

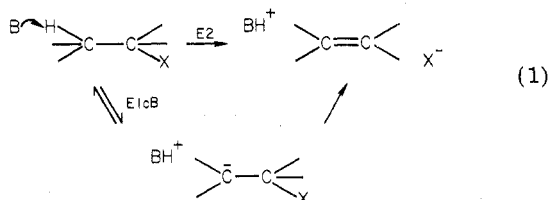
## When Is an Intermediate Not an Intermediate? Enforced Mechanisms of General Acid-Base Catalyzed, Carbocation, Carbanion, and Ligand Exchange Reactions<sup>1</sup>

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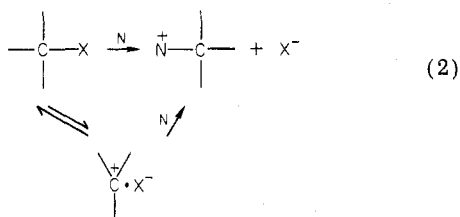
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Two important problems regarding reaction mechanisms are (a) why is a particular mechanism followed in preference to some other mechanism and (b) what is the nature of the transition from one mechanism to another as reactants or conditions are changed. The answers to these questions are determined in large part by reaction intermediates—whether intermediates are formed, what is their structure, and what they do—and many of the controversies regarding mechanism reflect uncertainty or disagreement about the existence and behavior of intermediates. For example, the assumption that most olefin-forming elimination reactions proceed through a one-step concerted E2 mechanism has been challenged by the proposal that the predominant reaction pathway is some variety of a stepwise E1cB mechanism with a carbanion intermediate (eq 1),<sup>2</sup>

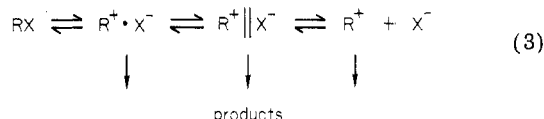


and the classical mechanism of concerted S<sub>N</sub>2 displacement reactions has been challenged by the proposal that such reactions occur through a stepwise mechanism with rate-determining attack of the nucleophile on a reversibly formed ion pair (eq 2).<sup>3</sup> The



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controversy over classical and nonclassical carbonium ions revolves around the question of whether or not there is a barrier for the interconversion of two unstable species,<sup>4</sup> and the study of solvolysis reactions is presently concerned largely with attempts to fit various experimental phenomena into the classical Winstein scheme of intimate, "solvent-separated", and completely separated ion-pair intermediates (eq 3).<sup>5</sup> The most



difficult problems in the diagnosis of reaction mechanisms arise in the region of so-called borderline or "merging" mechanisms. The purpose of this Account is to review some examples of reaction mechanisms, and transitions between mechanisms, that are enforced in a simple way by the lifetimes of intermediates. A knowledge of these lifetimes often provides an explanation for why a particular mechanism is followed and makes possible the diagnosis and prediction of the mechanism.

It is essential to define what we are talking about. For the purposes of this discussion we will divide all of chemistry into two types of reactions: stepwise reactions that proceed through at least two steps and at least one intermediate and reactions that do not proceed in steps and are therefore concerted (diffusion together of the initial reactants in either direction is not usually counted as a step in making this distinction). An intermediate is, therefore, defined as a species with

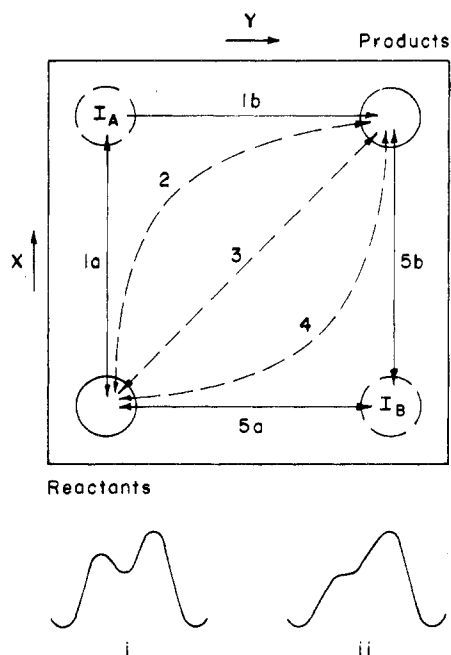
(1) Publication No. 1303 from the Graduate Department of Biochemistry, Brandeis University, Waltham, MA 02254. Supported in part by grants from the National Science Foundation (BG-31740) and the National Institutes of Health (GM 20888).

(2) F. G. Bordwell, *Acc. Chem. Res.*, **5**, 374-381 (1972); but see W. H. Saunders, Jr., *ibid.*, **9**, 19-25 (1976).

(3) R. A. Sneen, *Acc. Chem. Res.*, **6**, 46-53 (1973); but see D. J. McLennan, *ibid.*, **9**, 281-287 (1976).

(4) P. D. Bartlett, Ed., "Nonclassical Ions", W. A. Benjamin, New York, 1965; H. S. Brown, "The Nonclassical Ion Problem", Plenum Press, New York, 1976.

(5) (a) S. Winstein and G. C. Robinson, *J. Am. Chem. Soc.*, **80**, 169-181 (1958); J. M. Harris, *Prog. Phys. Org. Chem.*, **11**, 89-173 (1974); P. v. R. Schleyer, *Ions Ion Pairs Org. React.*, **2**, 247-374 (1974); (b) but see T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, **14**, 1-67 (1977).



**Figure 1.** Reaction-coordinate diagram for a reaction that involves two processes, as indicated by the  $x$  and  $y$  axes (the energy contour lines are omitted). Reaction paths 1 and 5 proceed in two steps through the intermediates  $I_A$  and  $I_B$ , respectively, and paths 2-4 represent concerted reactions with varying mixtures of processes  $X$  and  $Y$  in the transition state. The energy profiles *i* and *ii* describe stepwise and concerted reactions, respectively.

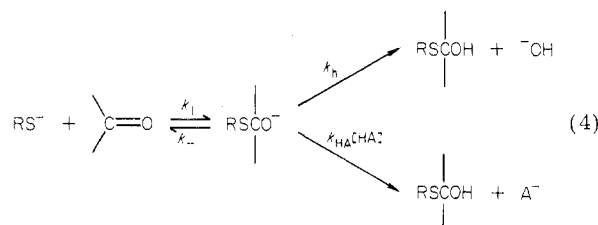
a significant lifetime, longer than that of a molecular vibration of  $\sim 10^{-13}$  s, that has barriers for its breakdown to both reactants and products. As More O'Ferrall pointed out for elimination reactions,<sup>6</sup> there is a real and clear-cut distinction between a mechanism that proceeds in two steps through an intermediate  $I$  in a potential well (Figure 1, path 1a,1b, or 5a,5b) and a concerted mechanism that does not proceed through an intermediate (paths 2-4). The reaction path for the stepwise mechanism has a well and two barriers and if either of the barriers disappears the reaction becomes concerted (profiles *i* and *ii*, respectively, in Figure 1; note that our definition of "concerted" says nothing about the difficult question of the degree of coupling between the two processes, such as proton removal and leaving-group expulsion, that are indicated by the  $x$  and  $y$  axes). Thus, it should be possible to devise experiments to assign a "borderline" reaction to one or the other mechanism, and "merging" of mechanisms must involve a qualitative change from one to the other.

