INGOLD LECTURE*

How Does a Reaction Choose Its Mechanism?

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1 Introduction

Ingold laid the foundation of modern organic chemistry by constructing a classification of reactions and their mechanisms.[1] Progress in science requires a language and Ingold's examination of reaction mechanisms led to a classification that provides a rational language for communication, generalization, and prediction in organic chemistry. This language has had an important influence on the development of synthetic organic chemistry and other branches of chemistry, as well as on our present understanding of organic reaction mechanisms.

Much of the experimental work on reaction mechanisms has been concerned with fitting reactions into the Ingold scheme or other schemes, such as Winstein's classification of ion-pair intermediates in solvolysis reactions.[2] In comparison there has been surprisingly little inquiry into the question of *why* a reaction should follow one mechanism rather than another under a particular set of experimental conditions. For example, it is generally agreed that nucleophilic substitution on carbon follows an S_N2 mechanism for methyl transfer and an S_N1 mechanism when a stable carbocation intermediate can be formed easily, but it is not so clear what is responsible for changing mechanisms in the 'borderline' region (Figure 1). It is particularly important to have a clearly defined classification of mechanism in this borderline region, which may well be larger than the regions of well established mechanism. In chemistry, as in other areas, lack of agreement upon the position of sharp borderlines invariably leads to conflict.

Distinctions between mechanisms of chemical reactions in solution are concerned in large part with the sequence in which reactants are assembled and dispersed in relation to the bond-making and -breaking steps. The purpose of this review is to examine the extent to which the choice of reaction mechanism is dictated by the lifetime of intermediates that may be formed in a reaction. It appears that many reaction sequences are enforced in a simple way by these lifetimes; a relatively small number have been shown not to be enforced.

It has frequently been suggested that a clear-cut distinction between reaction

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[1] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', 2nd Edn., Cornell Univ. Press, Ithaca, New York, 1969.
[2] S. Winstein and G. C. Robinson, *J. Am. Chem. Soc.*, 1958, **80**, 169.

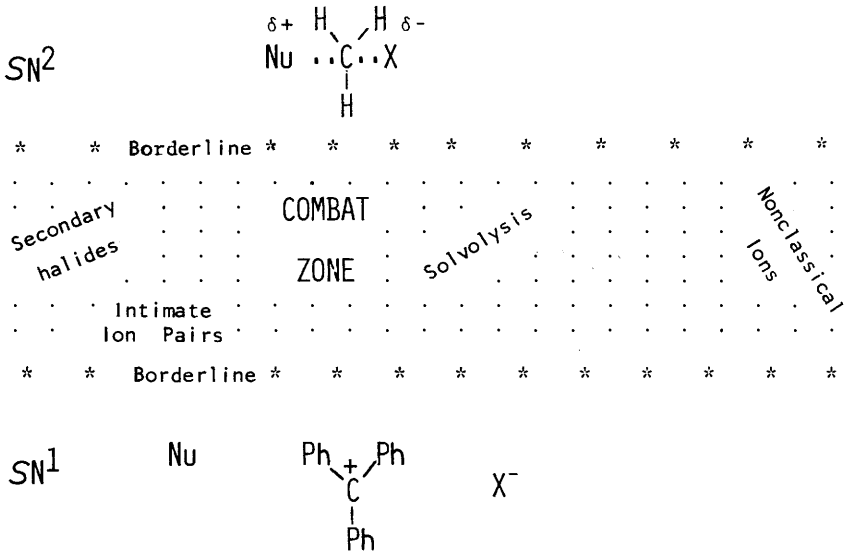


Figure 1 *Mechanisms and borderlines for substitution on carbon*

mechanisms is impossible because, for example, there is a gradual transformation of an S_N2 into an S_N1 mechanism with no sharp borderline as the transition state develops more carbocation character.[3] However, a clear distinction can be made if the classification of mechanism is based upon the lifetime of intermediates rather than the character of the transition state. The lifetime of intermediates permits a fairly sharp *qualitative* distinction between mechanisms, whereas the character of the transition state or the degree of assistance in a reaction gives only a *quantitative* description with no sharp boundaries.

It is useful to illustrate the distinction with reaction co-ordinate–energy contour diagrams as described by More O'Ferrall in 1970 for elimination reactions[4] (Figure 2). A reaction can proceed either through an intermediate in a potential well that provides barriers for *both* the formation and breakdown of the intermediate (A and B), as in an *E*1cb elimination mechanism, or through a concerted, one-step mechanism with a single barrier and no intermediate (1, 2, or 3), as in an *E*2 elimination. If an intermediate is said to exist if it has a lifetime longer than a vibration frequency, of the order of 10^{13} s^{-1}, there is a sharp borderline between the stepwise and concerted mechanisms.* A concerted mechanism with no intermediate can proceed through transition states with varying degrees

*Encounter complexes of the reactants or products are not kinetically significant intermediates in this sense, except in the case of diffusion-controlled reactions.

[3] See, for example, S. Winstein, E. Grunwald, and H. W. Jones, *J. Am. Chem. Soc.*, 1951, 73, 2700.

[4] R. A. More O'Ferrall, *J. Chem. Soc. B*, 1970, 274.

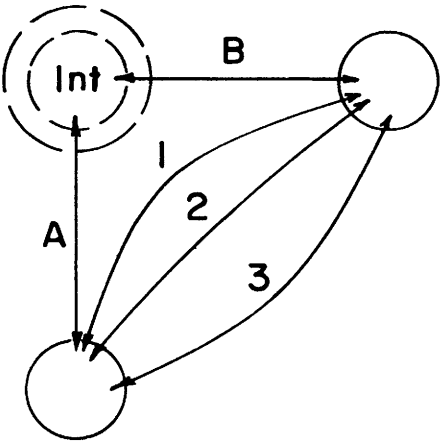


Figure 2 *Reaction co-ordinate–energy diagram to show how a reaction that requires two processes,* A *and* B, *can occur in two steps through an intermediate with a significant lifetime,* Int, *or through concerted mechanisms,* 1, 2, or 3, *in which the transition states have varying degrees of resemblance to the structure of the intermediate*

of resemblance to the structure that an 'intermediate' might be expected to have and with varying degrees of coupling of the two processes that are involved in the formation and breakdown of the 'intermediate', as shown in 1, 2, and 3 (Figure 2). The qualitative distinctions between mechanisms are naive in the sense that they do not take explicit account of the degree of coupling and mechanisms of energy transfer in the activation process. Energy transfer can be relatively slow and energy diagrams certainly do not provide a complete description of the course of a reaction. Nevertheless, these distinctions may be useful as a simple guide for describing and predicting reaction mechanisms.

The question remains of what is the meaning of the 'merging' of mechanisms? How is one mechanism changed into another as the structure of the reactants or the reaction conditions are changed? One possibility is that one mechanism becomes, or is transformed into, the other. This can happen when the intermediate in a stepwise mechanism becomes progressively less stable and eventually ceases to exist, so that the well corresponding to the intermediate in Figure 2 disappears and the reaction becomes concerted. The other possibility is that the two mechanisms can exist concurrently, so that there is a well for the intermediate in the stepwise path but the reaction also proceeds through a concerted path, *i.e.* 1, 2, or 3. In this case there is a change in the predominant mechanism when there is a reversal of the relative Gibbs energies of the rate-determining transition states for the two coexisting mechanisms. The change in mechanism then may not be enforced by the lifetime of the intermediate, if the reactants are in approximately the same position relative to each other. A change between two coexisting mechanisms will usually give a sharp upward break in structure–reactivity correlations as the second mechanism becomes predominant. However,

upward curvature may also occur with a single mechanism as the structure of the transition state changes. There are only a few cases in which this question can be answered at the present time.

A scheme for distinguishing reaction mechanisms is shown in Figure 3. This

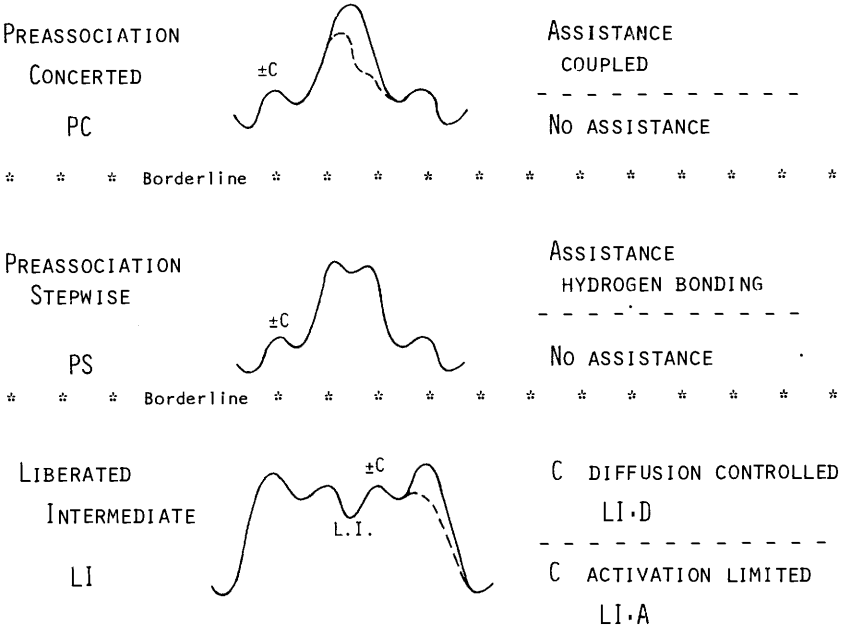


Figure 3 *Classification of reaction mechanisms*

scheme provides borderlines between mechanisms that depend on the lifetimes of intermediates. We consider here only unstable, steady-state intermediates that do not accumulate during the reaction. There are two primary distinctions or borderlines: (i) between mechanisms that are concerted with no intermediate (except for encounter complexes of reactants and products) and mechanisms that proceed through one or more intermediates in a stepwise process, (ii) between mechanisms in which the intermediate either does or does not have a sufficient lifetime to diffuse through the solvent before reacting with a catalyst or another reactant. When the intermediate does not exist or is too unstable to diffuse through the solvent the reaction must occur through a preassociation mechanism in which the reactants, including the final reactant or catalyst, C, are assembled before the first bond-making or -breaking step occurs. The preassociation mechanism can be either concerted with no intermediate, PC, or stepwise with an intermediate, PS (Figure 3).** If the intermediate lives long enough to diffuse out

**The term preassociation has often been applied to stepwise reactions. There is also preassociation of the reactants in concerted reactions and the term is properly applied to both concerted and stepwise reactions in which a final reactant is present at the time of the initial bond cleavage or formation.

of the solvent cage in which it is formed, it becomes a liberated intermediate and can react with a final reactant or catalyst, C, either at a diffusion-controlled rate, LI · D, or in an activation-limited reaction, LI · A (Figure 3, bottom).

