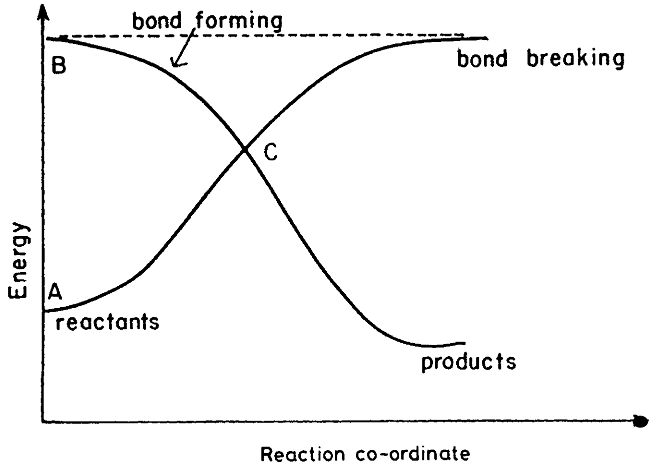
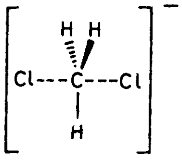
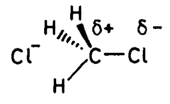


Figure 1. Evans–Polanyi plot for a normal (IB) reaction.



(**1**)



(**2**)

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* Calculations given in ref. 8(*a*),(*b*) were carried out with inadequate geometry optimization using a wholly inadequate model (STO-3G), and lead to unrealistic estimates (*ca.* −418.4 kJ mol^{-1}) of the heats of reaction for the formation of tetrahedral adducts. Ref. (*c*) referred to a reaction of formaldehyde, not of a carboxylic acid derivative.

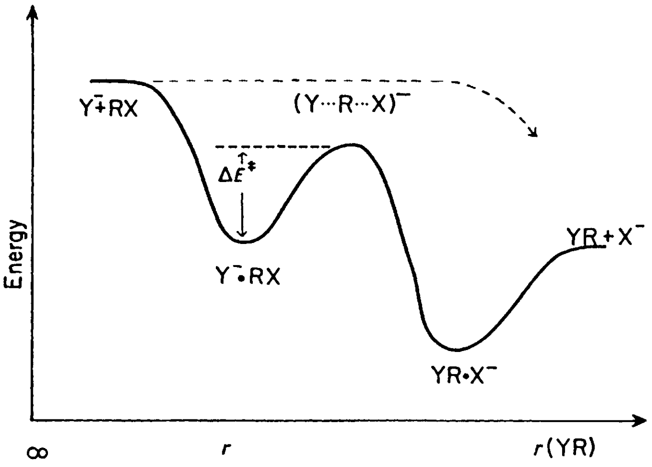

Figure 2. Reaction profile for an S_N2 reaction, *r* being the Y–C distance. The crossing point (C) of the bond breaking and bond-forming curves corresponds to the transition state.

reactions of this kind might lack activation barriers, no reliable conclusions could be drawn from them because the procedures used were inadequate[8] and their implications were in fact ignored. While our calculations referred only to the reactions of methoxide and ethoxide ions with methyl formate, *N*-methylformamide, and formic acid, and while no certain conclusions can be drawn from calculations by any current theoretical procedure, tests of AM1 in various connections[9] make it unlikely that our conclusions could have been incorrect. They have, moreover, been confirmed by subsequent * high level *ab initio* studies.[10,11]

There can therefore be little doubt that reactions of this kind normally take place without activation in the gas phase and that the barriers in solution must indeed be due entirely to the solvent, representing the energy needed to desolvate the ion in order that the other reactant can approach.[6] The retardation in solution clearly cannot be explained in a conventional manner, in terms of a difference in solvation energy between the reactants and TS, because in the gas phase there is no TS. While barriers of this kind had been recognized as a possibility in very fast reactions, nobody, other than Dougherty, had ever suggested in print that such a barrier could be large enough (>80 kJ mol^{-1}) to account for the rate of a typical 'slow' organic reaction. The potential consequences for chemical theory are clearly far reaching. Current theory discusses chemical reactivity in terms of the differences in bonding energy between the reactants and the TS. Here the differences are due to solvent effects, not to changes in bonding.

Reactions of ions with neutral molecules can thus be divided into two classes. In the first, the activation barrier is of conventional type, due to the changes in (covalent) bonding during the reaction. Bonds that break during the reaction have to be weakened before new bonds can begin to form. Since barriers of this kind are commonly termed intrinsic, the corresponding reactions may be termed intrinsic-barrier (IB) reactions.

In reactions of the second type, the barrier in solution is due entirely to desolvation. In the gas phase there is no barrier. The barriers in solution are again due to the need to break old bonds before new ones can form. However, the bonds that break are electrostatic, representing the attractions between the ions and the molecules of solvent that have to be displaced in order that the other reactants can approach. Reactions involving such desolvation barriers may be termed desolvation-barrier (DSB) reactions. These terms seem preferable to the rather clumsy alternatives, 'autoactivated' and 'solvactivated,' suggested in our preliminary communication.[6]

While our main purpose here is to analyse the nature of desolvation barriers and their role in chemistry, we will begin by presenting in full the results of our calculations for a number of $B_{AC}2$ reactions, only a few of which have as yet been reported.[6]

Experimental

Theoretical Procedure.—Calculations were carried out using AM1[7] and MNDO[12] as implemented in the AMPAC[13] package of computer programs. All geometries were optimized with respect to all geometrical parameters, without making any assumptions. Reactions were followed in reverse, by studying the decompositions of the relevant tetrahedral complexes, using the length of the breaking bond as the reaction co-ordinate.[14] Transition states found in this way were refined by minimizing the scalar gradient of the energy.[15]