A different distinction between mechanisms, which is easier to test experimentally, depends on whether or not the intermediate in a stepwise mechanism has a long enough lifetime to become diffusionally equilibrated in the solution. The existence of a solvent-equilibrated intermediate can usually be diagnosed by trapping the intermediate (e.g., by isotope exchange and inhibition of substrate disappearance with added leaving group in solvolysis reactions), by demonstrating a constant partitioning ratio to products of a common intermediate derived from different reactants, by observing a change in rate-limiting step with increasing concentration of reactant or catalyst, or by demonstrating a diffusion-controlled reaction with the inter-

mediate. When the lifetime of the intermediate becomes shorter, the reaction may be forced to proceed through an enforced *preassociation mechanism*, in which a molecule that will react in a second step (or process) forms an encounter complex with the other reactant(s) before the first step (or process) takes place. A concerted mechanism also requires preassociation of the reactants and can be considered as a special case of a preassociation mechanism. The preassociation mechanism is best described by a specific example and this will be done in the next section.

**General Acid-Base Catalysis of Addition-Elimination Reactions.** The reversible addition of nucleophilic reagents to the carbonyl group and related reactions proceed through a sequence of reaction mechanisms that are enforced by the lifetime of an addition intermediate in many (but not all) cases. This sequence has been reviewed in an earlier Account;<sup>7</sup> it will be illustrated here with some examples involving general acid catalysis of additions to the carbonyl group.

1. The addition of  $\text{EtS}^-$ , a strong nucleophile, to acetaldehyde, a reactive electrophile, gives a relatively stable anionic addition intermediate with a lifetime long enough to diffuse through the solution and abstract a proton from water before it reverts to reactants (eq 4,  $k_{-1} = 6 \times 10^6 \text{ s}^{-1}$  and  $k_h = 8 \times 10^8 \text{ s}^{-1}$ ).<sup>8</sup> This reaction



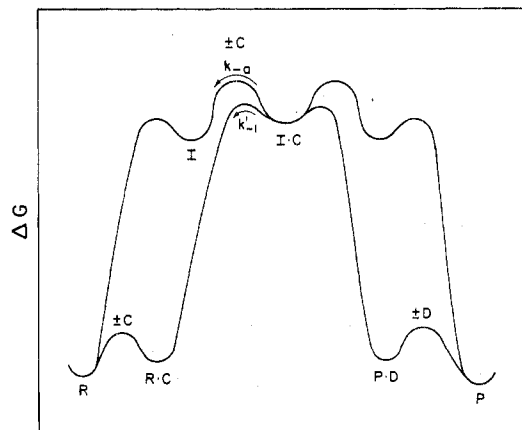
has no requirement for general acid-base catalysis and none is observed (other reactions in this class may exhibit weak general acid-base catalysis by hydrogen bonding).

2. When the nucleophile is weaker or the electrophile is more stable, a point will be reached at which the intermediate reverts to reactants faster than it abstracts a proton from water so that not every molecule of intermediate that is formed goes on to products (eq 4,  $k_{-1} > k_h$ ). When this happens a buffer acid can increase the rate by protonating the intermediate so that more molecules of product are formed ( $k_{\text{HA}}$ , eq 4). This kind of trapping becomes significant for the addition of methyl mercaptoacetate to acetaldehyde, for which  $k_{-1} \approx k_h \approx 5 \times 10^7 \text{ s}^{-1}$ . When  $k_{-1} \approx k_h$  there is a change in rate-determining step with increasing buffer concentration because the addition step ( $k_1$ ) becomes rate determining when every molecule of intermediate that is formed is trapped by buffer. This can be used as a "clock" to estimate the lifetime of the addition intermediate, based on the rate constant for diffusion-controlled protonation.<sup>8</sup> This kind of *enforced catalysis by trapping unstable intermediates* is diffusion controlled for strong acids or bases and gives a characteristic nonlinear "Eigen curve" in a Brønsted plot of catalytic constants. It has turned out to be the mechanism of a considerable number of general acid-base catalyzed reactions, including some reactions that have

(7) W. P. Jencks, *Acc. Chem. Res.*, **9**, 425-432 (1976).

(8) H. F. Gilbert and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 7931-7947 (1977).

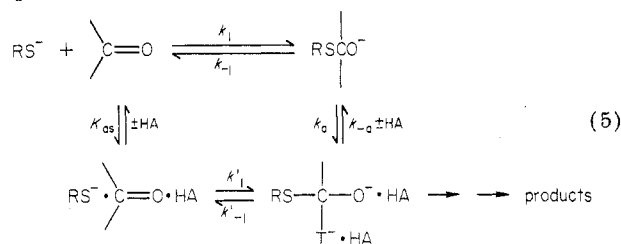
(6) R. A. More O'Ferrall, *J. Chem. Soc. B*, 274-277 (1970).



**Figure 2.** Reaction-coordinate diagram showing how a reaction will proceed through a preassociation complex (R·C) when the intermediate I·C reverts to reactants ( $k_{-1}$ ) faster than it separates to I and C ( $k_{-a}$ ).

diffusion-controlled proton transfer as the rate-determining step but take hours to days to occur because of an extremely unfavorable equilibrium constant for formation of the addition intermediate.<sup>7</sup>

3. When the intermediate becomes still less stable, a point will be reached at which it reverts to reactants faster than the catalyst can diffuse away from it and the reaction must proceed through an *enforced preassociation mechanism*.<sup>7-12</sup> This occurs for the addition of pentafluorothiophenolate anion to acetaldehyde,<sup>8</sup> for which  $k_{-1} \approx 10^{10} \text{ s}^{-1}$ . Protonation of the intermediate requires the formation of the complex T·HA (eq 5; the



dot indicates an encounter complex with HA in position to donate a proton). This complex can be formed either by addition of the nucleophile ( $k_1$ ) followed by encounter with HA ( $k_a$ ) in a trapping mechanism, according to the upper path in eq 5, or by preassociation of the reactants and catalyst in an encounter complex ( $K_{\text{as}}$ )<sup>13</sup> followed by nucleophilic addition ( $k_1'$ ), according to the lower path in eq 5. The lower preassociation pathway will be followed when the complex T·HA breaks down to reactants ( $k_{-1}'$ ) faster than HA diffuses away from it ( $k_{-a}$ ).

The reason for this is shown on the left side of the reaction-coordinate diagram of Figure 2, which describes the general case of one or more reactant molecules (R) that react with an additional reagent or cat-

(9) W. P. Jencks and K. Salvesen, *J. Am. Chem. Soc.*, **93**, 1419-1427 (1971).

(10) L. D. Kershner and R. L. Schowen, *J. Am. Chem. Soc.*, **93**, 2014-2024 (1971).

(11) W. P. Jencks, *Chem. Rev.*, **72**, 705-718 (1972).

(12) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **95**, 5637-5649 (1973).

(13) A termolecular collision in the gas phase is improbable, but the formation of a termolecular encounter complex at equilibrium in solution is not improbable. If the equilibrium constant for formation of a bimolecular encounter complex in solution is  $0.1 \text{ M}^{-1}$  and the equilibrium constant for addition of one more molecule is also  $0.1 \text{ M}^{-1}$ , the overall equilibrium constant for formation of a termolecular encounter complex is  $0.01 \text{ M}^{-2}$ .