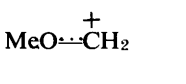
The mechanism can be described further by the degree of assistance that is provided by a catalyst or reactant in the rate-determining transition state. It is important to separate this quantitative criterion from the qualitative distinction based on lifetimes, because assistance may be either present or absent in both concerted and stepwise mechanisms. A concerted reaction can occur through a coupled mechanism with assistance by the final reactant or catalyst, as in a classical S_N2 displacement, or through an uncoupled mechanism in which there also is no intermediate, but the second process has little or no influence on the energy of the rate-determining transition state. These two mechanisms might be described by the solid and dashed lines, respectively, at the top of Figure 3. A stepwise preassociation mechanism can also occur either with assistance, such as hydrogen bonding of an acid catalyst to a basic site in a transition state, or without assistance, as in a 'spectator' mechanism in which the catalyst is present but does not stabilize the rate-determining transition state of the preassociation mechanism.[5] Assistance by the solvent is more difficult to characterize and is not generally useful as a criterion for distinguishing mechanisms.

2 Preassociation Concerted Mechanisms

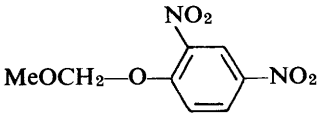
A. Substitution Reactions.—Ingold's definition of an S_N2 substitution is a model of clarity and deserves quotation. The mechanism '. . . contains only one stage, in which two molecules simultaneously undergo covalency change.'[6] Few will argue today against such a concerted mechanism for nucleophilic displacements on the methyl group, which certainly cannot form a carbocation intermediate with a significant lifetime in the presence of any respectable nucleophile.[7–9]

It is surprising, however, that several reactions of methoxymethyl derivatives also appear to proceed by concerted mechanisms, in spite of the potential of these compounds to form the relatively stable oxocarbonium ion (1). Methoxymethyl derivatives, such as methyl chloromethyl ether and formaldehyde acetals, certainly react through transition states that resemble (1) and have been widely believed to react through a monomolecular mechanism with (1) as an intermediate.[10–12] However, the methoxymethyl derivatives (2) and (3), with dinitrophenolate ion or *NN*-dimethylanilines as the leaving group, undergo second-order displacement reactions in aqueous solution with various nucleophilic reagents.[13,14] The second-

[5] L. D. Kershner and R. L. Schowen, *J. Am. Chem. Soc.*, 1971, **93**, 2014.
[6] C. K. Ingold in ref. 1, p. 423.
[7] W. von E. Doering and H. H. Zeiss, *J. Am. Chem. Soc.*, 1953, **75**, 4733.
[8] M. H. Abraham and D. J. McLennan, *J. Chem. Soc., Perkin Trans. 2*, 1977, 873.
[9] W. J. Albery and M. M. Kreevoy, *Adv. Phys. Org. Chem.*, 1978, **16**, 87.
[10] W. Cocker, A. Lapworth, and A. Walton, *J. Chem. Soc.*, 1930, 440.
[11] P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Presit, *J. Chem. Soc.*, 1955, 3641.
[12] T. C. Jones and E. R. Thornton, *J. Am. Chem. Soc.*, 1967, **89**, 4863.
[13] G. A. Craze, A. J. Kirby, and R. Osborne, *J. Chem. Soc., Perkin Trans. 2*, 1978, 357.
[14] B. L. Knier and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 6789.



(1)



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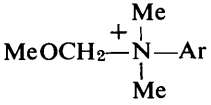

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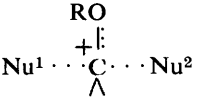


(4)

order rate constants show a small dependence on the structure of the nucleophilic reagent, which is intermediate between that expected from the Swain–Scott scale for substitution on methyl halides and the Ritchie N^+ scale for addition to carbonium ions. The rate constant for solvolysis is accounted for by the rate constant for the second-order displacement reaction with water that is predicted by these correlations, *i.e.* there is no indication of any solvolysis reaction that proceeds by a different mechanism. There is a large amount of bond-breaking at the leaving group. The reactions of both strong and weak nucleophiles with (3) cannot be accounted for by ion-pair or ion-dipole intermediates. The reactions occur through an open, 'exploded' transition state (4) that closely resembles the oxocarbonium ion (1) but there is significant stabilization of this transition state by the incoming nucleophilic reagent.

The concerted reaction mechanism appears to be enforced by the short lifetime of the oxocarbonium ion (1). A lifetime of $\sim 10^{-15}$ s for (1) in water was estimated from an extrapolation of measured lifetimes of oxocarbonium ions derived from acetophenone acetals.[15] Although this estimate is too uncertain to give a definitive conclusion, the estimated 'lifetime' of $\sim 10^{-23}$ s for (1) in the presence of RS^- is too short to reconcile with a stepwise mechanism for substitution that proceeds through an intermediate with a significant lifetime.[14] The reactions exhibit variable secondary α-deuterium isotope effects ranging up to $k_H/k_D = 1.18$ with different nucleophiles, which must reflect differences in the nature of nucleophilic interactions with the central carbon atom in the transition state. The large values for these second-order reactions also show that α-deuterium isotope effects of this magnitude cannot be taken as evidence for a monomolecular reaction mechanism. The transition state (4) may be regarded either as an unusually loose transition state for an S_N2 reaction or as a carbocation that is stabilized by interactions with both the attacking and leaving groups.

Substitution and solvolysis reactions at the anomeric carbon atom of sugars have also been widely believed to proceed through an oxocarbonium ion intermediate, but these reactions certainly proceed through a preassociation mechanism and may well proceed through a concerted mechanism with assistance in

[15] P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, 99, 8238.

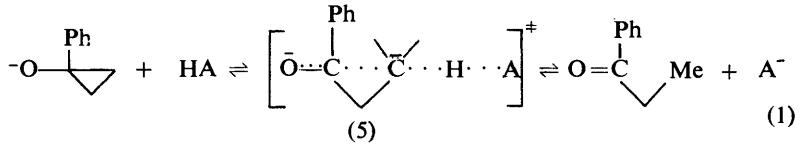
nucleophilic solvents. The rate of acid-catalysed hydrolysis of methyl β-D-glucopyranoside is $\sim 10^3$ slower than that of formaldehyde dimethyl acetal,[16,17] so that the oxocarbonium ion derived from sugars is unlikely to be more stable than that derived from formaldehyde derivatives. Solvolysis of a series of α- and β-glucosides in 50% ethanol–trifluoroethanol gives different product ratios with different leaving groups, which shows that no common intermediate is formed that has a lifetime sufficient to become liberated from the leaving group by diffusion into the bulk solvent.[18] These reactions also give product ratios in which substitution by ethanol is favoured over trifluoroethanol by factors of up to 20, which shows that the incoming group can stabilize the transition state by corresponding ratios. Ion-pair intermediates cannot be formed with the uncharged leaving groups, and when phenol is the leaving group there must be bond-breaking in the rate-determining step (phenol is a weaker nucleophile than the solvent, so that if an intermediate were formed it would give a product rapidly after the bond-breaking step). Thus, the C-1 atom of the sugar is interacting with both the leaving group and the entering group in the transition state (4).

It is even more surprising that the relatively small fraction of the reaction that goes with retention of configuration gives similar product ratios that require a similar stabilization of the transition state by the more basic solvent molecule. This is presumably made possible by the open, 'exploded' transition state, which resembles the transition state for diffusion away of the leaving group. Front-side substitution is not usually expected for S_N2 displacements on carbon but is well known for displacement on silicon, for which there is some theoretical rationale, and for displacement on metals, which also can occur through open, 'exploded' transition states that allow a weak interaction with both the entering and leaving groups.[19]

Lysosyme and related enzymes must provide considerable stabilization to a glycosyl–enzyme intermediate and to the transition state for its formation, because these enzymes catalyse glycosyl transfer to dilute sugars with retention of configuration, as well as to water. The intermediate cannot be an oxocarbonium ion because an oxocarbonium ion would not have a sufficient lifetime to permit diffusion and reaction with a molecule of sugar before it reacts with water. The intermediate is presumably a species that is stabilized by some degree of bonding to the aspartate carboxylate group at the active site of lysosyme.[15]

B. Carbanion and Elimination Reactions.—Condensation and elimination reactions that are generally thought to proceed through carbanion intermediates must proceed through a concerted mechanism when the carbanion is not stabilized and has no significant barrier for protonation, condensation, or elimination. The reverse aldol-type cleavage of 1-phenylcyclopropanol to 1-phenylpropanone [equation (1)], for example, would certainly proceed through a

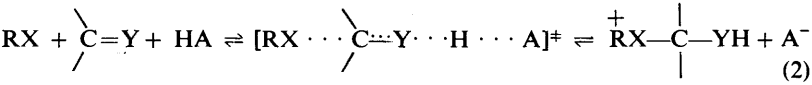
[16] P. Salomaa, *Suom. Kemistil. B*, 1960, **33**, 11.
[17] D. Cocker and M. L. Sinnott, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1391.
[18] M. L. Sinnott and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 2026.
[19] N. T. Anh and C. Minot, *J. Am. Chem. Soc.*, 1980, **102**, 103.



(5) (1)

carbanion intermediate if that intermediate had a significant lifetime. However, this reaction proceeds through a preassociation mechanism that probably is concerted because the unactivated primary carbanion has a p$K \geqslant 48$ and no significant barrier for protonation; a crude calculation suggests that the carbanion is less stable than the transition state of the observed reaction.[20-22] The reaction shows general acid catalysis by buffer acids with a Brønsted slope of $\alpha = 0.25$ and a primary deuterium isotope effect of $k_H/k_D = 1.9 \pm 0.2$, consistent with a concerted S_E2 reaction mechanism that proceeds through an open, 'exploded' transition state (5).[21] The same mechanism must hold for aldol-type condensations through a transition state resembling a homoenolate ion in the reverse direction.[21,22] Other elimination reactions of compounds with little or no activation at the β-carbon atom or with leaving groups that are expelled with no activation barrier must proceed by an analogous enforced concerted mechanism.[23] It is conceivable that assistance through a preassociation mechanism of this kind facilitates enzyme-catalysed reactions that would require the rapid formation of unstable carbanions.[21]

C. General Acid–Base Catalysis of Complex Reactions.—A concerted mechanism is probable, although not proved rigorously, for general acid catalysis of trifluoroethanol addition to formaldehyde, with catalysis at the electrophilic reagent through a class *e* reaction [equation (2); RX = ROH, $\rangle C{=}Y$ = HCHO].[24] In the reverse direction this mechanism corresponds to concerted general base catalysis of the elimination of ROH from the protonated addition

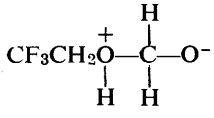


(2)

compound to give the carbonyl compound. The rate constant for this elimination is $\sim 10^5$ higher than the calculated rate constant for proton removal to form the

