Elimination–Addition Mechanisms of Acyl Transfer Reactions

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I. Introduction

Acyl transfer reactions proceeding via addition–elimination mechanisms have been studied extensively, and, although this mechanism is not as thoroughly mapped as would be hoped, there exists a large body of work in the literature stemming in the main from the early '50's.[1a] The elimination–addition mechanism for certain acyl-transfer reactions has been known since the early part of the century in contrast to the relatively late knowledge about the former mechanism, and it therefore seems somewhat paradoxical that until only recently have detailed mechanistic studies been reported for reactions in aqueous solution. This article reviews the recent and early work on the subject.

We shall be discussing compounds which can undergo a 1,2-elimination from the acyl function and the atom α to it (eq 1) and omit topics such as cyclizations (for example, the hydrolysis of 4-nitrophenyl hippurate)[2a] and 1,4-eliminations. Reactions involving elimination of an electrophile other than the proton and compounds where the central acyl atom is other than carbon, phosphorus, or sulfur are not included. Metal ion complexes able to hydrolyze via an elimination–addition mechanism are reviewed elsewhere.[2b]

$$E—A—B—X \rightleftharpoons A{=}B + E—X \qquad (1)$$

A. Control of Mechanism

Mechanisms which are available for acyl transfer can be exemplified by transfer of a carbamoyl group from an acceptor to hydroxide and are illustrated in Figure 1. The mechanisms illustrated are limiting ones with respect to timing of bond making and bond breaking in a particular pathway, and the only concession to an intermediate mechanism is the E2 decomposition where leaving group and proton are abstracted simultaneously. In nonaqueous systems the process involving ionization (SN1) can prevail as, for example, in the Friedel–Crafts type reaction,[3a,b] but we are concerned with aqueous media; the compounds involved do not necessitate possession of a proton on the α atom. Let us consider a free energy diagram (Figure 2) for A–E[3c] attack of hydroxide ion on an ester and for the E1cB process for the same reaction; in the former an addition intermediate T^- is formed and in the latter, after ionization to yield conjugate base A^-, elimination occurs to give the intermediate I which adds to give product. The E1cB profile is governed by the equilibrium constant between base and ester and the transition-state energy for intermediate formation which is presumably connected with the free energy of formation of I.[4] The stability of the transition-state for intermediate formation is related among other things to steric constraints; for example, the formation of an endocyclic carbodiimide in a five-membered ring is very difficult

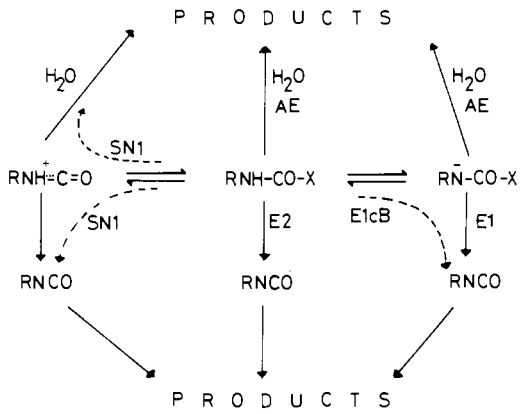


Figure 1. Mechanisms available for acyl transfer illustrated by the hydrolysis of a carbamate; the figure shows only limiting mechanisms with respect to the timing of bond formation and fission. The mechanistic symbolism used here and later is explained in ref 3c.

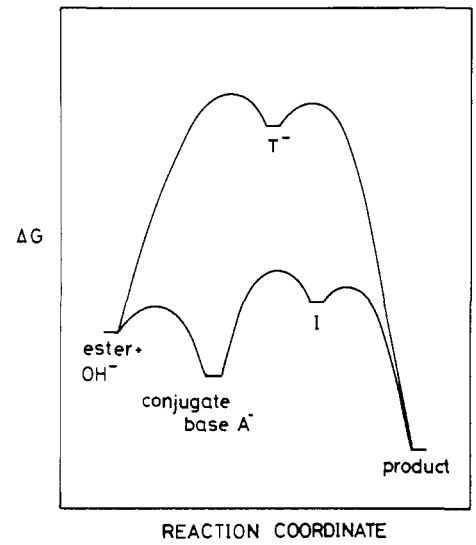


Figure 2. Free-energy diagram for hydrolysis of an ester proceeding via A–E attack of hydroxide on the acyl atom and via the E1cB pathway; symbols are described in the text.

energetically and could force a reaction to take an A–E pathway.

Considerable discussion has centered on the question of concerted 1,2-eliminations as opposed to stepwise processes,[5] and factors controlling the path taken, either E2 or E1cB, have been discussed theoretically.[6] Recently a rule has been proposed which defines the pK_a limits of the base in which a concerted proton transfer is possible;[7a] for example, the base pK_a must lie between that of the carbamate NH and the NH of RN^+HCO for an E2 mechanism to be *possible* in carbamoyl transfer.