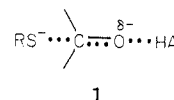
**Table I**  
Enforced Mechanisms of General Acid Catalysis

$$\text{N}^- + \text{C}=\text{O} \xrightleftharpoons[k_{-1}]{k_1} \text{I}^- \rightarrow \text{IH}$$

I <sup>-</sup>	$k_{-1}, \text{ s}^{-1}$	$\alpha$	mechanism of catalysis
EtSCHO <sup>-</sup>	$6 \times 10^6$	0	none
$\begin{array}{c} \text{CH}_3 \\   \\ \text{MeOOCCH}_2\text{SCHO}^- \\   \\ \text{CH}_3 \end{array}$	$5 \times 10^7$	Eigen curve	trapping
$\begin{array}{c} \text{CH}_3 \\   \\ \text{ArSCHO}^- \\   \\ \text{RS-CHO}^- \\   \\ \text{H} \end{array}$	$10^8-10^{10}$	0.16-0.26	preassociation, hydrogen bonding probably concerted
$\begin{array}{c} \text{CH}_3 \\   \\ \text{ROCH}_2\text{O}^- \\   \\ \text{H} \end{array}$	$\sim 10^{13}$	0.36	

alyst (C) to give products (P and D) through an intermediate complex (I·C) that contains the elements of all reactants. As the intermediate I·C (T·HA in eq 5) becomes less stable, the barrier for its reversion to reactants ( $k_{-1}'$ ) will become smaller than that for separation to give I + C ( $k_{-a}$ ). The preassociation mechanism then provides the lowest energy pathway for the reaction in the forward as well as the reverse direction. This can be described as a "spectator" mechanism when C does not stabilize the transition state for the  $k_1'-k_{-1}'$  step.<sup>10</sup>

4. When an enforced preassociation mechanism requires the acid catalyst to wait next to the carbonyl oxygen atom, so that the intermediate will be protonated as soon as it is formed, the acid is very likely to stabilize the transition state for the addition step by hydrogen bonding (1). This will occur when the oxygen



atom in the transition state is more basic than water,<sup>14</sup> resulting in *enforced catalysis by hydrogen bonding*. This is observed for catalysis of the addition of pentafluorothiophenolate anion to acetaldehyde by acids of  $\text{pK} < 10$ , which follow a Brønsted plot with a slope of  $\alpha = 0.26$ . With weaker acids, the proton transfer becomes slow and rate determining, which results in a downward break in the Brønsted plot; for weak acids the Brønsted plot follows the same Eigen curve as for trapping reactions (mechanism 2).<sup>8</sup>

5. When the intermediate becomes still less stable, the barrier for its breakdown will become insignificant, its decomposition will be faster than a vibration frequency, it will cease to exist, and the reaction will become *concerted*. This probably occurs for the acid-catalyzed addition of free thiols to acetaldehyde, which has a larger Brønsted slope of  $\alpha = \sim 0.7$ ;<sup>15</sup> the dipolar species 2 that would be formed in a stepwise mechanism



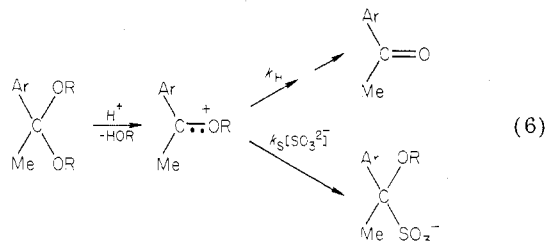
(14) J. Hine, *J. Am. Chem. Soc.*, **94**, 5766-5771 (1972).

(15) G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982-3995 (1966).

should have a much shorter lifetime than the anionic intermediates formed from thiol anion addition. A concerted mechanism is also likely for the acid-catalyzed addition of trifluoroethanol to formaldehyde, which follows a Brønsted slope of  $\alpha = 0.36$  and for which the species 3 has an estimated rate constant for breakdown of  $\sim 10^{13} \text{ s}^{-1}$ .<sup>16</sup>

The mechanisms and the lifetimes of the intermediates that enforce the mechanisms are summarized in Table I.

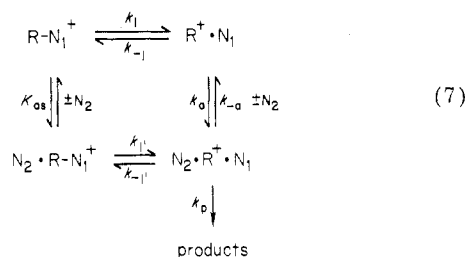
**Carbocations.** The observation that the oxocarbenium ion intermediate in the hydrolysis of acetophenone ketals can be trapped by sulfite dianion (eq 6) provided a clock with which it was possible to esti-



mate the lifetime of the oxocarbenium ion in water.<sup>17</sup> Several lines of evidence indicate that the reaction with sulfite ion is diffusion controlled, so that the rate constant for reaction of the intermediate with water ( $k_H$ ) could be estimated from the observed partitioning ratio between water and sulfite ( $k_H/k_S$ ) and the assumption that the rate constant for diffusion-controlled trapping is  $5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ . The values of  $k_H$  were found to be in the range  $7 \times 10^6$ – $4 \times 10^8 \text{ s}^{-1}$  for a series of ring-substituted acetophenone ketals; very similar values were found by extrapolation of rate constants for the directly measured disappearance of these ions in strong-acid solution.<sup>18</sup>

These rate constants give a linear correlation with the rate constants for the addition of sulfite ion to the parent acetophenones. Extrapolation of this correlation to other compounds gives values of  $k_H$  in the range  $10^9$ – $10^{12} \text{ s}^{-1}$  for the addition of water to oxocarbenium ions derived from substituted benzaldehydes and acetaldehydes and  $10^{15} \text{ s}^{-1}$  for the ion formed from formaldehyde derivatives. This extrapolation is crude, but it suggested that the less stable ions would not have a long enough lifetime to diffuse through the solvent so that they would be required to react through a preassociation or concerted mechanism.

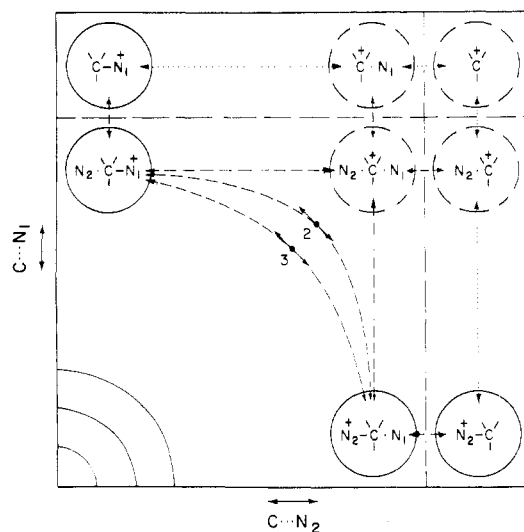
Stepwise and preassociation mechanisms for reactions of carbocations are described by the upper and lower pathways of eq 7, respectively, in which  $N_1$  is the leaving



(16) L. H. Funderburk, L. Aldwin, and W. P. Jencks, *J. Am. Chem. Soc.*, **100**, 5444–5459 (1978).

(17) P. R. Young and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 8238–8248 (1977).

(18) R. A. McClelland and M. Ahmad, *J. Am. Chem. Soc.*, **100**, 7031–7036 (1978).