[20] C. H. DePuy, *Trans. N. Y. Acad. Sci., Ser. 2*, 1966, **28**, 561.
[21] A. Thibblin and W. P. Jencks, *J. Am. Chem. Soc.*, 1979, **101**, 4963.
[22] D. H. Hunter, J. B. Stothers, and E. W. Warnhoff in 'Rearrangements in Ground and Excited States', ed. P. de Mayo. Academic Press, New York, 1980, Vol. 1, p. 400.
[23] W. H. Saunders, jun., *Acc. Chem. Res.*, 1976, 9, 19.
[24] L. H. Funderburk, L. Aldwin, and W. P. Jencks, *J. Am. Chem. Soc.*, 1978, **100**, 5444.

dipolar intermediate (6) in a stepwise mechanism. The rate constants that would be required for reaction of (6) in order to account for the observed rate have been estimated to be $\geq 10^{13}$ s^{-1} for the expulsion of ROH and $> 10^{14}$ s^{-1} for proto-



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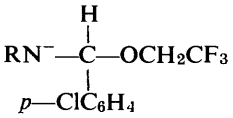
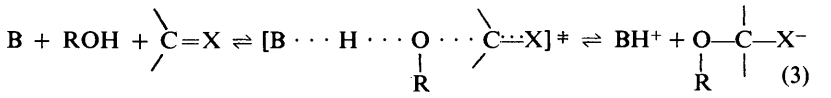


(7)

nation by H_3O^+ in an encounter complex. Rate constants of this magnitude are inconsistent with the existence of two significant barriers for a stepwise reaction through this 'intermediate'. It is even more unlikely that the reaction proceeds through a dipolar intermediate analogous to (6) when the driving force for its breakdown is larger, as in the formation of a more stable carbonyl product such as a ketone or a resonance-stabilized ester or amide. A higher 'rate constant' of $\sim 10^{16}$ s^{-1} would be required for the expulsion of trifluoroethoxide ion from the anion (7; R = *p*-$MeC_6H_4SO_2NH$) through a stepwise mechanism, which requires that base-catalysed hydrazone formation from the parent carbinolamine must proceed through a concerted mechanism.[25]

There is strong evidence supporting a concerted mechanism for catalysis by general bases of the addition of alcohols and water to electrophilic carbon centres, with catalysis at the nucleophilic reagent through a class *n* mechanism [equation (3)]. In the reverse direction this mechanism corresponds to general acid



(3)

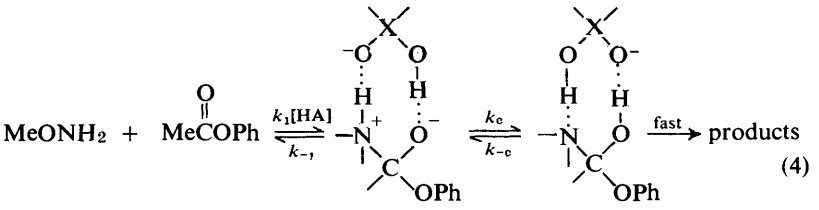
catalysis of the expulsion of RO^-. This is a widespread mechanism, which is responsible for hydrolysis and hydration reactions, for example. The concerted mechanism is supported by the occurrence of solvent deuterium isotope effects, usually in the range k_{ROH}/k_{ROD} = 2—4, and a large body of structure–reactivity data, which provide evidence that both proton transfer and C—O bond-formation or -cleavage are taking place in the transition state.[24,26–28] The simplest

[25] J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, 99, 464.
[26] N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 507.
[27] J. L. Palmer and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 6466.
[28] J. L. Palmer and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 6472 and references therein.

such evidence is that there is a smooth transition between the development of net positive or negative charge on the central oxygen atom in the transition state, as shown by the changing dependence of the rate on the pK_a of the alcohol (β_{nuc} or β_{lg}). This requires that there be a changing balance between the amounts of proton transfer and C—O bond-formation (or -cleavage) in the transition state with changing substituents on the oxygen atom or the catalyst. The direction and amount of these changes can be explained by a concerted mechanism that corresponds to a diagonal reaction co-ordinate on an energy contour diagram with separate axes for proton transfer and C—O bond formation. The structure–reactivity data suggest that the reaction is best described as an electrophilic attack on the central oxygen atom by the proton or by the electrophilic carbon centre, which drives the reaction by withdrawing electrons from the bond to the carbon or to the proton, respectively.[28]

Concerted catalysis of the addition and elimination of amines is less common because the greater stability of protonated amines favours a stepwise mechanism with a protonated addition intermediate. There is evidence for a concerted class *n* mechanism for a few reactions that would be expected to give highly unstable intermediates with little or no significant lifetime.[29–31]

With a bifunctional acid–base catalyst two protons can be transferred in a concerted process through an 8-membered cyclic transition state, because the transfer of each proton increases the basicity of the adjacent basic site and the acidity of the other acidic site by an electrostatic effect. This has been observed for catalysis of the methoxyaminolysis of phenyl acetate by phosphate, arsenate, and similar catalysts [equation (4)].[32] Acid catalysts catalyse methoxyamine



(4)

attack by hydrogen bonding to the carbonyl group in a stepwise preassociation mechanism (k_1). With monofunctional catalysts there is downward curvature of the Brønsted plot and a sharp maximum in the solvent isotope effect with decreasing acid strength, as the proton-transfer step becomes kinetically significant near $\Delta pK = 0$. The same proton-transfer step would be required for bifunctional catalysts if the two proton transfers were stepwise, so that the absence of both downward curvature of the Brønsted plot and an isotope effect

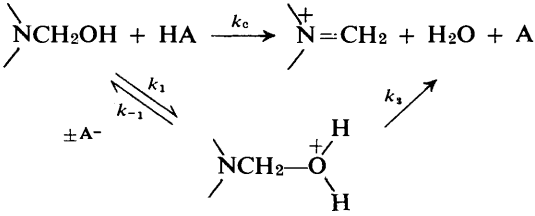
[29] M. I. Page and W. P. Jencks, *J. Am. Chem. Soc.*, 1972, **94**, 8828.
[30] R. Kluger and C.-H. Lam, *J. Am. Chem. Soc.*, 1978, **100**, 2191.
[31] J. J. Morris and M. I. Page, *J. Chem. Soc., Perkin Trans. 2*, 1980, 685.
[32] M. M. Cox and W. P. Jencks, *J. Am. Chem. Soc.*, 1981, **103**, 580.

maximum provides evidence that the two proton transfers with these catalysts occur through a fast, concerted process that never becomes kinetically significant.

D. Are Concerted Mechanisms Enforced?—It is true by definition that a reaction is concerted when it proceeds in one step because all 'intermediate' species are too unstable to exist. This appears to be the most common reason that reactions do proceed by a concerted mechanism. The converse question remains: when an intermediate and a stepwise mechanism are known to exist, can a reaction also proceed through a concerted mechanism with the reactants in approximately the same position relative to each other? If the answer is no, the merging of mechanisms represents the transformation of a stepwise into a concerted mechanism as the intermediate ceases to exist whereas, if the answer is yes, the merging of mechanisms represents a change in relative transition-state energies such that the concerted becomes faster than the stepwise mechanism under conditions in which both mechanisms occur concurrently (Figure 2).

If a reaction occurs in two steps A and B with an activation barrier for each step, the coexistence of a concerted reaction requires that there be a large advantage from coupling the two steps into one so that the barrier for the concerted reaction becomes comparable to or lower than that of both of the steps of the stepwise reaction. In an elimination reaction, for example, this requires that the effective sum of the barriers for proton removal from carbon and for carbon-leaving group cleavage be reduced by coupling between these two processes to give a low-energy transition state for the concerted reaction. This is not so likely when the individual barriers are large, as in many substitution and elimination reactions of carbon compounds; it becomes progressively more likely as the individual barriers for collapse of the intermediate become smaller and is very likely when they disappear, if the geometry of the system is favourable. It is still not clear at what point the concerted pathway appears and whether or not stepwise and concerted mechanisms with a similar geometry can coexist for activation-limited processes of this kind. The notion does not appear to have been disproved that concerted reactions of this kind are concerted simply because intermediates of the corresponding stepwise mechanisms are too unstable to exist, *i.e.* the reaction will proceed through an intermediate if it can.

The barriers for proton transfer between electronegative atoms are generally much smaller than for carbon, so that it is more likely that the advantage from coupling of such a proton transfer with some other step will outweigh the disadvantage of adding the barriers for the two steps into a single concerted step. Consequently, stepwise and concerted mechanisms do coexist for complex general acid–base catalysis. For example, dehydration of the carbinolamine of formaldehyde and semicarbazide proceeds by concerted general acid catalysis [k_c, equation (5)] in spite of the fact that the leaving oxygen atom is protonated (k_1) some 10^4 faster than the observed dehydration rate under the same conditions. The protonated hydroxy-group and a stepwise mechanism of specific acid catalysis must exist, although the equilibrium constant for protonation



(5)

and the barrier for C—O cleavage (k_1k_2/k_{-1}) are too unfavourable for this pathway to make a significant contribution to the observed reaction rate.[27]

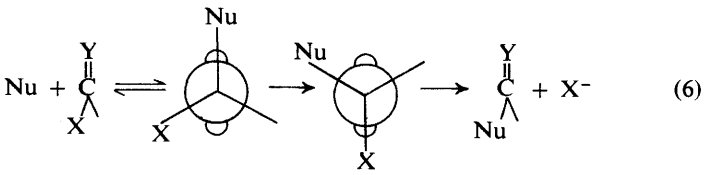
Two kinds of circumstances can favour the coexistence of concerted and stepwise mechanisms. (*a*) Stepwise and enforced concerted mechanisms can coexist when the individual steps are separated in space and one step occurs by the diffusion-controlled reaction of an intermediate. The reaction then occurs by two separate pathways, in which the first step occurs either in the absence or in the presence of the final reactant. For example, a carbocation may have a significant lifetime in a solvent but no lifetime when it is in contact with azide ion, so that a reaction could occur by a stepwise mechanism, with diffusion-controlled combination of N_3^- and the intermediate, and by a concurrent nucleophilic attack of azide through an enforced concerted displacement mechanism. Similar parallel pathways are possible for general acid–base catalysis and other reactions. They may be described by adding one or more 'wings' to the diagram of Figure 2 for the diffusional combination steps.[33,34] (*b*) Different requirements for the concerted and stepwise mechanisms can facilitate their coexistence if the barriers for the two mechanisms are not very different. For example, a concerted *E*2 elimination may require an antiperiplanar conformation of the reacting atoms that is sterically unfavourable. A concurrent *E*lcb mechanism that does not require this conformation will then be facilitated, even if the carbanion expels the leaving group with no barrier when it is in the correct conformation. An analogous situation is possible for the arrangement of solvent molecules to solvate the leaving group in the concerted reaction.