Extensive studies[16] of proton affinities and enthalpies of deprotonation have shown that AM1 gives satisfactory results for anions, except when almost a whole unit of negative charge is localized on a single atom. In such cases (HO^-, H^-, H_2N^-) the calculated energies are much too positive. The error seems to be due[16] to failure to allow for orbital expansion. The parametrization of AM1 is apparently flexible enough to compensate for such changes in orbitals in most cases but in anions where the negative charge is almost completely localized, even moderate delocalization is sufficient to remedy the situation. Thus AM1 gives satisfactory estimates of the heats of formation of alkoxide ions, even that of methoxide.[16]

Discussion

Reactions of Anions with Carboxylic Acid Derivatives.—We investigated the reactions of each of seven anions [hydroxide (**3a**), methoxide (**3b**), ethoxide (**3c**), hydroperoxide (**4**), amide (**5a**), methylamide (**5b**), formylamide (**6**), and hydride (**7**)] with each of seven carbonyl compounds [formic acid (**8a**), methyl formate (**8b**), formamide (**9a**), *N*-methylformamide (**9b**), methyl acetate (**10**), and formaldehyde (**11**)] to form the corresponding tetrahedral adducts (**12**)–(**14**). The MNDO results[17] are not reported here because they were similar to the AM1 ones but probably less reliable in view of the known[12] tendency of MNDO to overestimate interatomic repulsions in crowded molecules. This would be expected to lead to corresponding errors for tetrahedral adducts where three or four substituents are attached to a single carbon atom.

Table 1 shows the heats of formation calculated for the various reactants and for some related species, together with experimental values where available. The agreement is within the limits normally expected for AM1 and MNDO, except for (**3a**), (**5a**), and (**7**), where the calculated values are much too positive. The reason for this was discussed in the previous section.

Table 2 shows the heats of reaction calculated by AM1 for the 42 reactions studied. The values for reactions of hydroxide (**3a**), amide (**5a**), and hydride (**7**) ions are undoubtedly much too large because of the errors in their calculated heats of formation. However, since the errors are confined to anions where the negative charge is concentrated on a single atom, no such problems should arise in the tetrahedral adducts. Satisfactory estimates for the corresponding heats of reaction should then

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* No reference is made to ref. 6 in refs. 11(*a*),(*b*). While ref. 10 was submitted shortly before ref. 6 was published, refs. 11(*a*),(*b*) were each submitted nearly a year after ref. 6 appeared in print.

RO^- (3) a; R = H; b; R = Me; c; R = Et

HOO^- (4)

RNH^- (5)

$HCONH^-$ (6)

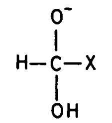
H^- (7)

HCO_2R (8)

$HCONHR$ (9)

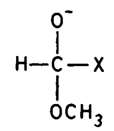
$H_3CO_2CH_3$ (10)

$H_2C{=}O$ (11)



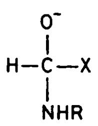
$H{-}C(O^-)(OH){-}X$

(12) a; X = OH
b; X = Me
c; X = Et
d; X = NH_2
e; X = NHMe
f; X = NHCHO
g; X = H



$H{-}C(O^-)(OCH_3){-}X$

(13)



$H{-}C(O^-)(NHR){-}X$

(14)

Table 1. Heats of formation.

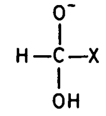
Compound	ΔH_f/kJ mol^{-1} Calc.	Obs.[a]
$CH_3CO_2CH_3$	−403.3	−410.0
$HCONHCH_3$	−173.6	−238.5
$HCONH_2$	−187.4	−166.5
HCO_2H	−407.5	−379.1
H_2CO	−131.8	−108.8
HCO_2CH_3	−380.7	−355.6
$C_2H_5O^-$	−190.4	−197.9
CH_3O^-	−161.1	−151.5
HOO^-	−74.9	
CH_3NH^-	138.5	127.6
H_2N^-	219.7	106.3
HO^-	−59.0	−141.0
H^-	358.2	139.7
H_2O	−247.7	−241.8
NH_3	−30.5	−46.0

[a] J. D. Cox and G. Pilcher, 'Thermochemistry of Organic and Organometallic Compounds,' Academic Press, New York, NY, 1970. Data for ions: ref. 12.

be obtained by using experimental values for the heats of formation of (**3a**), (**5a**), and (**7**). Correspondingly corrected heats of reaction are given in parentheses in Table 2.

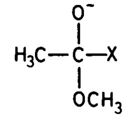
Table 3 compares our heats of reaction with those from *ab initio* calculations, using our corrected values for reactions of HO^-. Since no experimental values are available for comparison, no definite conclusions can be drawn. However, since AM1 has given good results for a very large number (140) of very varied anions,[16] there is no reason to doubt its performance here.

Reaction paths were calculated by AM1 for each of the 42 reactions. As indicated above, these were studied in reverse, *i.e.* dissociation of the tetrahedral adduct into its components. The calculated path corresponded in each case to a monotonic increase in energy, with no indication of a minimum corresponding to a stable intermediate. Details are not given here because such paths have no chemical significance. They serve only as a means for locating TSs. The geometries of the adducts (**10**)–(**15**) are also omitted because they showed no unexpected features. The preferred conformations corresponded to those expected on the basis of current theory, in particular the anomeric effect.