**Figure 3.** Diagram describing a stepwise reaction through a diffusively equilibrated carbocation intermediate around the outside of the diagram (dotted lines) and preassociation reaction paths with both the entering and leaving groups present in the transition state (inner box, dashed lines).<sup>27</sup>

group and  $N_2$  is the solvent or another nucleophile that replaces  $N_1$ . As shown in Figure 2 (in which  $R$  is  $\text{>C-N}_1^+$  and  $C$  is  $N_2$ ), the preassociation mechanism will be followed when the reaction proceeds through an intermediate ( $\text{N}_2 \cdot \text{R}^+ \cdot \text{N}_1$ ) that reverts to reactants ( $k_{-1}'$ ) faster than  $N_2$  can diffuse away from it ( $k_{-a}$ ).<sup>19</sup> In many cases this will simply mean that the carbocation reacts non-selectively with the first molecule it sees, but if the carbon atom develops significant electrophilic character in the transition state and is not too shielded the solvent molecule or some other nucleophile that is waiting to accept the carbocation will tickle the transition state enough to provide significant stabilization. When this happens with an added nucleophile, a second-order reaction will be observed; when it happens with solvent, it represents "solvent assistance".<sup>5b</sup> If the carbocation becomes still less stable there will be no barrier for its reaction with the nucleophile and a concerted displacement reaction will be observed.<sup>20</sup>

These pathways are summarized in the reaction-coordinate diagram of Figure 3, which is oriented in accord with eq 7 and the usual convention for displacement reactions<sup>21</sup> and has "wings" for the transport steps.<sup>22</sup> The fully stepwise mechanism through a

(19) The initial step within the preassociation complex,  $k_1'$ , will be rate determining when the subsequent step is fast ( $k_p > k_{-1}'$ ). If the subsequent step becomes slow ( $k_p < k_{-1}'$ ) it will be rate determining; the intermediate will be formed by a preassociation mechanism in a fast equilibrium step. This is the case for general acid catalysis by weak acids (eq 5) when proton transfer becomes rate determining, for example. This is likely to occur for reactions of carbocations (eq 7) and metals (eq 11) when the solvent is weakly nucleophilic and for reactions of carbanions (eq 8) when the solvent is a poor proton donor. If  $k_p$  becomes still slower, as in a nonnucleophilic or aprotic solvent, the intermediate may become diffusively equilibrated. At sufficiently low concentrations of the final reactant  $C$ , there will then be no advantage to the preassociation mechanism and the reaction will proceed through solvent-equilibrated intermediates without the formation of a complex containing the elements of all reactants.

(20) M. J. S. Dewar, *Annu. Rep. Prog. Chem.*, **48**, 121 (1951); W. v. E. Doering and H. H. Zeiss, *J. Am. Chem. Soc.*, **75**, 4733–4738 (1953).

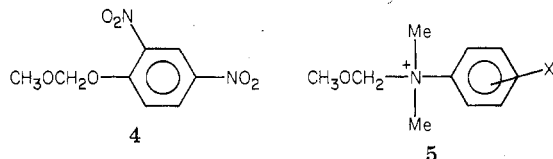
(21) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **34**, 11–29 (1938); E. D. Hughes, C. K. Ingold, and U. G. Shapiro, *J. Chem. Soc.*, 225–236 (1936).

(22) S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7986–7998 (1974); W. J. Albery and M. M. Kreevoy, *Adv. Phys. Org. Chem.*, **16**, 87–157 (1978).

solvent-equilibrated intermediate proceeds around the outside of the diagram, a reaction with an ion pair in a weakly nucleophilic solvent enters the center of the diagram at the upper right, and a preassociation mechanism can proceed through the intermediate in the central box, if it exists, or through concerted pathways 2 and 3 with varying amounts of cationic character in the transition state.

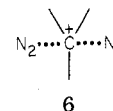
It has been almost universally believed that formaldehyde derivatives react through a monomolecular or A1 mechanism to give an intermediate oxocarbenium ion.<sup>23,24</sup> For formaldehyde acetals and acylals, this conclusion has been based on the acidity dependence for hydrolysis, analogy with other reactions of acetals, and large negative values of  $\rho$  or  $\rho^*$ , such as  $\rho = -3$  for the hydrolysis of  $\text{ArOCH}_2\text{OAc}$ .<sup>24</sup> For halomethyl methyl ethers it is based on the  $5 \times 10^6$  faster rate of solvolysis of  $\text{CH}_3\text{OCH}_2\text{Cl}$  than of *tert*-butyl chloride, the identical dependence on solvent-ionizing power ( $Y$ ) for the solvolysis of these two compounds, and a secondary  $\alpha$ -deuterium isotope effect of  $k_{\text{H}}/k_{\text{D}} = 1.24$  (per deuterium) for the solvolysis of chloromethyl methyl ether.<sup>25</sup> However, the correlation described above suggested that the oxocarbenium ion  $\text{CH}_3\text{OCH}_2^+$  is too unstable to exist as a free intermediate and predicted that these reactions should proceed through a preassociation or concerted mechanism.<sup>17</sup>

A preassociation or concerted mechanism is supported, in fact, by Craze, Kirby, and Osborne's demonstration that methoxymethoxy-2,4-dinitrobenzene (4)



undergoes second-order reactions with a variety of nucleophilic reagents in water that exhibit secondary  $\alpha$ -deuterium isotope effects in the range  $k_{\text{H}}/k_{\text{D}} = 1.05$ – $1.16$ ; water does not appear to react by a different mechanism.<sup>26</sup> Knier has obtained similar results with the cationic compound 5, which removes any possible doubts that might arise from the possibility of a reaction of 4 through an ion-pair intermediate.<sup>27</sup> The second-order rate constants for 5 show a small dependence on the nucleophilicity of the attacking reagent and appear to follow behavior intermediate between that expected for an  $\text{S}_{\text{N}}2$  reaction, with a value of  $s = 0.3$  in a Swain–Scott correlation, and that expected for reactions with carbocations, with a slope of 0.35 in a correlation using the  $\text{N}^+$  scale. The value of  $\beta_{\text{nuc}}$  is 0.14 for a series of primary amines and values of  $\beta_{1\text{g}}$  are  $-0.70$ , for *n*-propylamine, and  $-0.89$ , for water, with a series of substituted dimethylaniline leaving groups. These results support an open transition state with a small amount of bond formation and a large amount of

bond cleavage that can be regarded, equivalently, as either a loose “exploded” transition state for an  $\text{S}_{\text{N}}2$  reaction or an oxocarbenium ion that is stabilized through interactions with both attacking and leaving groups (6). This description is supported by compar-



ison of the small difference of 3-fold in the rate constants for the reactions of  $\text{Cl}^-$  and  $\text{F}^-$  as nucleophiles with 5 and the large difference of  $>3 \times 10^6$  for these two ions as leaving groups from halomethyl methyl ethers.<sup>28</sup>

The secondary  $\alpha$ -deuterium isotope effects for second-order reactions of 5 increase with increasing size and polarizability of the nucleophile from  $k_{\text{H}}/k_{\text{D}}$  (per deuterium) = 0.99 for  $\text{F}^-$  to 1.18 for  $\text{I}^-$  in the halide series; intermediate values that generally follow the same trend are found for oxyanions, amines, water, and thiol anions.<sup>27</sup> These and other<sup>26,29</sup> results show that such isotope effects do not provide proof of a monomolecular  $\text{S}_{\text{N}}1$  mechanism and that they may not be reliable indicators of the amount of bond formation in the transition state when different nucleophilic atoms are compared. The differences may reflect interaction of the large polarizable nucleophiles with the central carbon atom from a greater distance, so that there is less restriction to the vibrations of the hydrogen atoms than in the transition states for smaller nucleophiles.<sup>30</sup> Whatever the explanation, they confirm the existence of a significant interaction of the nucleophilic reagent with the carbon center in the transition state that is different for different nucleophiles.