E. Uncoupled Concerted Reactions.—When the coupling between two processes such as nucleophilic attack and leaving-group expulsion is weak because of unfavourable geometry and orbital overlap, a reaction will be concerted only when there is no barrier for one of the steps. All such concerted reactions therefore proceed by an enforced concerted mechanism, as indicated by the dashed line in the top diagram of Figure 3. Although there are few quantitative data available such mechanisms are probable for displacements at sp^2 carbon, such as acyl-group transfer, nucleophilic aromatic substitution, and nucleophilic vinylic substitution

[33] S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, 96, 7986.

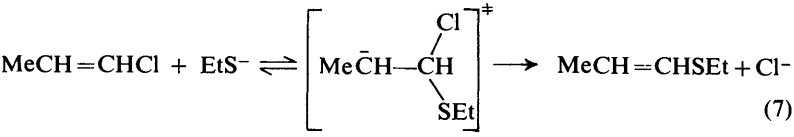
[34] J. M. Sayer, B. Pinsky, A. Schonbrunn, and W. Washtien, *J. Am. Chem. Soc.*, 1974, 96, 7998

with retention, when substrates have good leaving groups and cannot form a stable intermediate. Changes in bond angles are required for expulsion of the leaving group in these reactions [equation (6)].[35–37]



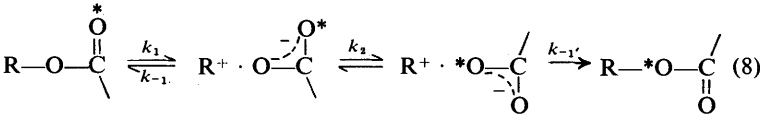
(6)

Disappearance of the barrier for expulsion of a good leaving group can give a concerted mechanism when there is strong stabilization of the carbonyl group by resonance, as in amides, and when the carbanion is unstable in nucleophilic aromatic or vinylic substitution, as in the reaction of equation (7).[37]



(7)

A special problem is posed by certain isomerization and racemization processes that are commonly cited as evidence for reaction intermediates, but may not proceed through intermediates with a significant barrier for collapse to reactants or products. For example, scrambling of labelled oxygen atoms during the solvolysis of esters may proceed through a process in which there is always some degree of electrostatic, if not covalent, bonding between the reacting groups and no significant barrier for the collapse of a carbonium–carboxylate ion pair during the course of the reaction [equation (8); k_{-1}, $k_{-1'} > 10^{13}$ s^{-1}].[14] The



(8)

reaction will then proceed by the concerted mechanism shown by the solid line in Figure 4A, rather than by the stepwise mechanism shown by the dashed line. An analogous situation is likely for several other isomerization and racemization reactions. Some of these reactions will proceed with no chemical barrier in the usual sense for collapse to reactants or products in the course of the reaction, but may nevertheless require appreciable time, longer than a vibration frequency, for rotation or other motions within the solvent cage while contact is maintained

[35] I. G. Csizmadia, M. R. Peterson, C. Kozmutza, and M. A. Robb in 'The Chemistry of Acid Derivatives', Suppl. B, ed. S. Patai, Wiley, New York, 1979, Pt. 1, pp. 1—58.
[36] Z. Rappoport, *Acc. Chem. Res.*, 1981, **14**, 7.
[37] G. Modena, *Acc. Chem. Res.*, 1971, **4**, 73.

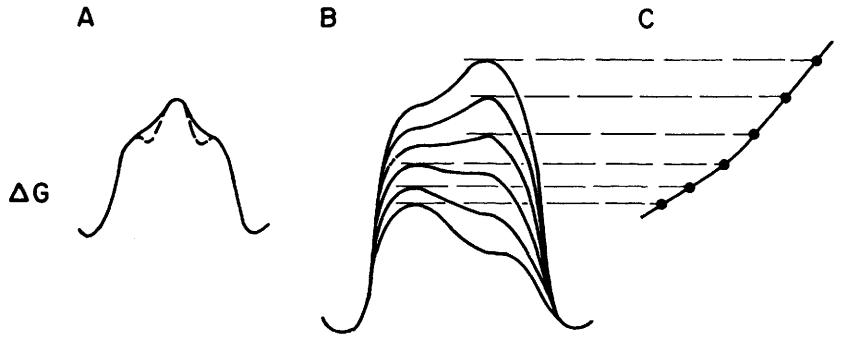


Figure 4 (A) *Reaction co-ordinate diagram for scrambling of labelled oxygen atoms during solvolysis through a concerted mechanism when there is no barrier for collapse of the ion pair (solid line) and through a stepwise mechanism when there is a barrier and intermediates exist (dashed lines).* (B) *Reaction co-ordinate diagrams for an uncoupled concerted reaction that involves two processes, with differing sensitivities to change in the structure of a leaving group, for example, so that there is a change in the nature of the transition state with changing structure.* (C) *Structure–reactivity correlation for the reaction in* (B), *showing a non-linear change in* $\Delta G^{\ddagger}$ *with changing substituents as the nature of the transition state changes*

between the reactants. There is no ideal solution to this problem, but it appears most satisfactory to include such reactions in the uncoupled concerted category if there is no intermediate with a significant activation barrier for its collapse.

It is important to note that stepwise and uncoupled concerted reactions will often show similar structure–reactivity behaviour, because the unsymmetrical transition state of the uncoupled concerted reaction (Figure 4B) will resemble one or the other transition state of the stepwise reaction.[14,38] A coupled reaction will have a single, more central transition state that represents both processes (Figure 3, upper solid line). Thus, the leaving-group ability of different halide ions will have little effect on the observed rate of nucleophilic vinylic substitution when the transition state represents primarily nucleophilic addition, even if the reaction is concerted.[36,37] A change in the relative leaving ability of the entering and leaving groups, so that the transition state represents predominantly leaving-group expulsion rather than nucleophilic attack, will give the same kind of break in a structure–reactivity correlation for an uncoupled concerted reaction as for a fully stepwise reaction, as shown in Figure 4B and C.[14,38]

3 Preassociation Stepwise Mechanisms

When an intermediate has a short but significant lifetime, a reaction is likely to proceed through a preassociation mechanism in which all of the reactant and catalyst molecules are assembled in an encounter complex before the first covalent change occurs. This is shown in the lower path through the K_{as} and k_1 steps of equation (9) for the general case of a reactant(s), R, that can form an

[38] J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 837.

$$\begin{array}{ccccc} R & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & I & & \\ K_{ss}\Big\uparrow\Big\downarrow \pm C & & k_a\Big\uparrow\Big\downarrow k_{-a} \pm C & & \\ R \cdot C & \underset{k_{-1'}}{\overset{k_{1'}}{\rightleftharpoons}} & I \cdot C & \xrightarrow{k_2} & \text{products} \end{array} \qquad (9)$$

intermediate, I, either before or after association with a catalyst or final reactant, C, that is required in order to form products. When the intermediate complex I · C breaks down to reactants ($k_{-1'}$) faster than C diffuses away from it (k_{-a}), the lowest energy pathway for both the breakdown and the formation of I · C will be through the lower, preassociation pathway.

The reason that the preassociation mechanism must become the favoured pathway when an intermediate becomes sufficiently unstable is shown in Figure 5A. When $k_{-1'}$ becomes large enough that the lowest-energy pathway for reversion

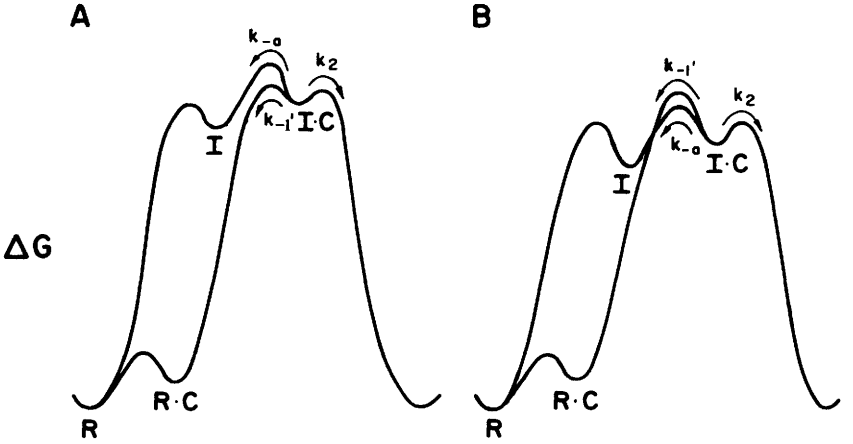


Figure 5 *Reaction co-ordinate diagram to illustrate the reason that* (A) *a preassociation mechanism is preferred when the intermediate* I · C *reverts to reactants faster than it separates into* I *and* C, $k_{-1'} > k_{-a}$, *and* (B) *a stepwise mechanism through a free intermediate is preferred when the intermediate is more stable, so that* $k_{-a} > k_{-1'}$

of the I · C complex to reactants is through the $k_{-1'}$ step, the reverse, $k_{1'}$, step provides the lowest-energy pathway for formation of the complex. This behaviour is expected for condensation reactions that require reaction with C in a final step, as in nucleophilic additions to carbonyl compounds and olefins, and in substitution reactions that proceed through a ternary complex containing the elements of all of the reacting molecules.

When the intermediate has a longer lifetime, so that $k_{-a} > k_{-1'}$, the I · C complex will break down more rapidly by diffusion away of C, as shown in

Figure 5B. The lowest-energy pathway for the formation of I · C will then be through the free intermediate I, followed by rate-determining diffusion together of I and C with the rate constant k_a [equation (9), upper path]. It is important to note that it is the rate of the *back* reaction, $k_{-1'}$, not the k_2 step, that determines whether the reaction proceeds by a preassociation or a diffusion-controlled trapping mechanism. When the intermediate becomes still more stable, the k_1 step will become rate determining.

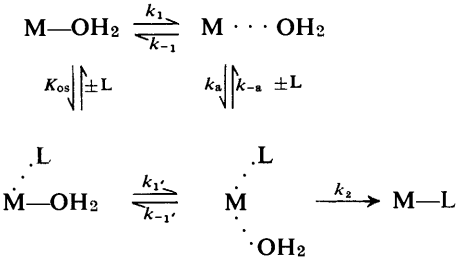
The kinetic requirements for the preassociation mechanism were apparently first described by Sutin, as an explanation for the replacement of water by a ligand on a metal through the dissociative interchange or 'outer-sphere' mechanism.[39] This mechanism involves preassociation of the hydrated metal and the incoming ligand before bond cleavage occurs because the lifetime of the ligand-deficient metal, after bond cleavage, is shorter than the time required for diffusion away of the incoming ligand.* Preassociation was described for nitration, nitrosation, and halogenation reactions by Hartshorn and Ridd,[40,41] for general acid–base catalysed reactions by Kershner and Schowen as a 'spectator' mechanism, for the case in which the catalyst C does not stabilize the transition state for heavy-atom reorganization,[5] and by the reviewer for several classes of reactions.[42–46]

A. Examples and the Question of Assistance.—Preassociation mechanisms were first identified experimentally for reactions in which the final reactant or catalyst C does not directly stabilize the transition state of the bond-making or bond-breaking step. The preassociation mechanism provides a lower-energy pathway than a mechanism that proceeds through a free intermediate because it avoids the higher-energy rate-determining step for diffusion of C to I [k_a, equation (9), Figure 5A].