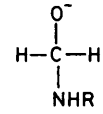
$H{-}C(O^-)(OH){-}X$

(**15**)



$H_3C{-}C(O^-)(OCH_3){-}X$

(**16**)



$H{-}C(O^-)(NHR){-}H$

(**17**)

As Table 2 shows, AM1 predicts all seven anions to add exothermically to the carbonyl groups of the acid derivatives and of formaldehyde. Note that the heats of reaction for addition of a given anion to formic acid (**8a**), methyl formate (**8b**), or methyl acetate (**10**) are similar to those for addition to formaldehyde (**11**). This result is contrary to expectations based on current theory and the reactivities observed in solution. The greater reactivity of (**11**) in solution is normally attributed to stabilization of carboxylic acids and esters by resonance interactions between hydroxy or alkoxy and carbonyl. Our calculations predict the energetic effect of such interactions to be small. Any difference in reactivity between (**11**) and (**8**) or (**10**) must be explained in some other way.

On the other hand, our calculations (Table 2) predict the additions of anions to amides to be less exothermic than addition to esters by *ca.* 60 kJ mol^{-1}. This difference can reasonably be taken as an indication of the resonance energy of the amide group. While the barriers[18] to rotation about the C–N bonds in amides are usually somewhat larger than this, the

Table 2. Heats of reaction/kJ mol^{-1} for formation of tetrahedral adducts.

Substrate	ETO^-	MeO^-	HOO^-	$HCONH^-$	HN_2^-	OH^-	H^-
HCO_2H	−143.5	−148.0	−182.0	−179.1	−270.3	−276.1 (−194.1)	−399.1 (−180.7)
HCO_2CH_3	−124.7	−146.4	−199.9	−182.0	−273.6	−277.0 (−195.0)	−401.2 (−182.8)
$HCONH_2$	82.0	−87.0	−127.2	−127.1	−215.0	−211.7 (−129.7)	−336.8 (−141.4)
$HCONHCH_3$	−84.5	89.5	−127.6	−115.1	−214.6	−215.1 (−133.1)	−362.6 (−143.4)
$CH_3CO_2CH_3$	−127.6	−132.6	−166.5	−143.5	−263.6	−265.3 (−183.3)	−407.1 (−188.7)
CH_2O	−126.3	−131.4	−168.6	−184.9	−272.4	−257.7 (175.7)	−387.4 (−168.9)

Table 3. Comparison of heats of reaction for formation of tetrahedral adducts calculated by AM1 and by *ab initio* methods.

Reactants	Heat of reaction[a]/kJ mol^{-1}			
	4-31G	6-31G*	4-31 + G*	AM1
$HO^- + HCO_2H$	−219.2[b]	−206.3[b]	−123.4[b]	−194.1[c]
$HO^- + HCO_2CH_3$	−210.0[b]	—	−117.2[b]	−195.0[c]
$CH_3O^- + HCO_2H$	−127.6[b]	—	−127.6[b]	−148.1
$CH_3O^- + HCO_2CH_3$	−135.6[b]	—	−100.0[b]	−146.4
$HO^- + HCONH_2$	−162.8[d]	166.5[d]	—	−129.7[c]

[a] Heat of reaction for formation of the tetrahedral adduct from the named reactants. [b] Data from ref. 10. [c] Using the experimental value for the heat of formation of HO^-. [d] Data from ref. 9.

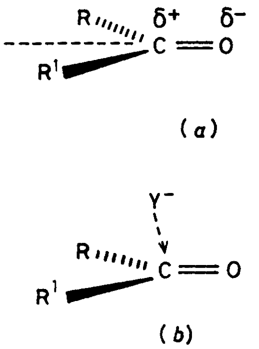


Figure 3. Approach of an anion (Y^-) to a carbonyl compound (RR′CO) for (*a*) formation of a CD complex; (*b*) addition to the C=O bond.

difference can be attributed to an increase in the resonance energy of the amide group by solvation, the resonance interaction leading to an increase in polarity.

Our results indicate that these reactions take place in the gas phase without any intervening barrier. Gas-phase studies[19] of some of them have indicated that the reactants can combine to form stable CD complexes, rearrangement of which to the tetrahedral adduct requires activation. The geometry of such a complex is determined by the electrostatic attractions between the components, these being greatest when the anion lies in the plane of the carboxy or amide group; see Figure 3(*a*). This interpretation has been supported by *ab initio* calculations[11a] for the corresponding complex formed by hydroxide ion with formaldehyde. Formation of such an adduct is irrelevant to the corresponding $B_{AC}2$ reaction which involves a sideways attack on the carbonyl; see Figure 3(*b*). Formation of the CD complex represents an alternative side reaction. The situation is quite different from that in an S_N2 reaction where the CD complex lies directly on the reaction path.

Nature of Desolvation Barriers.—The barriers in solution to $B_{AC}2$ reactions of anionic nucleophiles, *e.g.* alkaline hydrolysis of esters, must then be due in some way to the solvent. Polar solvents greatly accelerate reactions in which ions are generated because the solvation energies of ions are much greater than those of neutral molecules. Here the effect of solvation should be much less because no charges are formed or destroyed. According to the conventional representation, there the solvent is treated in effect as a continuous medium, the difference in solvation energy between the reactants and TS or products should be quite small, corresponding to differences in the way the charge is distributed in the species involved. This indeed was the conclusion reached by Hughes and Ingold many years ago in their classic studies of solvent effects in S_N2 reactions involving anionic nucleophiles.[20] It now appears that the effects in apparently analogous B_{AC} reactions are very much greater.

The simplest interpretation would be to assume that the difference in solvation energy is enough to make the tetrahedral adduct the TS. However, several arguments suggest that this is unlikely, even apart from the well known evidence that such species represent stable intermediates, not TSs.