There is no indication that the solvolysis reaction occurs through any pathway that is different from the bimolecular pathway that is followed for nucleophiles other than water: the rate constant for water falls on or slightly below the lines for the Swain–Scott,  $\text{N}^+$ , and  $\beta_{\text{nuc}}$  correlations for other nucleophiles; the values of  $\Delta\text{S}^\ddagger$  for solvolysis and the second-order reaction with *n*-propylamine are  $-1.2$  and  $-2.1$   $\text{cal K}^{-1} \text{mol}^{-1}$ , respectively; and the rate constants for these two reactions show a similar dependence on the solvent in ethanol–water and trifluoroethanol–water mixtures. Similar results for most of these criteria were found for the reactions of 4.<sup>26</sup>

These results confirm the prediction that this class of reactions should proceed through an enforced preassociation or concerted mechanism. It is likely, although not proved rigorously, that the carbocation has no significant lifetime in the presence of nucleophiles and that the reaction is concerted. The estimated lifetime for the carbocation of  $10^{-15}$  s in water is crude, but thiol anions react with carbocations some  $10^8$  faster than water<sup>31</sup> so that it seems virtually certain that there will be no energy barrier for the collapse of a species  $\text{RS}^-\text{R}^+$  with a “lifetime” of  $10^{-23}$  s. If there is an intermediate, either its formation or breakdown must be

(23) P. Salomaa, *Chem. Carbonyl Group*, 1, 184 (1966); B. M. Dunn and T. C. Bruice, *J. Am. Chem. Soc.*, **93**, 5725–5731 (1971).

(24) G. Modena, G. Scorrano, and P. Venturello, *J. Chem. Soc., Perkin Trans. 2*, 1–6 (1979); E. G. Cordes and H. G. Bull, *Chem. Rev.*, **74**, 581–603 (1974); R. A. McClelland, *Can. J. Chem.*, **53**, 2763–2771 (1975).

(25) P. Ballinger, P. B. D. de la Mare, G. Kohnstam, and B. M. Prestt, *J. Chem. Soc.*, 3641–3647 (1955); E. R. Thornton, *J. Am. Chem. Soc.*, **89**, 2915–2927 (1967).

(26) G. A. Craze, A. J. Kirby, and R. Osborne, *J. Chem. Soc., Perkin Trans. 2*, 357–368 (1978).

(27) B. Knier and W. P. Jencks, *J. Am. Chem. Soc.*, submitted for publication.

(28) F. C. Kokesh and J. Hine, *J. Org. Chem.*, **41**, 1976–1978 (1976).

(29) J. P. Ferraz, H. G. Bull, and E. G. Cordes, *Arch. Biochem. Biophys.*, **191**, 431–436 (1978); K. C. Westaway, *Can. J. Chem.*, **57**, 1089–1097 (1979).

(30) C. H. Gray, J. K. Coward, K. B. Schowen, and R. L. Schowen, *J. Am. Chem. Soc.*, **101**, 4351–4358 (1979).

(31) C. D. Ritchie, *J. Am. Chem. Soc.*, **97**, 1170–1179 (1975); C. D. Ritchie and J. Gandler, *J. Am. Chem. Soc.*, **101**, 7318–7323 (1979).

Table II  
Solvolytic of Glucosyl-X in 50% EtOH/CF<sub>3</sub>CH<sub>2</sub>OH<sup>32</sup>

	inversion retention	OEt OCH <sub>2</sub> CF <sub>3</sub> product	
		α	β
α-glucosides			
X = F	2.1	0.9	20
X = OPh(H <sup>+</sup> )	1.8	3.5	9.8
β-glucosides			
X = F	3.7	3.7	1.6
X = OPh(H <sup>+</sup> )	4.1	2.2	12

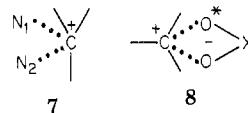
rate limiting. Many of the amines and other attacking reagents are stronger nucleophiles than the leaving group so that an intermediate would collapse rapidly to give products and the initial bond-breaking step would be rate determining with these nucleophiles ( $k_1'$ , eq 7). However, other nucleophiles are weaker than the leaving group so that there should be a change to  $k_p$  as the rate-limiting step. Such a change should cause a break in structure-reactivity correlations for these nucleophiles, but there is no indication of any such break. The data suggest that the reaction proceeds through a single open transition state that is symmetrical when the entering and leaving groups are similar.

The cleavage of glycosides is widely believed to proceed through an intermediate oxocarbenium ion, but the acid hydrolysis of glycosides is even slower than that of formaldehyde acetals so that the "intermediate" is expected to have a lifetime of  $\leq 10^{-15}$  s and the reactions should proceed through a preassociation or concerted mechanism. The solvolysis of a series of glucosides in ethanol-trifluoroethanol mixtures, with fluoride ion, pyridines, 2,4-dinitrophenolate ion, phenol, and nitrogen as leaving groups, has been shown by Sinnott to give different product ratios with different leaving groups and with the α- and β-glucosides.<sup>32</sup> Some examples are shown in Table II. This shows that the leaving group is a participant in the transition state; there is no free oxocarbenium ion intermediate, in agreement with the conclusions of earlier work.<sup>33</sup>

The surprising result is that there is a large discrimination of up to 20-fold favoring ethanol over trifluoroethanol as the entering reagent N<sub>2</sub>. This discrimination is different for different leaving groups. This shows that the incoming nucleophile as well as the leaving group is involved in the product-determining transition state and that ethanol stabilizes the transition state by up to nearly 2 kcal compared with trifluoroethanol. However, this does not represent attack on a reversibly formed ion pair or ion-dipole pair because there is no time for diffusion and discrimination is observed with phenol and nitrogen as leaving groups; these are weaker nucleophiles than the solvent so that the bond-cleavage step must be rate determining if an intermediate exists. Even more surprising is the finding that although most of the reaction goes with inversion in 50% ethanol-trifluoroethanol the 15–40% that goes with retention shows a similar selectivity.

These results require an open transition state that is close to that expected for diffusional separation of the leaving group from R<sup>+</sup> but is significantly stabilized by

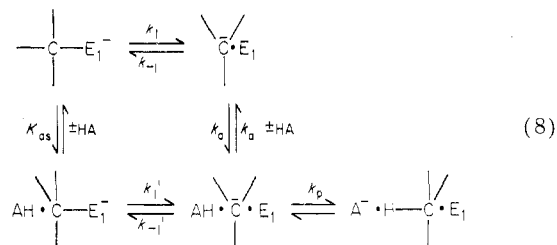
interactions with both the entering and leaving groups. The observation of high selectivity for both inversion and retention means that this stabilization occurs when both groups are on the same as well as on the opposite side; i.e., the incoming nucleophile can tickle the front side (7) as well as the back side (8) of the transition



state. Whether this stabilization is simply electrostatic or involves some degree of electron donation and orbital overlap is not presently known.