For example, a limiting dissociative interchange mechanism of ligand exchange (I_D) proceeds through rate-determining dissociation of the metal–ligand bond with the rate constant $k_{1'}$ [equation (10)] and has a rate constant that is identical for all incoming ligands, except for differences that arise from differences in the equilibrium constant for formation of the initial outer-sphere complex, K_{os}.[39,47] Similarly, the addition of 2-methyl-3-thiosemicarbazide to *p*-chlorobenzaldehyde is catalysed by general bases through a preassociation mechanism because the base catalyst must be present in the transition state of the $k_{1'}$ [equation (9)] step

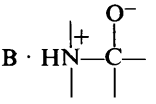
*A dissociative interchange mechanism could also occur by an uncoupled concerted mechanism, if there is no barrier for the $k_{-1'}$ step.

[39] N. Sutin, *Annu. Rev. Phys. Chem.*, 1966, **17**, 119.
[40] S. R. Hartshorn and J. H. Ridd, *J. Chem. Soc. B*, 1968, 1068.
[41] J. H. Ridd, *Adv. Phys. Org. Chem.*, 1978, **16**, 1.
[42] W. P. Jencks and K. Salvesen, *J. Am. Chem. Soc.*, 1971, **93**, 1419.
[43] W. P. Jencks, *Chem. Rev.*, 1972, **72**, 705.
[44] J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, 1973, **95**, 5637.
[45] W. P. Jencks, *Acc. Chem. Res.*, 1980, **13**, 161.
[46] W. W. Reenstra and W. P. Jencks, *J. Am. Chem. Soc.*, 1979, **101**, 5780.
[47] C. H. Langford and H. B. Gray, 'Ligand Substitution Processes', W. A. Benjamin, New York, 1965.



(10)

in order to remove a proton from the amine immediately after formation of the unstable addition complex (8) [k_2, equation (9)] and thereby prevent reversion of the dipolar addition intermediate to reactants.[44] The base does not stabilize the transition state for the $k_{1'}$ step significantly, so that the Brønsted slope is $\beta = 0$. With weaker bases the Brønsted plot curves downward because the proton-transfer step and, finally, diffusion away of the protonated base become rate determining.



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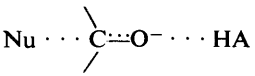


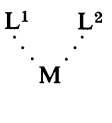
(9)

However, if the catalyst or final reactant C is required to be present during the rate-determining step ($k_{1'}$), because of the short lifetime of the intermediate (large $k_{-1'}$), it will often stabilize the transition state by facilitating the change in electron density so that there is significant assistance by interaction with the catalyst. This is observed for general *acid* catalysis of the addition of 2-methyl-3-thiosemicarbazide to *p*-chlorobenzaldehyde. Hydrogen bonding of buffer acids to the developing negative charge on the carbonyl group (9) stabilizes the transition state and results in a Brønsted slope of $\alpha = 0.2$.[44] Similar stabilization in a pre-association mechanism has been observed for several carbonyl addition reactions of amines and weakly basic thiol anions, including the attack of methoxyamine on phenyl acetate.[48–51]

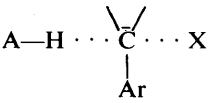
Similarly, the rate constants for ligand exchange on metals by a dissociative interchange mechanism often show small differences that cannot easily be accounted for by differences in K_{os}. These differences probably represent weak interactions with the incoming ligand that stabilize the transition state for

[48] H. F. Gilbert and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, 99, 7931.
[49] J. J. Ortiz and E. H. Cordes, *J. Am. Chem. Soc.*, 1978, **100**, 7080.
[50] J. M. Sayer and C. Edman, *J. Am. Chem. Soc.*, 1979, **101**, 3010.
[51] M. M. Cox and W. P. Jencks, *J. Am. Chem. Soc.*, 1981, **103**, 572.

departure of the outgoing ligand.[52,53] Such a weak interaction is not unexpected for an open, 'exploded' transition state (10) of a preassociation mechanism that is almost identical to the transition state for diffusion away of the leaving group.[46]



(10)



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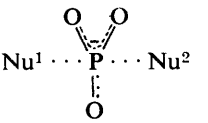


(12)

The cleavage of 1-phenyl-2-arylcyclopropanol anions shows general acid catalysis with $\alpha \sim 0$ that probably represents stabilization of the developing benzyl carbanion in the transition state (11) by weak hydrogen bonding in a pre-association mechanism.[21] Similar electrophilic assistance to carbanion formation is indicated by the primary isotope effect of $k_H/k_D = 2.1$—2.5 for the methoxide-induced cleavage of benzyltrimethylstannanes in MeOH–MeOD (11; A—H = MeOH or MeOD).[54] Electron-withdrawing substituents on the benzyl group in this class of reaction cause a sharp increase in the discrimination isotope effect to $k_H/k_D \simeq 10$,[55] which suggests that the more stable benzyl anions have a sufficient lifetime to diffuse through the solvent and discriminate between MeOH and MeOD.[21]

Solvolysis and substitution reactions of mono-substituted phosphates that have been thought to proceed through a metaphosphate monoanion intermediate almost certainly proceed by a preassociation mechanism in hydroxylic solvents, since no free intermediate is formed that can diffuse through the solvent to be trapped or give a constant solvent discrimination.[56–59] These reactions occur through an open, 'exploded' transition state with little bond formation and much bond cleavage (12) so that there is only a small amount of assistance by the entering group and β_{nuc} values are small or zero.[59–61] It remains uncertain whether there is an unstable metaphosphate intermediate with a significant lifetime, or whether the reaction occurs by a concerted displacement.

A preassociation mechanism is also probable for reactions of mono-substituted

[52] C. K. Poon, *Coord. Chem. Rev.*, 1973, **10**, 1.
[53] J. O. Edwards, 'Inorganic Reaction Mechanisms', W. A. Benjamin, New York, 1964, p. 100.
[54] R. Alexander, W. A. Asomaning, C. Eaborn, I. D. Jenkins, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1974, 490.
[55] C. Eaborn, D. R. M. Walton, and G. Seconi, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1857; *ibid.*, 1978, 834.
[56] S. J. Benkovic and K. J. Schray in 'Transition States of Biochemical Processes', ed. R. D. Gandour and R. C. Schowen, Plenum Press, New York, 1978, pp. 493—527.
[57] J. D. Chanley and E. Feageson, *J. Am. Chem. Soc.*, 1963, **85**, 1181.
[58] W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 1964, **86**, 1410.
[59] A. J. Kirby and A. G. Varvoglis, *J. Am. Chem. Soc.*, 1967, **89**, 415.
[60] G. Di Sabato and W. P. Jencks, *J. Am. Chem. Soc.*, 1961, **83**, 4400.
[61] A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, 1965, **87**, 3209.

sulphates with nucleophilic reagents, which show similar characteristics.[62] It is also not known for this system whether there is a barrier for reaction of the presumed SO_3 'intermediate' with good nucleophiles that makes the reaction stepwise rather than concerted.

A preassociation mechanism for acid-catalysed halogenation by hypobromous acid is supported by rate constants that are larger than can be accounted for by diffusion-controlled reactions with Br^+ or H_2OBr^+ and that show a large dependence on the structure of the aromatic substrate.[41,63] This provides an example of a reaction in which the preassociation mechanism is enforced by the rapid dissociation of a proton from a protonated reactant, H_2OBr^+ [equation (11);

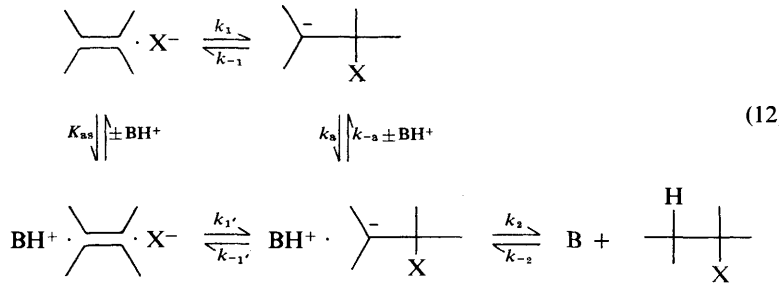
$$\begin{array}{ccc} H^+ + HOBr & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & \overset{+}{H_2O}Br \\ \Big\downarrow K_{as} \Big\uparrow \pm ArH & & \Big\downarrow k_a \Big\uparrow k_{-a} \pm ArH \\ H^+ \cdot HOBr \cdot ArH & \underset{k_{-1'}}{\overset{k_{1'}}{\rightleftharpoons}} & \overset{+}{H_2O}Br \cdot ArH \xrightarrow{k_2} \text{products} \end{array} \qquad (11)$$

$k_{-1'} > k_{-a}$]. The large dependence of the rate on substrate structure is consistent with either rate-determining halogenation (k_2) or a fully concerted preassociation mechanism in which proton transfer is assisted by attack of the substrate.

Further work is needed to clarify the relationship between assistance and the lifetime of intermediates in the solvolysis of carbon compounds. When the intermediate is unstable the preassociation mechanism, with the incoming nucleophile present in the transition state for bond cleavage, should provide a lower-energy pathway than a Sneen-type mechanism[64] involving diffusion and reaction of a nucleophile with an ion pair, for the reason illustrated in Figure 5A. It has been suggested that the solvent plays an important role in assisting the formation of intermediates by nucleophilic participation, as in the S_N2 (intermediate) or 'ion sandwich' mechanisms,[65,66a] but it has been difficult to prove the existence of intermediates in reactions that show such assistance. α-*p*-Nitrophenylethyl tosylate does not give an intermediate with an appreciable lifetime in hydroxylic solvents and exhibits a healthy second-order reaction with azide, but the small selectivity toward ethanol compared with trifluoroethanol shows that there is little or no solvent assistance in the solvolysis of this compound.[66b]

Olefin-forming elimination reactions are addition reactions in the reverse direction [equation (12)]. The '*E*lcb (ion-pair)' mechanism[67] is a stepwise preassociation mechanism with the catalyst present in the transition state and $k_2 > k_{-1'} > k_{-a}$. The *E*lcb (irreversible) mechanism[67] can be a preassociation

[62] J. P. Guthrie, *J. Am. Chem. Soc.*, 1980, **102**, 5177.
[63] H. M. Gilow and J. H. Ridd, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1321.
[64] R. A. Sneen, *Acc. Chem. Res.*, 1973, **6**, 46.
[65] T. W. Bentley and P. von R. Schleyer, *Adv. Phys. Org. Chem.*, 1977, **14**, 1.
[66] (*a*) F. G. Bordwell, P. F. Wiley, and T. G. Mecca, *J. Am. Chem. Soc.*, 1975, 97, 132; (*b*) J. P. Richard and W. P. Jencks, in preparation.
[67] F. G. Bordwell, *Acc. Chem. Res.*, 1970, **3**, 281.