(*a*) A detailed solvent simulation[10] has indicated that in alkaline hydrolysis of formamide in water, the tetrahedral adduct is a stable intermediate.

(*b*) Studies of secondary kinetic isotope effects[21] have indicated that the TS in alkaline ester hydrolysis is an early one where the HO–CO bond is still very weak.

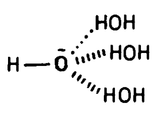
(*c*) Our results (Table 2), and the analogous *ab initio* ones (Table 3), indicate that formation of the tetrahedral adducts in the gas phase is exothermic by 80–120 kJ mol^{-1}. Since the activation energies in solution are of this order, the tetrahedral adducts could be TSs only if their solvation energies were less than those of the reactants by *ca.* 200 kJ mol^{-1}. This seems very unlikely.

The evidence thus suggests that the TS corresponds to formation of the tetrahedral adduct, not to the tetrahedral adduct itself. The activation barrier must therefore be due in some way to a change in the solvation energy during the association of the reactants. The reactants cannot approach one another until at least one molecule of solvent has been removed from the anion, creating a hole in its solvation shell. Once it has been removed, associaton of the reactants will be exothermic because of the electrostatic attraction between them.

In our original communication[6] we assumed that the anion and neutral substrate cannot even begin to approach until one molecule of solvent has been almost completely removed from the ion. This is neither essential nor likely. The decrease in energy due to attachment of successive solvent molecules to an ion is less for each successive addition, due to the repulsions between them. The total number of molecules in the solvation shell is set by the condition that the energy of attachment of the last one be negative. The energy required to add one more, or to squeeze in a molecule of the other reactant, may well be less than the energy needed to remove one, particularly in the case of large anions where the number of solvent molecules is large.

Barriers of the kind we are considering are therefore likely to be large only if the number of solvent molecules in the solvation shell is small. This is the case for anions where the charge resides on a first-row element because the co-ordination number is then four. There is also a strong tendency for the solvent molecules to be tetrahedrally oriented, due to the effective localization of the lone pairs of electrons in the ion which leads to strongly directed electrostatic 'bonds' to polar solvent molecules. Additional molecules of solvent are held less tightly, in a second solvation shell. This ordered structure is assisted by the small size of first-row atoms, the strain energy involved in packing five groups round such an atom being large. The desolvation barriers to B_{AC} reactions in solution are thus due simply to the large amount of energy needed to squeeze an extra molecule, *i.e.* the reactant, into the solvation shell. Once it gets close to the ion, the approach is assisted first by electrostatic interactions between them, and later by bonding interactions. However, the energy of the system will begin to decrease before significant changes in bonding occur.

The situation bears an unexpected analogy to that in an S_N2 reaction. As Dewar and Carrion[4] and Dewar and Healy[22] have shown, the barriers to such reactions are steric in origin, due to the strain involved in packing five atoms or groups round a given carbon atom. Calculations for reactions where a co-ordination number of four for carbon is not exceeded, in particular S_N2' and $B_{AC}2$ reactions,[4,6] have indicated that they take place without activation and the same is true for S_N2 substitution at silicon,[17] silicon being large enough to bond five



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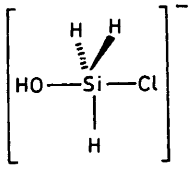

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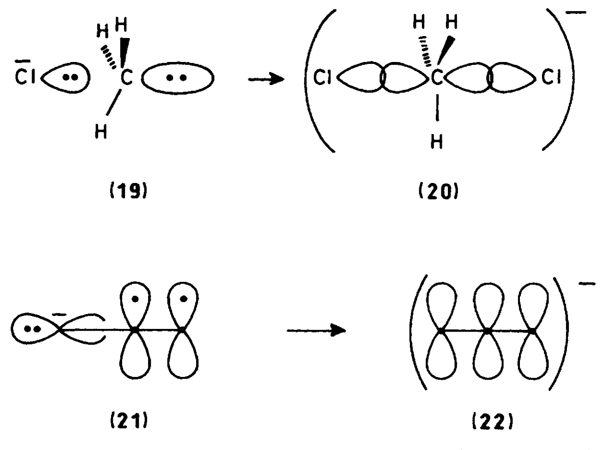


Figure 4. Illustrating the simple MO argument, that S_N2 reactions should not involve activation barriers. (21) and (22) represent the 2p AOs of allyl anion in orthogonal and planar geometries, respectively.

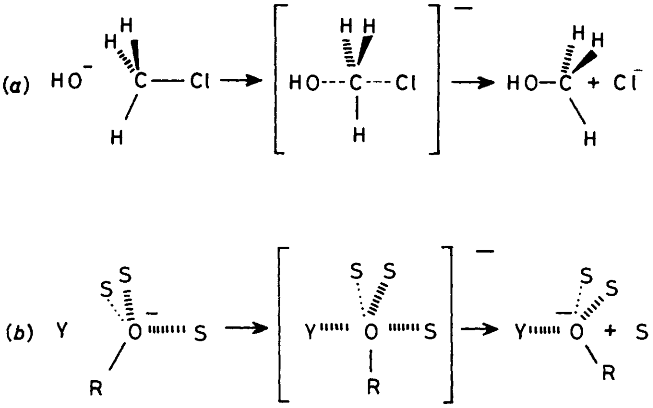


Figure 5. Illustrating the analogy between (*a*) an S_N2 reaction and (*b*) displacement of solvent (S) from an anion (RO^-) by a polar molecule (Y). The barrier is due in each case to the steric strain involved in packing five groups round a first-row atom.

groups simultaneously without excessive strain. The fact that compounds of silicon are more reactive than analogous ones of carbon is due primarily to the small size of carbon, not to participation by silicon d atomic orbitals (AO). This interpretation now seems to be widely accepted by silicon chemists and most of the other differences between first-row and later elements, *e.g.* the failure of nitrogen to form a pentafluoride, can be explained likewise. $B_{AC}2$ reactions can take place without activation in the gas phase because the central carbon atom in the tetrahedral adduct has only four neighbours.