The small or insignificant lifetimes of these carbocations suggest that the "intermediates" formed from compounds with less effective electron donors than oxygen, such as derivatives of secondary alkanes, also have no significant lifetime in the presence of moderately good nucleophiles. Many reactions that are thought to proceed through an intimate ion-pair intermediate will then be forced to proceed through a concerted mechanism in which the transition state is an ion pair with no barrier for its collapse to reactants, such as 8 for oxygen exchange with carboxylate and other oxyanion leaving groups.

**Carbanions.** When a carbanion reacts with the electrophilic reagent from which it was formed (E1) faster than a proton donor diffuses away from it and also reacts rapidly with the proton donor,<sup>19</sup> the lowest energy path for its formation will be through a preassociation mechanism with the proton donor in place during the initial bond-cleavage step ( $k_1'$ , eq 8) rather



than through the fully stepwise upper path of eq 8 ( $k_1$  and  $k_a$ ). This is apparent from Figure 2, in which R = >C-E<sub>1</sub> and C = HA, when  $k_{-1}' > k_{-a}$ . An analogous situation holds for the reverse reaction with an electrophilic reagent of a carbanion that is generated by proton removal. If the transition state for generation of the carbanion has sufficient electron density on carbon and is sterically accessible, it will be stabilized by hydrogen bonding to the proton donor, so that there will be partial proton transfer in the transition state and catalysis by proton donors that are more acidic than the solvent, i.e., general acid catalysis. A still less stable carbanion that has no barrier for reaction with the proton donor or with the electrophile will react by a concerted mechanism.

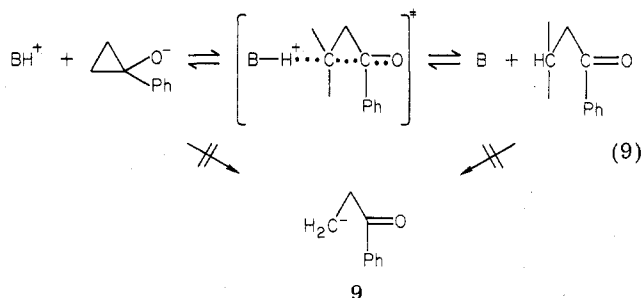
This kind of behavior was suggested by the observation that the decomposition of cyclopropanol anions shows discrimination between protium and deuterium in the product formed in H<sub>2</sub>O-D<sub>2</sub>O mixtures.<sup>34</sup> It is unlikely that an unstabilized carbanion intermediate would have a long enough lifetime to diffuse and discriminate among proton donors. Thibblin has shown

(32) M. L. Sinnott and W. P. Jencks, *J. Am. Chem. Soc.*, 102, 2026–2032 (1980).

(33) B. E. C. Banks, Y. Meinwald, A. J. Rhind-Tutt, I. Sheft, and C. A. Vernon, *J. Chem. Soc.*, 3240–3246 (1961).

(34) C. H. DePuy, *Trans. N.Y. Acad. Sci.*, Ser. 2, 28, 561–568 (1966).

that there is a small kinetic as well as a discrimination deuterium isotope effect for the cleavage of 1-phenylcyclopropanol anion and that the cleavage is catalyzed by substituted quinuclidinium ions through general acid catalysis with a Brønsted  $\alpha$  value of 0.25.<sup>35</sup> This is consistent with an  $S_E2$  displacement mechanism in which an open transition state is stabilized by weak interactions with the proton donor and with the developing carbonyl group (eq 9). The primary carbanion



species 9 that would be formed in a stepwise mechanism is the conjugate base of a carbon acid of  $pK \approx 60 \pm 10$  and would be expected to react with a carbonyl group or a buffer acid with little or no activation barrier, so that the reaction is expected to proceed through an enforced preassociation mechanism or, more likely, an enforced concerted preassociation mechanism.

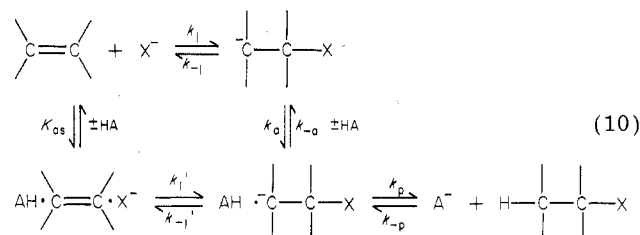
The 1,2-diphenylcyclopropanol anion exhibits weaker general acid catalysis with a smaller Brønsted slope of  $\alpha \leq 0.1$  and a small inverse kinetic isotope effect of  $k_{OH}/k_{OD} = 0.7$ . This is the behavior that would be expected from structure-reactivity considerations for the more stable benzylic carbanion: stabilization of the carbanion should exert an "anti-Hammond", perpendicular effect on the reaction coordinate to give a more carbanionic transition state with a smaller amount of proton removal from the acid.<sup>35</sup>

The reverse of this cleavage reaction is an aldol condensation of a carbon acid with a carbonyl compound, and the same sequence of preassociation and concerted mechanisms must be followed for such reactions and for other electrophilic reactions when the carbanion becomes sufficiently unstable (although many such reactions will be too slow to observe). It is conceivable that electrophilic assistance of this kind is significant in enzymic carbon-carbon condensation reactions, which sometimes are faster than can readily be accounted for by the formation of an unstabilized carbanion intermediate.

The base-catalyzed expulsion of a carbanion from ring-substituted benzyltrimethylsilanes in MeOH-MeOD gives only a small isotope discrimination of  $k_H/k_D = 1.1-1.3$  for the unsubstituted and other strongly basic benzyl carbanions, but a sudden increase to  $k_H/k_D \approx 10$  is observed for *p*-nitrobenzyl and other less basic carbanions.<sup>36</sup> A reasonable explanation for this dramatic change is that the lifetime of the basic carbanions is too short to permit solvent equilibration, so that they react with the first solvent molecule that they encounter ( $k_{-1}' > k_{-a}$ ), whereas the less basic res-

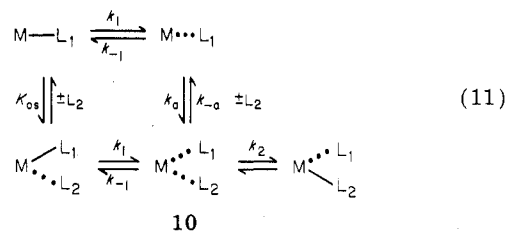
onance-stabilized carbanions have a sufficient lifetime to pick and choose between MeOH and MeOD as proton donors ( $k_{-a} > k_{-1}'$ ).<sup>35</sup> In the benzyltrimethylstannane series, the primary deuterium isotope effect for the analogous reactions is  $k_H/k_D = 2.1-2.4$ , which suggests that proton donation provides significant electrophilic assistance to the carbon-metal bond-cleavage process ( $k_{-1}'$ ).<sup>36</sup>

Olefin-forming elimination reactions are addition reactions in the reverse direction (eq 10) that are



analogous to carbonyl addition reactions, except for the more difficult proton-transfer process. The reaction proceeds through a fully stepwise E1cB mechanism, with a solvent-equilibrated carbanion intermediate, when the barriers for expulsion of  $X^-$  ( $k_{-1}$ ) and proton transfer ( $k_p$ ) are large. When the barrier for expulsion of  $X^-$  decreases so that  $k_{-1}' > k_{-a}$ , the reaction proceeds through a preassociation "E1cB<sub>ip</sub>" mechanism<sup>2,37</sup> when  $k_{-1}' < k_p$  and through the more common E1cB (irreversible) mechanism when  $k_{-1}' > k_p$  (Figure 2, R =  $>C=C < X^-$ , C = HA).<sup>38</sup> When the barrier for either proton transfer or  $X^-$  expulsion disappears, the reaction must proceed through a concerted (but not necessarily coupled) E2 mechanism. This is very likely to occur when the  $\beta$ -carbon atom is unactivated or weakly activated for carbanion formation.