(12)

mechanism with $k_{-1'} > k_2$ or a liberated intermediate mechanism if $k_{-a} > k_{-1'}$. Almost nothing is known about the importance of assistance in these stepwise mechanisms.

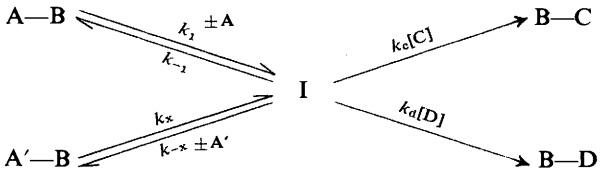
B. Differential Diagnosis.—It is relatively easy to distinguish between preassociation and liberated intermediate mechanisms, but difficult to distinguish between concerted and stepwise preassociation mechanisms. Criteria for the former distinction include the following:

(i) Absolute rate constants for the k_{-1} and $k_{-1'}$ steps of the reaction [equation (9)] may be estimated by extrapolation from known rate constants of related compounds or calculated from the reverse rate constant and the equilibrium constant of a reaction.[41,44,48,50]

(ii) The reaction of C with a reactive free intermediate is often diffusion controlled [k_a, equation (9)], whereas the rate-determining step for a preassociation mechanism is not diffusion controlled [$k_{1'}$, equation (9)]. Thus, diffusion-controlled trapping by catalysts or final reactants, C, is sensitive to the viscosity of the solvent (although this may be difficult to differentiate from other solvent effects)[50,51,68–70] and will show rate constants that are independent of the basicity, acidity, nucleophilicity, or other chemical properties of C.[15,71] Such independence does not exclude a preassociation mechanism with no assistance,[44] but the observation of different rate constants with different C rules out rate-determining diffusion-controlled trapping of a free intermediate.[48]

(iii) A free intermediate with a given structure, I, must show constant partitioning, regardless of its source, in its reactions with different solvent components, isotopes, added reagents, or reaction paths [equation (13)].[15,72] An intermediate complex of a preassociation mechanism that contains the leaving group commonly shows different partitioning with different leaving groups.[17] Unfortunately, constant partitioning between different products, such as the products

[68] C. Cerjan and R. E. Barnett, *J. Phys. Chem.*, 1972, **76**, 1192.
[69] M. F. Aldersley, A. J. Kirby, P. W. Lancaster, R. S. McDonald, and C. R. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1487.
[70] H. Fischer, F. X. DeCandis, and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 1340.
[71] R. E. Barnett and W. P. Jencks, *J. Am. Chem. Soc.*, 1969, **91**, 2358.
[72] D. J. Raber, J. M. Harris, and P. von R. Schleyer, 'Ions and Ion Pairs in Organic Reactions,' Wiley, New York, 1974, Vol. 2, pp. 247—374.



(13)

of elimination and solvolysis, does not *prove* the existence of an intermediate because the same result is expected for late transition states of uncoupled concerted reactions that closely resemble the presumed intermediate. However, only a free intermediate that is formed irreversibly and reacts rapidly with two final reagents, C and D {equation (13); $(k_c[C] + k_a[D]) > k_{-1}[A]$}, will give product ratios that are proportional to the concentration ratio [C]/[D] without affecting the overall rate when the concentrations of C and D are varied.[72] Racemization is a special case of constant partitioning, *i.e.* a free, planar carbanion or carbocation must have the same reactivity on both sides and give complete racemization (in the absence of an asymmetry that hinders reaction on one face).

(iv) A reaction that proceeds through a free intermediate frequently shows a *change in rate-determining step* with changing concentration of the final reactant or catalyst C [equation (14); reaction of A—B with C].[41,71,72] There is no such

$$\text{A—B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{B} + \text{A} \xrightarrow{k_2[C]} \text{B—C} \qquad (14)$$

change in rate-determining step for a preassociation mechanism, because C is present in the transition state of every kinetically significant step [equation (9)]. Thus an increase in the concentration of catalyst or nucleophile can make trapping of a free intermediate so fast that formation of the intermediate (k_1) becomes rate-determining and the observed rate becomes independent of the concentration of C. Conversely, if a molecule, A, is released upon formation of the free intermediate [equation (14)], addition of this molecule can make the intermediate revert to reactants by a mass law effect, so that there is a change from rate-determining formation to rate-determining reaction of the intermediate and an inhibition of the observed rate. Such inhibition will be accompanied by incorporation of isotopically labelled A into the reactant. At low [A] the rate of this exchange corresponds to the amount of inhibition. The 'special salt effect', a sharp increase in the rate of solvolysis reactions with added salt to a rate that is characteristic of the 'normal' salt effect, represents a change in rate-determining step from solvolysis or separation of some ion-pair intermediate to the formation of this intermediate.[72,73]

[73] A. Fava in 'The Chemistry of Organic Sulfur Compounds', ed. N. Kharasch and C. Y. Meyers, Pergamon Press, New York, 1966, Vol. 2, p. 80.

(v) Changing the *structure* of C can give a change in rate-determining step that is different for preassociation and liberated intermediate mechanisms. Rate-determining trapping of an intermediate by proton transfer to or from electronegative atoms commonly gives a Brønsted plot that follows an Eigen curve for different acids or bases, with limiting slopes of 0 and ± 1.0 for strong and weak catalysts that correspond to diffusion-controlled encounter and separation of the catalyst and intermediate, respectively. These lines intersect close to the pK_a of the intermediate, at $\Delta pK \sim 0$. The preassociation mechanism follows the same Brønsted curve for weak catalysts [k_2 rate determining in equation (9)] but has a faster rate when $k_{1'}$ is rate determining (Figure 5A). Consequently, the intersection of the limiting lines of the Brønsted curve is shifted and, if it is larger than the estimated error for the pK_a of the intermediate, this shift can provide evidence for the preassociation mechanism.[44,51]

(vi) The *initial* rate of a reaction in which reversible proton removal from carbon gives a free intermediate, such as an *E*1cb elimination, can exhibit large inverse solvent deuterium isotope effects, such as $k_{D_2O}/k_{H_2O} = 6$. This is the result of a pseudo-equilibrium in the initial step, in which H is removed but D is added back to the carbanion intermediate so that its steady-state concentration is increased in deuterium oxide.[74] After exchange of deuterium into the starting material is complete such a reaction will not exhibit the primary deuterium isotope effect that is expected for a concerted *E*2 elimination.[75]

Criteria for distinguishing stepwise and concerted preassociation mechanisms include the following:

(1) Extrapolation of structure–reactivity correlations or calculation of the rate constant that would be required for reaction of an intermediate in order to account for an observed rate constant may give a lifetime of an 'intermediate' species that does not correspond to a significant barrier for its breakdown, so that the reaction must proceed by a concerted mechanism.[14,25]

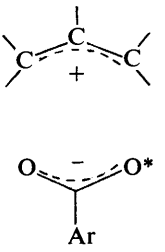
(2) Structure–reactivity correlations and isotope effects can provide evidence that two processes are occurring simultaneously in the transition state to a greater extent than would be expected for a stepwise mechanism with an intermediate.[28,76] For example, a concerted *E*2 elimination reaction can show a significant isotope effect and Brønsted β value for proton removal and a significant heavy-atom isotope effect and dependence on leaving-group ability ($-\beta_{lg}$, 'element effect') for bond cleavage. A coupled concerted mechanism with a single, central transition state should give a linear or smoothly curved structure–reactivity correlation, whereas a stepwise or uncoupled concerted mechanism should give a sharp break as one or the other process becomes rate determining, as noted above (Figure 4C).[14]

(3) A coupled concerted mechanism may be described by a diagonal reaction co-

[74] J. Keeffe and W. P. Jencks, *J. Am. Chem. Soc.*, 1981, **103**, 2457.
[75] R. A. More O'Ferrall and S. Slae, *J. Chem. Soc. B*, 1970, 260.
[76] W. H. Saunders, jun. and A. F. Cockerill, 'Mechanisms of Elimination Reactions', Wiley, New York, 1973, p. 87.

ordinate on a reaction co-ordinate–energy contour diagram that is defined in terms of structure–reactivity parameters. Changes in structure–reactivity parameters and in the position of the transition state on such a diagram with changing reactant structure can provide evidence for an interaction between reacting groups in the transition state and for a concerted mechanism.[24,26,28,77]

(4) The demonstration that some time-dependent process occurs faster than collapse of an intermediate through either of two alternative paths shows that there must be a barrier for collapse of the intermediate and that the mechanism is not concerted. An example is the demonstration of equal rate constants for racemization of *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate and for equilibration of the carboxyl oxygen atoms in *both* enantiomers during solvolysis in 80% aqueous acetone.[78] This result requires that an intermediate ion pair, (13),



(13)

must have a sufficient lifetime to allow rotation and complete randomization of the carboxylate oxygen atoms before it collapses to either product or reactant. Most examples of oxygen scrambling and racemization do *not* prove that there is an intermediate with a significant lifetime, as noted above.

(5) Strict stereochemical specificity in the absence of severe steric effects, such as substitution with complete inversion or *anti*-elimination, provides support for a concerted mechanism.

(6) A stepwise preassociation mechanism of general acid–base catalysis involving electronegative atoms, such as the acid-catalysed methoxyaminolysis of phenyl acetate, shows a sharp solvent isotope effect maximum when the proton-transfer step becomes rate determining near $\Delta pK = 0$, whereas a concerted mechanism shows a solvent isotope effect that does not change with changing pK of the catalyst.[51,70] However, this criterion needs testing with additional examples.

Several of the above criteria can provide evidence for a coupled concerted mechanism but do not distinguish between an uncoupled concerted and a step-

[77] D. A. Jencks and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 7948.
[78] H. L. Goering, J. T. Doi, and K. D. McMichael, *J. Am. Chem. Soc.*, 1964, **86**, 1951.

wise preassociation mechanism. For example, both stepwise and uncoupled concerted mechanisms for vinylic, acyl, or aromatic substitution and for elimination reactions can show small values of β_{lg}, element effects, and heavy-atom isotope effects in the leaving group, when attack of the nucleophile or base is the predominant process in the transition state. It is also important to remember that the converse of a criterion need not hold; for example, a reaction that does *not* show strict stereochemical specificity can be either stepwise or concerted.

C. Requirements and Perturbations.—The critical role of the solvent in determining reaction mechanisms by controlling the lifetime of intermediates cannot be emphasized too strongly. The solvent can determine the lifetime of an intermediate, I, in two ways that should be distinguished: (*a*) by its reactivity toward I as the final reactant or catalyst, C, and (*b*) by altering the stability of I through a solvent effect. A carbocation, for example, is expected to have a shorter lifetime in ethanol than in water because ethanol has both a larger nucleophilicity and a smaller dielectric constant compared to water, whereas acetonitrile will stabilize the cation by its low nucleophilic reactivity and destabilize it by its poor ion-solvating ability.