While this conclusion concerning the S_N2 reactions may seem surprising, it would, in fact, be expected on the basis of simple MO theory, according to which, the addition of an anion to an alkyl halide, leading to a trigonal bipyramidal adduct, should take place exothermically and without activation. The argument is illustrated in Figure 4. The three-centre four-electron bond in the trigonal bipyramidal adduct (**20**) from chloride ion and methyl chloride (**19**) is completely analogous to the three-centre four-electron π bond in allyl anion (**22**). The situation in the reactants (**19**), where two of the relevant electrons occupy a 3p AO of the Cl^- ion while two form a two-centre CCl σ bond, is likewise analogous to that in the orthogonal form (**21**) of allyl anion where one terminal methylene group has been rotated through 90° and where two of the relevant electrons occupy the 2p AO of the rotated methylene while two form a two-centre π bond. Since (**22**) is lower in energy than (**21**), (**20**) should likewise be lower in energy than (**19**).

While this argument must have occurred to many organic chemists, it seems not to have been cited, no doubt because it seemed to lead to a ridiculous conclusion and was therefore written off as a typical example of the inadequacy of simple MO theory. However, as time goes on, it becomes increasingly clear that simple MO theory is nearly always right. 'Anomalies' of this kind invariably turn out in the end to have been due simply to inadequate consideration of the situation in question. Here the 'anomaly' should have served as a warning that some vital factor had been overlooked.

The arguments given above imply that the barriers to $B_{AC}2$ reactions in solution have a similar origin, *i.e.* the strain involved in packing five atoms or groups round a first-row atom. Indeed, as the following argument shows, the strain energies involved are of the same order.

Addition of an anion to an alkyl halide would be expected to be at least as exothermic as an analogous addition to silicon, were it not for the steric repulsions. The strain energy due to these in a carbon S_N2 TS must therefore be about the same as the exothermicity of the analogous addition to silicon plus the activation energy of the S_N2 reaction, *i.e. ca.* 200 kJ mol^{-1}. The corresponding strain energy in a $B_{AC}2$ reaction in solution should likewise be roughly a sum of the exothermicity of the reaction in the gas phase (Table 2) and the activation energy (*ca.* 80 kJ mol^{-1}) of the corresponding reaction in solution, *i.e.* also *ca.* 200 kJ mol^{-1}. While this is only a very approximate estimate, the (desolvation) barriers to $B_{AC}2$ reactions in solution are indeed similar to the (intrinsic) barriers of S_N2 reactions in the gas phase, the latter corresponding to the difference in energy between the CD complex and the TS ($\Delta E^{\ddagger}$ in Figure 2). Both barriers have a common origin, being due to steric repulsions between five groups clustered round a first-row atom; see Figure 5.

Desolvation Barriers in IB Reactions.—A reaction between an anion and a neutral molecule cannot start until the reactants come together to form a CD complex. Our arguments imply that this may involve a desolvation barrier. If the reaction is of IB type, the overall reaction in solution will then be a two-step process involving two distinct activation barriers, one the desolvation barrier to association of the reactants and the other the intrinsic barrier of the reaction itself. The net effect will depend on their relative heights.

If the second (IB) barrier is the higher [Figure 6(*a*)], the reaction will behave 'normally' in solution, its rate being determined primarily by the changes in bonding involved in forming the TS. The solvent can influence the rate in two ways, first by modifying the heat of reaction for formation of the CD complex and secondly by modifying the height of the activation barrier separating the CD complex from the product.

Formation of the CD complex in solution involves replacement of one or more molecules of solvent in the solvation shell of the ion by the other (dipolar) reactant. Any corresponding change is enthalpy will tend to be compensated by a corresponding change in entropy because the more tightly the species in questions are held together, the more negative will be the entropy.[23] If the heat of formation of the CD complex in the

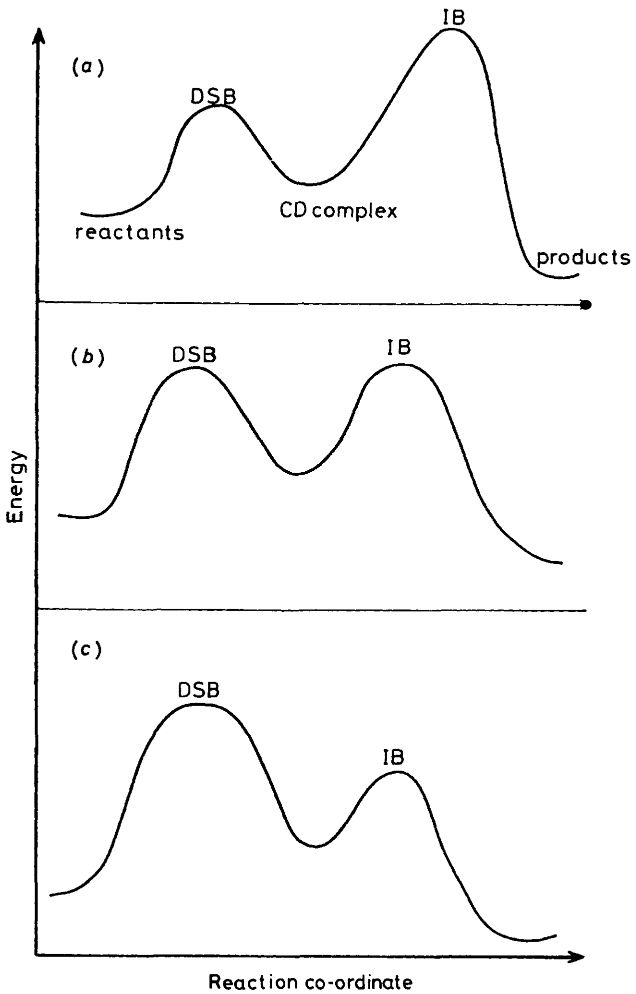


Figure 6. Reaction profiles for a reaction in solution between an anion (Y^-) and a neutral molecule (RX), for various relative heights of the initial solvactivation barrier (S) and intrinsic barrier (A).