**Metal-Ligand Exchange Reactions.** The same sequence of lifetimes of intermediate species provides a rationale for the mechanisms of ligand exchange on metal ions.<sup>39,40</sup> A pure dissociative mechanism (D) for an aquo hexacoordinate metal ion, for example, follows the upper pathway of eq 11 ( $L_1 = H_2O$ ) with initial



dissociation to pentacoordinate metal ( $k_1$ ) followed by encounter ( $k_a$ ) and addition ( $k_2$ ) of the incoming ligand  $L_2$ . Such mechanisms are rare in liganding solvents because the lifetime of the pentacoordinate intermediate is usually too short to permit a fully stepwise mechanism with a solvent-equilibrated intermediate. For a leaving ligand other than solvent, the initial product will be formed by addition of solvent if the

(37) W. K. Kwok, W. G. Lee, and S. I. Miller, *J. Am. Chem. Soc.*, **91**, 468-476 (1969); A. Thibblin, S. Bengtsson, and P. Ahlberg, *J. Chem. Soc., Perkin Trans. 2*, 1569-1577 (1977).

(38) A solvent-equilibrated E1cB (irreversible) mechanism is also possible when the carbanion is stable and proton transfer is rate limiting.

(39) W. W. Reenstra and W. P. Jencks, *J. Am. Chem. Soc.*, **101**, 5780-5791 (1979).

(40) C. H. Langford and H. B. Gray, "Ligand Substitution Processes", Benjamin, New York, 1965.

(35) A. Thibblin and W. P. Jencks, *J. Am. Chem. Soc.*, **101**, 4963-4973 (1979).

(36) R. Alexander, W. A. Asomaning, C. Eaborn, I. D. Jenkins, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 490-494 (1974); C. Eaborn and D. R. M. Walton, *ibid.*, 1857-1861 (1976); D. Macciantelli, G. Seconi, and C. Eaborn, *ibid.*, 834-838 (1978).

lifetime is too short to allow selection among different ligands. The addition of a ligand will proceed by an enforced preassociation mechanism through an outer-sphere complex ( $K_{os}$ ) followed by dissociation of  $L_1$  ( $k_{-1}$ ) and addition of the new ligand ( $k_2$ ), as described by the lower path of eq 11, when the pentacoordinate intermediate 10 collapses to reactants ( $k_{-1}$ ) faster than the incoming ligand can diffuse away from it ( $k_{-a}$ ).<sup>39,41</sup> The reason for this is shown by the Gibbs energy diagram of Figure 2, with R as the metal-ligand complex and I-C as the pentacoordinate complex 10. This mechanism is identical with the dissociative interchange ( $I_D$ ) mechanism.<sup>40</sup> Like all preassociation mechanisms, this reaction is first order with respect to the incoming reactant unless the initial outer-sphere or association complex is stable enough to accumulate to a significant extent under the conditions of the experiments. Pure dissociative mechanisms will exhibit a change in rate-limiting step to the  $k_1$  step, which is independent of the concentration of the incoming group, when the intermediate is trapped faster than it reverts to reactants through the  $k_{-1}$  step; this gives a nonlinear dependence of  $k_{obsd}$  on  $L_2$ .

When the incoming ligand is forced to be present in the transition state for expulsion of  $L_1$  through a preassociation mechanism, it is likely to interact weakly with the metal ion to stabilize the transition state if such interaction is not prohibited sterically. Such a transition state is open or "exploded" and closely resembles that for rate-determining diffusional separation of  $L_1$  from the metal (11); the incoming ligand may

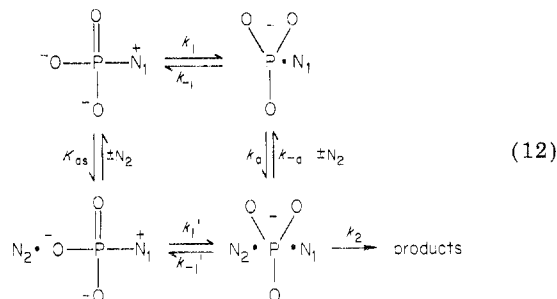


interact through an electron pair or dipole to help prevent collapse back to starting materials and thereby increase the rate of product formation in a manner similar to that for frontside displacement in the solvolysis of glucosides (7). This kind of interaction provides an explanation for the small differences in rate that are frequently observed for the addition of different ligands, such as the range of  $10^2$  for the addition of ligands to aquocobalamin to form complexes that differ in stability by factors of up to  $\sim 10^{11}$ .<sup>42</sup> This is sometimes called an associative interchange,  $I_a$ , mechanism and might be described by path 2 in Figure 1.

Pure dissociative stepwise mechanisms in both metal ion and carbon chemistry are much more likely to occur in unreactive or weakly reactive solvents because the lifetime of the intermediate is longer and dissociation to a free intermediate is more likely in such solvents. In a completely unreactive solvent the dissociative mechanism will always provide the lowest energy pathway in sufficiently dilute solution because the Gibbs free energy of the free intermediate that is formed in a monomolecular step must always be lower than that of a complex of two molecules (because of the unfavorable entropy of association).

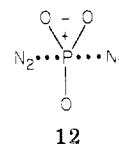
**Reactions of Monosubstituted Phosphates.** There is a considerable amount of evidence suggesting that reactions of phosphate monoesters, acyl phos-

phates, phosphoramidates, and other monosubstituted phosphates proceed through a monomeric metaphosphate intermediate (eq 12, upper path) or a me-



taphosphate-like transition state.<sup>43-47</sup> Methyl metaphosphate has been identified as an initial product of decomposition reactions in the gas phase and in non-hydroxylic solvents, but it has not yet been possible to demonstrate the existence of  $PO_3^-$  in water.<sup>45,46</sup> Monosubstituted phosphate dianions react with nucleophilic reagents in water in second-order reactions that show a small dependence on the basicity of the nucleophilic reagent and a very large dependence on the  $pK_a$  of the leaving group; for *p*-nitrophenyl phosphate and 2,4-dinitrophenyl phosphate,  $\beta_{nuc}$  is 0-0.2 for reactions with amines and for a series of acyl and phenyl phosphates the values of  $\beta_{lg}$  are in the range -1.0 to -1.2 for the reactions with amines and hydrolysis, for example.<sup>44</sup>

These characteristics suggest that the lifetime of the metaphosphate monoanion in water and other nucleophilic solvents may be so short that the initial product of bond cleavage  $N_2 \cdot PO_3^- \cdot N_1$  reverts to reactants ( $k_{-1}$ ) faster than the incoming reagent can diffuse away from it ( $k_{-a}$ ) and the reaction occurs through an enforced preassociation mechanism with an open "exploded" transition state (12).<sup>44,47</sup> This is described by Figure



2 with  $R = {}^+N_1-PO_3^{2-}$  and  $C = N_2$ . It is supported by the observation that the alcoholysis of phenyl phosphate monoanion proceeds with inversion in aqueous propanediol.<sup>48</sup> It is not known whether the intermediate has a significant lifetime when it is in contact with water or nucleophiles or whether the reaction occurs through a concerted mechanism with a symmetrical transition state. If the intermediate has no lifetime, the transition state 12 is qualitatively identical with that for an in-line  $S_N2$  displacement reaction and there is

(43) J. R. Cox, Jr., and O. B. Ramsey, *Chem. Rev.*, **64**, 317-352 (1964); S. J. Benkovic and K. J. Schray in "Transition States of Biochemical Processes", R. D. Gandour and R. L. Schowen, Eds., Plenum Press, New York, 1978, pp 493-527.