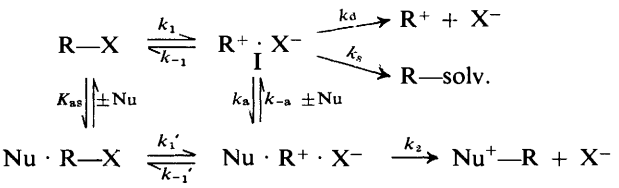
Solvent Reactivity. When the solvent is highly reactive as the final reactant or catalyst, C, an unstable intermediate will simply react non-selectively with the first solvent molecule it sees. A reaction with dilute solute molecules, C′, will be able to compete significantly with the solvent reaction only if C′ stabilizes the transition state for the *formation* of the intermediate, so that a significant amount of I · C′ is formed in the $k_{1'}$ step. In a mixed solvent or a concentrated solution of C′ the intermediate presumably has the option of reacting with one of several molecules in a surrounding solvent pool, as suggested by Grunwald *et al.*,[79] but little is known about the size or nature of this pool or about the nature of short-range reorientational and translational processes that may influence the relative reactivity of molecules in the pool. Electrostatic, steric, and statistical factors are presumably important. The products that are formed upon the photochemical generation of unstable intermediates may provide more information about these factors.

Reaction with the solvent predominates in the dissociative interchange, I_D, mechanism for ligand exchange on metals, for example, because the incoming ligand provides little or no stabilization of the rate-determining transition state. Exchange of one ligand for another in aqueous solution almost always proceeds through the aquo complex [equation (10) in reverse], because the solvent is the only significant nucleophile that reacts with the unstable intermediate that is formed upon loss of a ligand. The aquo complex then reacts with the incoming ligand in a second preassociation, outer-sphere step [equation (10) in the forward direction] to form the thermodynamically stable product.[80]

The solvolysis of R—X occurs by a preassociation mechanism when k_{-1} and

[79] E. Grunwald, A. Heller, and F. S. Klein, *J. Chem. Soc.*, 1957, 2604.
[80] R. G. Pearson and J. W. Moore, *Inorg. Chem.*, 1964, **3**, 1336.

$k_{-1'}$ are fast and $R^+ \cdot X^-$ reacts with solvent faster than X^- diffuses away [$k_s > k_d$, equation (15)]; when $R^+ \cdot X^-$ reacts more slowly, with $k_s < k_d$, it undergoes diffusional separation [the solvent is always present and is not shown in equation (15)]. When the leaving group is a better nucleophile than the solvent



(15)

or steric shielding inhibits solvolysis, so that I usually returns to reactants ($k_{-1} > k_s$), the solvolysis (k_s) or diffusional separation (k_d) step can be rate determining. If the leaving group stabilizes R^+ (as in some ion pairs), the preassociation mechanism should become more favourable because this stabilization is completely lost in the transition state for diffusional separation (k_d) and is only partly lost in the transition state for solvolysis (k_s).

Changes in secondary α-deuterium isotope effects are consistent with changes between rate-determining k_1, k_s, and k_d steps for solvolysis reactions with anionic and uncharged leaving groups.[81,82] For example, an increase in the α-secondary deuterium isotope effect for the acid-catalysed hydrolysis of benzaldehyde dimethyl acetal with increasing dioxan concentration can be accounted for by a change to k_d as the rate-determining step when k_{-1} becomes larger than k_s.[83] Such a reaction will ordinarily show no general acid catalysis, because the proton is completely transferred in the transition state.[84]

Molecules other than the solvent become important as the final reactant or catalyst C [equation (9); Nu in equation (15)] when (i) the solvent becomes less reactive or (ii) the molecule C provides assistance to the $k_{1'}$ step. In general acid catalysis, for example, catalysis by a preassociation mechanism becomes increasingly important as the pK of I decreases below 16, so that water becomes less reactive as a proton donor to I (the converse holds for general base catalysis). A strong acid or base can give proton transfer every time the intermediate I · C is formed [$k_2 > k_{-1'}$, equation (9)], so that the importance of the buffer-catalysed relative to the uncatalysed reaction depends inversely on k_2 for the water reaction.[85]

When bond cleavage occurs in the initial step, as in solvolysis-substitution reactions [equation (15)], diffusion apart of the intermediate into its components (k_d) competes with other pathways so that there is only a limited region in which

[81] V. J. Shiner, jun. in 'Isotope Effects in Chemical Reactions', ed. C. J. Collins and N. S. Bowman, Van Nostrand Reinhold, New York, 1970, p. 105.
[82] V. P. Vitullo and F. P. Wilgis, *J. Am. Chem. Soc.*, 1981, **103**, 880.
[83] P. R. Young, R. C. Bogseth, and E. G. Rietz, *J. Am. Chem. Soc.*, 1980, **102**, 6268.
[84] W. P. Jencks, *Acc. Chem. Res.*, 1976, 9, 425.
[85] W. P. Jencks and H. F. Gilbert, *Pure Appl. Chem.*, 1977, **49**, 1021.

solute molecules, Nu, can play a significant role in a preassociation mechanism without stabilizing the transition state for the $k_{1'}$ step. For example, an added nucleophile can cause a rate increase through a preassociation mechanism in the reaction of equation (15) when k_{-1}, $k_{-1'}$, and k_2 are fast. If k_2 is large it may be able to compete successfully with k_s and k_d (when $k_2 = 10^{11}\ s^{-1}$, $k_s = 10^9\ s^{-1}$, and $k_d = 10^{10}\ s^{-1}$, for example) and give rise to a significant second-order reaction with Nu, in spite of the unfavourable equilibrium constant for formation of the preassociation complex with the nucleophile. The ratio of the rate constants for reaction with Nu through the preassociation pathway and for reaction through I [when $k_{-1} \gg (k_s + k_d)$] is given by $k_2K_{as}[Nu]/[(k_d + k_s)(k_2/k_{-1'} + 1)]$. This situation has not been identified experimentally for a reaction in which the intermediate has been proved to have a significant lifetime in the presence of both solvent and the incoming nucleophile. Reaction through the preassociation mechanism will usually be accompanied by diffusion-controlled trapping of the intermediate by the nucleophile. With sufficiently reactive nucleophiles it will give second-order rate constants that are independent of the reactivity (but not the concentration) of reactive nucleophiles when $k_{1'}$ is rate determining. If k_2 becomes still larger, there will be no barrier for the k_2 step and the reaction will become concerted.

It is rare for a preassociation mechanism to be enforced by a fast $k_{-1'}$ step that is second-order, because the first-order diffusional separation step, k_{-a}, will be faster than the $k_{-1'}$ step under most conditions and must always become faster at a low concentration of the reactants for the second-order reaction. However, there are special circumstances in which a fast reaction with another molecule in the k_{-1} step can give a preassociation mechanism, as in the nitration of *p*-nitroaniline in 90% sulphuric acid with $k_{-1'}[H_2SO_4] > k_2 > k_{-a}$ [equation (16)].[40] The

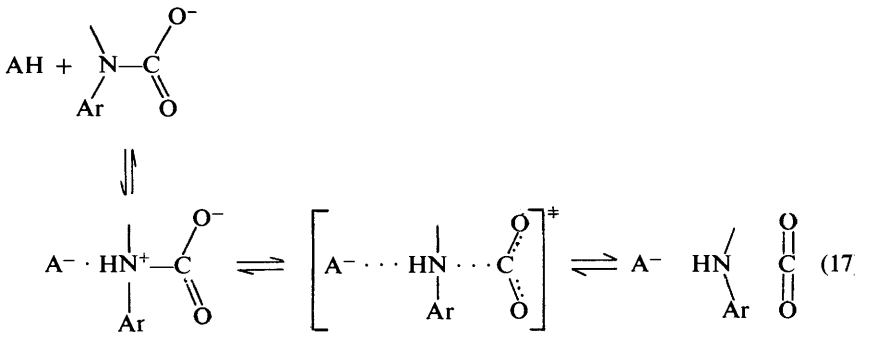
$$\begin{array}{ccc} ArNH_3^+ & \underset{k_{-1}[H_2SO_4]}{\overset{k_1[HSO_4^-]}{\rightleftharpoons}} & ArNH_2 \\ {\scriptstyle K_{as}}\Big\uparrow\Big\downarrow{\scriptstyle \pm NO_2^+} & & {\scriptstyle k_a}\Big\uparrow\Big\downarrow{\scriptstyle k_{-a}\ \pm NO_2^+} \\ ArNH_3^+ \cdot NO_2^+ & \underset{k_{-1'}[H_2SO_4]}{\overset{k_{1'}[HSO_4^-]}{\rightleftharpoons}} & ArNH_2 \cdot NO_2^+ \xrightarrow{k_2} \text{products} \end{array} \qquad (16)$$

reaction involves unprotonated aniline, which is probably reprotonated in this medium ($k_{-1'}$) faster than NO_2^+ can diffuse away from it (k_{-a}). Although the $k_{-1'}$ step is formally second order, it is effectively first order in 90% sulphuric acid and the mechanism could also be written with HSO_4^- in the preassociation complex.

Assistance, Non-enforced Catalysis, and Mixed Mechanisms. For acid–base catalysis involving electronegative atoms a necessary proton-transfer step to or from water will generally be faster than diffusion when the pK of the intermediate I is $\ll -2$ as an acid or $\gg 16$ as a base. The reaction with solvent will then be a preassociation mechanism. The observed reaction will be dominated by the solvent

and its components, *i.e.* it will be uncatalysed or will show specific acid or base catalysis with no buffer catalysis *unless* the catalyst can stabilize the transition state of the $k_{1'}$ step.

An example of such stabilization, by hydrogen bonding, is found in general acid catalysis of the cleavage of carbamates formed from weakly basic amines [equation (17)].[86] Cleavage of the carbamate of *p*-nitroaniline, which follows a



linear Brønsted plot with $\alpha = 0.84$, proceeds through a zwitterionic *N*-protonated intermediate with an estimated pK_a of -4.3 and $k_{-1'}$ of 2×10^{10} s^{-1} for cleavage of the intermediate. This cleavage reaction represents the preassociation mechanism of equation (9) in the reverse direction, with the $k_{-1'}$ step rate determining and catalysis at the nucleophilic reagent (class *n* catalysis).

Similar assistance is possible for reactions involving carbocation and metaphosphate intermediates but it remains uncertain whether such assistance is significant for reactions in which the intermediate has been proved to exist, as discussed above.