gas phase is large, the free energy of association of the reactants in solution is then likely to be small.[4] Detailed calculations by Jorgensen *et al.*[12c] have indicated that this is indeed the case for the S_N2 reaction between chloride ion and methyl chloride in water. Exceptions may be expected in the case of small anions in protic solvents where the solvent interactions are unusually large. Otherwise the effect of the solvent should be confined largely to its effect on the barrier separating the CD complex from the product, which should be small because it corresponds to the difference in solvation energy between two species with similar geometries and equal charges. The solvation energy of the TS should be less because the charge in it is more dispersed. A polar solvent should therefore tend to retard the reaction. This was the argument used by Ingold[20] to explain the relatively small changes in rate brought about in such reactions by changing the solvent. The changes in rate are large only in the cases indicated above, *e.g.* for HO^- or F^- in protic solvents.

Conversely, if the first (desolvation) barrier is the higher [Figure 6(*c*)], the rate will be determined by the rate of association of the reactants to form the intermediate CD complex, not by changes in bonding involved in the reaction itself. The reaction will then be a typical DSB process and the effect of structural changes in the reactants will not be interpretable in a conventional manner, in terms of their effect on the relative energies of the reactants and the TS.

As yet there is no clear evidence that the rate of an IB reaction in solution can be controlled by a desolvation barrier. This is not in any way surprising. Since no one has suspected that such a situation might arise, no attempts have been made to locate an example. One may, however, have been inadvertently provided by a recent remarkable and unexplained observation.

The work in question[24] referred to secondary deuterium kinetic isotope effects (SDKIE) in the E2 elimination of hydrogen halide from 1,1-dideuterio-2-phenylethyl chloride (**24a**) or fluoride (**24b**) by t-butoxide ion (**25**) and in the S_N2 reaction of thiophenoxide ion (**26**) with 1-chloro-1,1-dideuteriobutane (**27**). In each case the observed k_H/k_D ratio varied with changes in the concentrations of the reactants, a result without precedent for which the authors gave no explanation. Furthermore, quite small changes in the concentrations of the reactants led to large changes in the rate ratios; see Table 4. Such variations seem inexplicable in terms of a one-step mechanism and both the experiments themselves, and analogy with other E2 and S_N2 reactions, make it very unlikely that any change of mechanism could have taken place over the limited range of conditions used.

While no reliable theoretical studies of E2 reactions have been published, AM1 calculations[25] here imply that they are IB reactions with low (<41.84 kJ mol^{-1}) activation barriers. Since the reaction in question involved an ion (**25**) where the charge is largely localized on an oxygen atom and since it was carried out in a protic solvent (t-butyl alcohol), it could well have involved a significant desolvation barrier. If so, the intermediate must have been a CD complex in which no changes in bonding had taken place. Since the E2 reaction is of IB type, any change in bonding in the CD complex would lead to an increase in energy. The isotope effect for the DSB reaction between (**24**) and (**25**) should differ from that for the E2 reaction itself, being due to the effect of deuteriation on the hydrogen bonds linking the reactants in the CD complex, not to a normal secondary isotope effect. The isotope effect for the overall reaction will depend on the relative heights of the two barriers. If they are comparable [Figure 6(*b*)], it will depend on the heights of both barriers and any change in the conditions that alters their relative heights will alter the observed k_H/k_D ratio. In this case the relevant changes were in the concentrations of the ionic reactants; see Table 4. The resulting change in ionic strength would be expected to affect the height of the first (desolvation) barrier, but not that of the second. Such a change would be expected to lead to a change in the observed isotopic-rate ratio.

$PhCH_2CD_2X$ (**24**) **a**; X = Cl; **b**; X = F

$(CH_3)_3CO^-$ (**25**)

PhS^- (**26**)

$CH_3CH_2CH_2CD_2Cl$ (**27**)

This interpretation could be tested by carrying out the reaction in the presence of inert salts to see if changes in the ionic strength of the medium affect the SDKIE. In the meantime, it is difficult to see any other explanation of the reported results.

The other reaction mentioned above involved an anion (**26**) where the charge is largely localized on sulphur, a second-row atom. Let us consider the situation regarding desolvation barriers in such cases, starting with chloride ion.

Since second-row atoms are large enough to bind covalently six groups (*cf.* SF_6), at least six molecules of solvent may be able to fit round a chloride ion, provided they are small. Since solvent is held on an ion by charge–dipole forces and since these vary rapidly with distance, the binding energies of molecules of solvent to Cl^- should be less than those to a first-row ion. Since the electrostatic field round Cl^- has spherical symmetry, little energy should be needed to squeeze in a seventh group round

Table 4. Secondary deuterium kinetic isotope effects.