(44) A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, **87**, 3209-3216 (1965); A. J. Kirby and A. G. Varvoglis, *ibid.*, **89**, 415-423 (1967); *J. Chem. Soc. B*, 135-141 (1968).

(45) C. H. Clapp and F. H. Westheimer, *J. Am. Chem. Soc.*, **96**, 6710-6714 (1974); C. H. Clapp, A. Satterthwait and F. H. Westheimer, *ibid.*, **97**, 6873-6874 (1975); A. C. Satterthwait and F. H. Westheimer, *ibid.*, **100**, 3197-3203 (1978).

(46) An intermediate has been observed by J. Rebek and F. Gowiña in dioxane that may be  $PO_3^-$  or the dioxane adduct of  $PO_3^-$  (*J. Am. Chem. Soc.*, **97**, 1591-1592, 3221-3222 (1975)).

(47) D. G. Gorenstein, Y.-G. Lee, and D. Kar, *J. Am. Chem. Soc.*, **99**, 2264-2267 (1977).

(48) S. L. Buchwald and J. R. Knowles, personal communication.

(41) C. H. Langford, *Inorg. Chem.*, **4**, 265-266 (1965); N. Sutin, *Annu. Rev. Phys. Chem.*, **17**, 119-172 (1966).

(42) C. K. Poon, *Coord. Chem. Rev.*, **10**, 1-35 (1973).



no difference between a "metaphosphate mechanism" and a displacement mechanism with an open transition state.

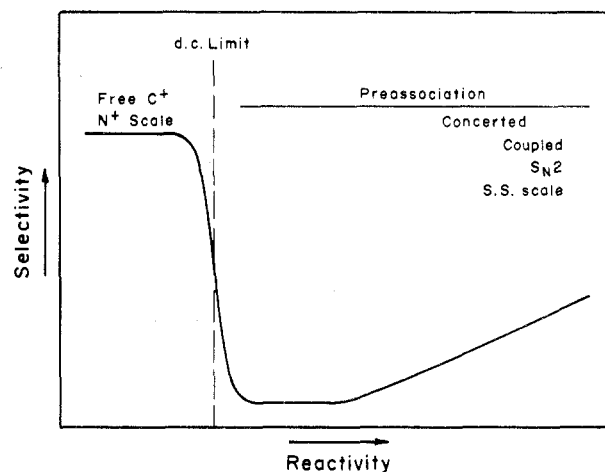
It has been proposed that the reactions of phosphate monoesters and phosphoramidates proceed through the top pathway of eq 12 by a mechanism involving encounter and reaction with an initially formed ion-induced dipole pair, similar to that proposed for bimolecular reactions on carbon.<sup>3,49</sup> There are a number of problems with such mechanisms, including a problem of microscopic reversibility for the symmetrical reaction with identical entering and leaving groups. (1) The different second-order rate constants that are observed with different nucleophiles require that the bond-forming step in the ternary complex ( $k_2$ ), not diffusion ( $k_a$ ), be rate limiting in the forward direction for many nucleophiles, but the corresponding bond-dissociation step in the reverse direction ( $k_{-1}$ ) is postulated to occur in the absence of  $N_2$ ; this leads to different reaction paths for the forward and reverse reactions. (2) In order for  $k_2$  to be rate limiting, the previous steps must be fast and at equilibrium with the reactants, so that dissociation of  $N_2$  from the intermediate complex  $N_2 \cdot PO_3^- \cdot N_1$  must be fast ( $k_{-a} > k_2$ ). But if the dissociation of  $N_2$  is fast the dissociation of  $N_1$  must also be fast. The complex will then not be at equilibrium with reactants in the initial part of the reaction when the concentration of  $N_1$  is low. (3) If dissociation is slow relative to  $k_2$  ( $k_2 > k_{-a}$ ), it will also be slow relative to  $k_{-1}'$  ( $k_{-1}' > k_{-a}$ ,  $k_{-1}' = k_2$  for a symmetrical reaction). The reaction will then proceed through a preassociation mechanism (lower path, eq 12).

**Summary.** When the lifetime of an intermediate becomes shorter than the time required for diffusion away from it of the final reactant or catalyst (C), a reaction that proceeds through a complex containing the elements of all reactants (I-C) will ordinarily form this complex by a preassociation mechanism, rather than by an initial step followed by encounter with the final reactant or catalyst (Figure 2, inner path through the intermediate in Figure 3).

When there is no significant barrier for collapse of the intermediate complex I-C in one or both directions, the intermediate does not exist and the reaction will proceed through a concerted mechanism (with rare exceptions in nonreactive solvents).

The amount and nature of the bonding between the entering and leaving atoms and the coupling of vibrations in the transition state generally involve quantitative rather than qualitative distinctions and do not provide a clear-cut basis for classifying reaction mechanisms.

(49) J. R. Baker and J. M. Lawlor, *Aust. J. Chem.*, **29**, 949-956 (1976); J. P. Guthrie, *J. Am. Chem. Soc.*, **99**, 3991-4001 (1977).



**Figure 4.** Diagram showing the changes in selectivity with changing reactivity of a carbocation. A stable intermediate will show a large selectivity toward nucleophiles; a less stable intermediate will react at a diffusion-controlled rate and show essentially no selectivity; a still less stable intermediate will show a small selectivity by stabilization of the transition state of a preassociation mechanism by the entering reagent; and a concerted reaction with an "intermediate" that is too unstable to exist will show a larger selectivity in an  $S_N2$  reaction.

It is a consequence of this sequence of mechanisms that selectivity toward the final reactant goes through a minimum with decreasing reactivity of the intermediate species, as illustrated for reactions of carbocations in Figure 4. When a carbocation or carbanion<sup>35</sup> reacts faster than it can diffuse, there will be virtually no selectivity. As it becomes more stable there will be a sudden increase to a large selectivity when it can diffuse and choose its partner. When it becomes less stable there will be a small selectivity from stabilization of the transition state of a preassociation mechanism by a weak nucleophilic or electrostatic interaction, and when it becomes still less stable there will be a progressive increase in the involvement and selectivity of the final reactant as the reaction becomes concerted and coupled, as in an  $S_N2$  displacement reaction.

The presently available evidence appears to be consistent with the notion that carbanion and carbocation reactions proceed through a solvent-equilibrated intermediate when they can do so; i.e., the existence of concurrent stepwise and concerted mechanisms or nonenforced concerted mechanisms has not been established. For substitution and solvolysis reactions this involves the outer path along the wings of the diagram in Figure 3. However, there are examples of concurrent stepwise and concerted mechanisms in other general acid-base catalyzed reactions, such as specific and general base catalysis of the cleavage of formaldehyde hemiacetals.<sup>16</sup>