Stabilization of the transition state of the $k_{1'}$ step by C will increase the importance of the preassociation mechanism compared with other mechanisms and, in some cases, can give rise to a non-enforced reaction by a preassociation mechanism. Hydrogen bonding of an acid catalyst to the oxyanion intermediate and the transition state for its formation in a carbonyl addition reaction (9), for example, can stabilize both the intermediate, T^-, and the transition state but will not affect the energy of the transition state for diffusional encounter or separation, k_a and k_{-a} (Figure 6). This provides an explanation for the non-linear Brønsted plot for general acid catalysis of the addition of *p*-methoxybenzenethiolate anion to acetaldehyde, which is consistent with a trapping mechanism that follows a Brønsted slope of zero for acids of intermediate strength and a preassociation mechanism with hydrogen bonding and $\alpha = 0.16$ for stronger acids.[48]

In this and other systems in which the transition state of the $k_{1'}$ step is stabilized by C, the reaction is likely to proceed concurrently by two different pathways, a trapping mechanism and a preassociation mechanism. These are conveniently

[86] S. P. Ewing, D. Lockshon, and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 3072.

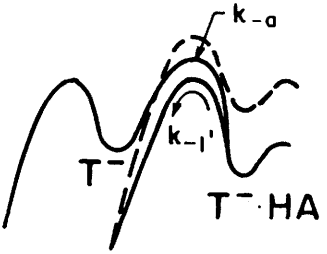


Figure 6 *Reaction co-ordinate diagram to show how hydrogen bonding of an acid,* HA, *to an addition intermediate,* T^-, *can stabilize the intermediate and the transition state for its formation so that a preassociation mechanism is favoured over a trapping mechanism. The dashed line shows that the preassociation mechanism is less favourable than the trapping mechanism in the absence of hydrogen bonding*

described by adding one or more 'wings' to the reaction co-ordinate diagram, as shown in Figure 7. The two pathways can have the same form of the rate law and the same composition of the rate-determining transition state, but one transition state represents diffusion together of I and C (k_a) and the other represents the chemical step for the formation of I · C ($k_{1'}$). The first chemical step for the trapping mechanism (k_1) does not involve C.[33,34]

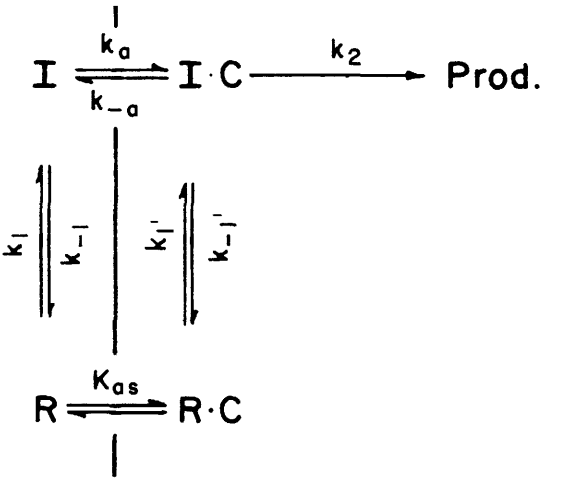


Figure 7 *Diagram with a 'wing' to show how a reaction can proceed concurrently by a trapping mechanism, with* k_a *rate determining, and a preassociation mechanism, with* $k_{1'}$ *rate determining. A similar diagram can illustrate concurrent trapping and concerted mechanisms, with a direct path for the conversion of* R · C *to products*

Stabilization of the transition state of the $k_{1'}$ step by hydrogen bonding (9) is also responsible for the weak general acid catalysis of the addition of sulphite to *p*-methoxybenzaldehyde, with $\alpha = 0.06$. This represents *non-enforced* catalysis, because the initial addition intermediate has a sufficient lifetime to diffuse through

the solvent and reach equilibrium with respect to proton transfer.[87] Non-enforced general acid catalysis with $\alpha = 0.13$ is also observed for the addition of $MeOOCCH_2S^-$ to acetaldehyde at high buffer concentrations, at which the proton-transfer step to the addition intermediate is fast and the addition step becomes rate determining.[48] Such reactions generally exhibit linear Brønsted plots in which the solvent and its components fall on or near the Brønsted line for buffer catalysts.*

'Stickiness' of the I · C complex that arises from hydrogen-bonding, electrostatic, dispersion, and hydrophobic interactions will decrease the rate constant for diffusional separation of the complex, k_{-a}, and therefore will favour the preassociation relative to the trapping mechanism (Figure 6).

Unreactive Solvents. When a reaction involves bond cleavage before the reaction with C takes place in a second step, it will proceed through a fully dissociative mechanism at sufficiently low concentration of the reactants when the solvent is unreactive. This is because a rate-determining transition state that contains C has a less favourable entropy than one that does not and a reaction will always proceed through a term in the rate law that does not include C when [C] becomes small.

Thus, ligand exchange of metal ions is likely to occur by a pure dissociative mechanism (D) in non-liganding solvents, in which the intermediate has an opportunity to diffuse away from the leaving ligand and find a new partner, whereas it is rare in liganding solvents.[47] In the cobalamin–cobaloxime series, for example, ligand exchange or addition to the aquo complex appears to follow an I_D mechanism in water but occurs through a D mechanism in inert solvents.[88–90]

Ion Pairs and Weak Complexes. There are few reactions in water and other good ionizing solvents in which an initial bond-breaking step gives an ion pair or other intermediate, I, that has a long enough lifetime to permit a dilute reactant C to encounter and react with it. Equilibrium constants for the formation of ion pairs from singly charged ions in water[91] are generally $< 1.0\ M^{-1}$ so that the first-order rate constant for dissociation of an ion pair is equal to or larger than the second-order, diffusion-controlled rate constant for its formation. The ion pair will then dissociate faster than it can encounter and react with C at a concentration of < 1 M, so that the reaction will proceed largely through the free ions[9] or, if $k_{-1'}$ and k_2 are fast, through a lower-energy preassociation mechanism.

In less ionizing solvents ion pairs have a longer lifetime so that they may diffuse through the solvent before reacting with the solvent or another molecule;

*The existence of non-enforced preassociation mechanisms raises a possible ambiguity for the classification of reaction mechanisms in terms of the lifetimes of intermediates. Since there is preassociation of C with the reactants, the intermediate complex I · C does not diffuse through the solvent, and k_2 is likely to be fast, it seems preferable to maintain the present nomenclature rather than to define a new category for this small group of reactions.

[87] P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, 99, 1206.
[88] D. Thusius, *J. Am. Chem. Soc.*, 1971, 93, 2629.
[89] R. J. Guschl, R. S. Stewart, and T. L. Brown, *Inorg. Chem.*, 1974, **13**, 417.
[90] R. C. Stewart and L. G. Marzilli, *J. Am. Chem. Soc.*, 1978, **100**, 817.
[91] C. W. Davies, 'Ion Association', Butterworths, London, 1962, pp. 77 and 168.

they then provide a major perturbation on the mechanism of solvolysis and substitution reactions. Excellent reviews are available that describe the different types of behaviour that can be explained by different types of ion pairs.[72,92] Although many experimental results can be assigned to reactions of these different ion pairs, relatively few experiments have been designed to provide a critical test of these assignments. It is not always clear that the behaviour attributed to one species could not be explained by another species or that all 'ion pairs' represent intermediates rather than transition states. Some 'solvent-separated' ion pairs may really be contact ion pairs and some 'intimate' ion pairs may be transition states, which would be consistent with their low reactivity toward nucleophilic attack.[93] In fact, the reactivity of an intramolecular carbonium–sulphonate ion pair toward nucleophiles has been shown to be very similar to that of a comparable free carbonium ion.[94] The most direct approach to the basic problems of mechanism and reactivity in organic chemistry would appear to be through the examination of reactions in polar solvents in which ion pairs are not formed or play a minimal role.

D. Liberated Intermediates.—When an intermediate has a sufficient lifetime to diffuse through the solvent and choose its partner it has crossed a moderately sharp borderline and is free to react with some degree of specificity. This will be the preferred pathway when the complex I · C of an intermediate with a final reactant or catalyst dissociates into I and C faster than it collapses to reactants [$k_{-a} > k_{-1'}$, equation (9) and Figure 5B] or when an intermediate that is formed by bond cleavage dissociates into its components [*e.g.* $k_d > k_s$, equation (15)]. The reaction will then proceed through some fully stepwise or trapping mechanism and will not contain the final reactant C in the transition state or rate law for the initial step of bond formation or cleavage, unless C is the solvent or accelerates this step. The rate law and rate-determining step of the overall reaction will, of course, include C if the initial step is reversible and trapping by reaction with C is rate determining.

An unstable liberated intermediate that encounters C will be likely to react with it faster than C can diffuse away, so that the reaction with C will be diffusion controlled and non-selective (LI-D mechanism, Figure 1). This is the case for a considerable number of reactions that require proton transfer between electronegative atoms and show diffusion-controlled trapping of an unstable intermediate by buffer acids or bases when the proton transfer is strongly favoured thermodynamically. Such reactions follow non-linear Brønsted plots that correspond to Eigen curves for simple proton-transfer reactions in water.[71,84] It is also the case for the reactions of sulphite and hydroxylamine with oxocarbonium ions derived from ketals of substituted acetophenones.[15]

The reaction with solvent is activation-limited and selective in these systems, so

[92] J. M. Harris, *Prog. Phys. Org. Chem.*, 1974, **11**, 89.
[93] L. P. Hammett, 'Physical Organic Chemistry', McGraw-Hill, New York, 2nd Edn., 1970, pp. 163—167.
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that as the structure of I changes there is a change in the relative reactivity of C and the solvent. For the oxocarbonium ions derived from substituted acetophenones the selectivity, $\log(k_{H_2O}/k_{SO_3^{2-}})$, has the surprisingly large value of $\rho = 1.6$.[15] This kind of situation, in which one reaction path is diffusion-controlled and non-selective and another is activation-limited, provides one explanation for changes in selectivity with changing reactivity of the reactant, the 'reactivity–selectivity principle'.[95,96]

Concerted general acid–base catalysis involving electronegative atoms requires that the pK of a reacting site must change during the reaction so that a proton transfer to or from the catalyst that was initially unfavourable becomes favourable and there is a driving force for the catalysis.[97] If the initial proton transfer is thermodynamically favourable it will take place rapidly and, if the immediate product is stable enough to reach equilibrium for the proton transfer step $\{k_{-1}[A^-] > k_2$ for an acid-catalysed reaction, equation (18)$\}$ it will react in a

$$S \underset{k_{-1}[A^-]}{\overset{k_1[HA]}{\rightleftharpoons}} SH^+ \xrightarrow{k_2} \text{products} \qquad (18)$$

subsequent rate-determining step in the absence of HA or A^-. This represents specific acid or base catalysis and is an example of an activation-limited LI-A mechanism (Figure 1) that is brought about by the long lifetime of the intermediate.[27]

When an intermediate is sufficiently stable to react through an LI-A mechanism, with an activation-limited process in the final step, this step will show the selectivity and other properties that are expected for such a stable chemical species and we can conclude this description of reaction mechanisms that are enforced by the lifetimes of intermediates.

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