	Reactants				
Reaction	X^-	Y	$[X^-]$/mol dm^{-3}	$[Y]/10^{-3}$ mol dm^{-3}	K_H/K_D
E2	**(25)**	**(24a)**	0.0896	4.044	0.808 ± 0.004
			0.3060	4.044	1.149 ± 0.010
	(25)	**(24b)**	0.1618	7.859	0.862 ± 0.012
			0.3264	7.891	1.036 ± 0.019
S_N2	**(26)**	**(27)**	8.6×10^{-3}	4.6×10^{-3}	1.085 ± 0.011
			4.5×10^{-3}	7.7×10^{-3}	1.190 ± 0.222

the ion. Indeed, a detailed theoretical study[25] of the S_N2 reaction between chloride ion and methyl chloride in aqueous solution failed to indicate a desolvation barrier.

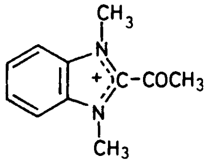
The situation could, however, be different in the case of the reaction between (**26**) and (**27**). In the first place, repulsion between the electron pair forming the C–S bond and the three lone pairs of valence-shell electrons should tend to localize the latter in a tetrahedral geometry, a point noted above in the discussion of analogous first-row anions. This should lead to strong binding of three solvent molecules to the sulphur, not five. Secondly, since the reaction was carried out[25] in a solvent (DMF) with molecules larger than those of water, steric effects could have helped to limit the number of molecules in the solvent shell.

It is therefore reasonable to suppose that the reaction between (**26**) and (**27**) in solution involves a preliminary desolvation barrier, comparable in height to the intrinsic barrier to the S_N2 reaction itself. The abnormal SDKIEs (Table 4) could then be explained in the same way as those for the E2 reactions of (**24**).

Our arguments imply that S_N2 reactions of first-row anions, *e.g.* hydroxide or alkoxide, should also exhibit a double barrier in solution. Theoretical studies of such a reaction would be of much interest. A recent paper[26] reporting calculations for the reaction of hydroxide ion with methyl chloride includes a reaction profile indicating the absence of a desolvation barrier in water. However, this was based not on calculations but on the assumption that no such barrier exists, by analogy with the corresponding reaction of chloride ion.[25] The argument above indicates that the cases are not, in fact, comparable.

Desolvation barriers can, in principle, intervene in any process involving ions in solution. The simplest case is the association of two ions of opposite sign to form an ion pair. It now seems to be generally agreed that such ion pairs can exist, at least in certain cases, in two forms; intimate ion pairs, where the ions are in contact, and solvent separated ion pairs, where the solvation shells of one or both ions intervene. If both forms are stable species, corresponding to minima on the potential energy surface, they must be separated by a desolvation barrier. Theoretical calculations[27] have indeed indicated the existence of a small barrier in the case of t-butyl chloride in water. Such barriers would be expected to be small because the electrostatic attraction between ions of opposite signs is very strong. If such barriers exist, analogous but much larger barriers should be expected in the case of ion–molecule reactions where the attractions are much smaller. The fact that such barriers can indeed be large is therefore in no way surprising. Indeed, in hindsight, one can see that their possible existence should have been suspected earlier, in view of the general recognition that barriers of this kind exist in the case of ionic association.

A striking illustration of the difference between the desolvation barriers in ionic association and ion–dipole reactions is provided by a recent study[28] of deacylation of 2-acetyl-1,3-dimethylbenzimidazolium ion (**28**) in aqueous solution.



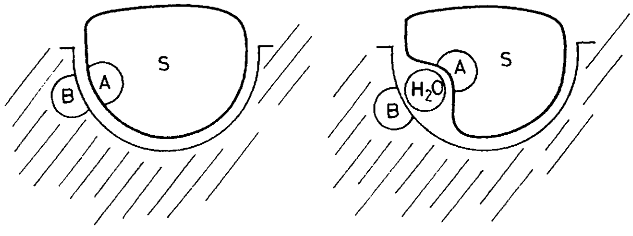
(**28**)

Hydroxide ion was found to react extremely rapidly with (**28**), so rapidly that no reaction could be observed with neutral bases. Only hydrolysis products were formed, derived from hydroxide ion generated by reaction of the base with water. This result would be expected in view of the arguments indicated above. Reaction of (**28**) involves association of two ions of opposite charge, whereas reaction of (**28**) with a neutral base involves an ion–dipole association. While both reactions are of DSB type, the barrier to the latter is much larger.

Hard–Soft Acid–Base Theory.— The rules relating structure to reactivity for anionic substitution at carbonyl carbon differ in well known respects from those for substitution at saturated carbon. These differences have been explained in terms of hard–soft acid–base (HSAB) theory,[29] alkyl halides and related species being regarded as 'soft' acids that react preferentially with 'soft' bases (*e.g.* RS^-) whereas carboxylic acid derivatives are 'hard' acids that react preferentially with 'hard' bases (*e.g.* HO^-). The arguments presented here suggest an alternative interpretation which may apply in other situations where HSAB theory has been invoked.

Substitution at carbonyl carbon by an anionic nucleophile is a DSB reaction in which little change in bonding takes place in the TS. The attraction between the reagents at this point is thus predominantly electrostatic. The effect of changes in the carbonyl derivative (Y) on the rate of its reaction with an anion (X^-) therefore depends primarily on the distribution of formal charges in Y, not on its ability to react with nucleophiles. As noted earlier, this conclusion invalidates conventional treatments of reactivity in this connection, these being based on the assumption that activation barriers are primarily intrinsic.

Klopman[30] has considered the TS of a bimolecular reaction in terms of SCF perturbation theory, the reactants representing the unperturbed system and the interaction between them being the perturbation. Here the first-order perturbation corresponds to electrostatic interactions between the reagents while higher order ones correspond to the changes in bonding that take place in forming the TS. Klopman identifies the former with 'hard–hard' interactions of HSAB theory and the latter with 'soft–soft' ones. According to the present analysis, the activation barrier in a DSB reaction is determined primarily by electrostatic interactions, *i.e.* by first-order perturbations between the reactants, while that in an IB reaction is determined primarily by changes in bonding, *i.e.* by the higher order perturbations.



(a) (b)

Figure 7. (*a*) When a proper substrate of an enzyme is adsorbed in its active site, water is excluded from between the centres involved in the subsequent reaction between them. (*b*) Adsorption of a 'poor' substrate leaves water attached to one or other of the reaction centres. This inhibits the reaction.

The difference between substitution at saturated carbon and carbonyl carbon has therefore nothing to do with the 'hardness' or 'softness' of the reactants. It is due to a difference in mechanism. The former is an IB reaction, the latter a DSB one. A DSB reaction is controlled by electrostatic ('hard–hard') interactions between the reactants because little or no change in bonding has occurred in the TS. An IB reaction is controlled by changes in bonding, *i.e.* 'soft–soft' interactions.

It seems likely that other situations where HSAB theory has been invoked could be explained likewise in terms of differences in mechanism rather than 'hardness' or 'softness' of acids and bases. This would be a useful simplification. It would also avoid the ambiguity of a classification where a given acid or base may be 'hard' in one context and 'soft' in another. Thus hydroxide ion behaves as a very strong nucleophile both with 'soft' acids (*e.g.* alkyl halides) in the absence of polar solvents and with 'hard' ones (*e.g.* esters) in aqueous solution. According to the present analysis, there is no reason why a given reagent should not be both 'hard' and 'soft,' depending on the mechanism of the reaction in question.

Catalysis and Enzyme Reactions.—The present evidence shows that activation barriers to reactions of anions in solution can be due entirely to the energy needed to remove solvent from the ion in order that the other reactant can approach. Once the reactants are in contact, the solvent should play only the minor role envisaged by Ingold.[20] Any subsequent reaction between them will lead only to a minor change in geometry. Any solvent effect will correspond to the difference in solvation energy of two species of similar size, shape, and ionic charge, differing only in the way the charge is distributed. Theoretical calculations[4] have indeed indicated that the rates of S_N2 reactions, starting from the CD complex, are similar in solution and in the gas phase.

The rate of a DSB reaction should be much greater under conditions where the reactants can approach one another without being impeded by intervening solvent. This is the case in the gas phase. Another way to achieve a similar though smaller effect is to decrease the tightness of binding of the solvent molecule by carrying out the reaction in a less polar solvent. Reactions of hydroxide and fluoride ions can be accelerated greatly by carrying them out in aprotic solvents (*e.g.* DMF or DMSO) and phase-transfer catalysis involves the same principle.

In these cases the acceleration is brought about by a change in the surrounding medium, either to a vacuum or to a less polar solvent. This, however, is not necessary. The medium surrounding the reactants plays only a minor role. It is the medium between them that matters. These considerations formed the basis of a recent interpretation[31,32] of the high activity and specificity of enzymes as catalysts. When a proper substrate is adsorbed in the active site of an enzyme, the reaction centres in them must be in contact; see Figure 7(*a*). If water were trapped between them, it would obstruct the reaction. The subsequent reaction between them will then be subject only to the intrinsic barrier characteristic of a parallel reaction in the gas phase. If the corresponding reaction in aqueous solution is of DSB type, the enzyme reaction will show a corresponding acceleration. It should indeed take place at a rate similar to that of an analogous reaction in the gas phase, starting with the reactants in contact. If the reaction has only a small intrinsic barrier, the rate of the enzyme reaction may be greater by many orders of magnitude than that of an analogous uncatalysed reaction in solution. The very large acceleration of reactions by enzymes can be explained immediately in this way, without any need for special factors or mechanisms of the kind invoked in earlier interpretations. Furthermore, if the substrate does not fit the active site sufficiently closely or is not adsorbed sufficiently strongly, water may remain attached to at least one of the groups involved in the reaction. The trapped water [Figure 7(*b*)] will impede the reaction in the same way that intervening water impedes an analogous DSB reaction in aqueous solution. This provides a simple explanation of the specificity of enzyme reactions, again without any need for the kinds of special assumption involved in previous interpretations.

Note that water need not be completely excluded from the active site; only from between the reactions centres. Note also that the reaction need not lack an intrinsic barrier. If it has one, the acceleration brought about by the enzyme will be correspondingly limited. In view of misunderstandings that have arisen, these points need to be emphasized.

Other factors may of course also contribute to the efficacy of enzymes as catalysts. Specific catalysis by transition metals clearly plays a role in corresponding metalloenzymes. In order to assess them, it is clearly necessary to determine first the effect of desolvation. In the case of one group of enzymes (serine-type proteases) calculations[31,33] and experimental studies of enzyme models[34] indicate strongly that the observed rates can be accounted for in terms of desolvation alone.

Our arguments also have implications concerning attempts to develop 'artificial enzymes.' In order to mimic the activity of a true enzyme, it will not be sufficient to include the relevant groups in the right orientation and to ensure adsorption of the substrate in more or less the right position. The system must be sufficiently rigid, and adsorption of the 'substrate' sufficiently rigid, to exclude rigorously unwanted water from between the reacting groups. These comments find support in the model studies[34] referred to above. Locking the essential parts of the catalytic system in chymotrypsin together in such a way that no solvent molecules could fit between them, by attaching them to a rigid support, led to a very large acceleration, in spite of the fact that the system as a whole was immersed in water.

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