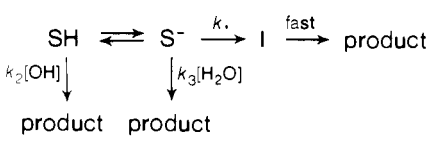
B. Effect of pH

Hydrolysis of an ester with a dissociable proton on the α atom possesses a sigmoid pH dependence for A–E, or E–A mechanisms (eq 2). The kinetic equation governing the hydrolysis is given by eq 3. The parameters are defined as: k_3,

$$k_{obsd} = k'/(1 + a_H/K_a) \quad (2)$$

$$= k_2K_W/[K_a(1 + a_H/K_a)] + (k_1 + k_3)/(1 + a_H/K_a) \quad (3)$$

attack of water on conjugate base; k_1, E1-elimination from conjugate base; k_2, A–E attack of hydroxide on neutral ester; K_a, ionization constant of the "α proton"; k', the observed plateau rate constant where k_{obsd} is independent of pH. Clearly the pH dependence is not an adequate tool for distinguishing between the various mechanisms (eq 4).



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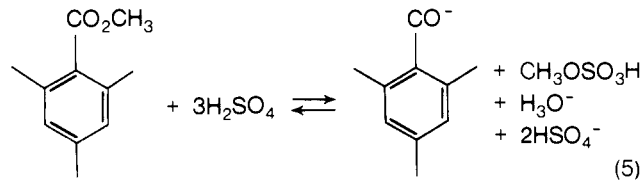
II. SN1 Mechanisms

All the evidence for SN1 mechanisms of aryl transfer is for acyl groups devoid of a labile "α proton". It is in any case unlikely that proton transfer from an electronegative α atom will be anything but diffusion controlled because the pK_a of the cationic intermediate should be less than that of the oxonium ion; for carbon α atoms this situation may not be true.

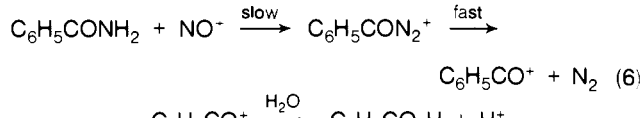
A. Carboxylic Acid Derivatives

Probably the first good evidence for an acylium ion was obtained by Treffers and Hammett in 1937[7b] using cryoscopic measurements of mesitoic acid in concentrated sulfuric acid. Evidence for acylium ion formation in methyl mesitoate hydrolyses comes from cryoscopic measurements using 100% sulfuric acid[8] and dependence of the rate constant for hydrolysis on a Hammett acidity function in strong sulfuric acid solutions.[9a] Positive entropies of activation close to zero and absence of exchange at carbonyl oxygen also indicate an SN1 mechanism.[9b] The absence of exchange at carbonyl oxygen



(5)

in the diazotization of benzamide together with dependence of the rate constant on an H_R acidity[10] was taken as consistent with acylium ion formation (eq 6). The arguments using



(6)

lack of exchange are strengthened by the observation that alkaline hydrolysis of methyl mesitoate has $k_{hydrolysis}/k_{exchange} = 6.8$.[11a] Further evidence for an SN1 mechanism in acid-catalyzed hydrolysis is a Hammett ρ of -3.22 for hydrolysis of methyl 4-substituted 2,6-dimethylbenzoates.[11b]

Benzoyl chlorides appear to hydrolyze via an A–E mechanism in solvents low in water content, but this shifts to SN1 as the water concentration increases.[12-15a] Trapping experiments with weak nucleophiles[15b] also suggest an acylium ion intermediate accounting for about 40% of the total reaction; this figure agrees with an estimate obtained by Hudson and Crunden[15c] from solvolysis of benzoyl chloride in solvents of "equal ionizing power".[15d] The powerful acceleration of the rate of hydrolysis of mesitoyl chloride by hydroxide and carbonyl oxygen exchange are not consistent with acylium ion intermediates under these conditions;[16,17] the Hammett ρ values for neutral and acid- and base-catalyzed hydrolyses of 4-substituted 2,6-dimethylbenzoyl chlorides are, respectively -3.85, -3.73, and $+1.20$ in 99% acetonitrile–water. Absence of carbonyl oxygen exchange for acid and neutral hydrolysis is consistent with an SN1 mechanism for acid and neutral reactions.[18a] Furthermore the neutral and acid Ham-

mett dependencies are on σ^+. Ethyl chloroformate hydrolysis in water is 50-fold less reactive than benzoyl chloride;[17b] if the acylium ion mechanism predominated, the reverse order would be expected.

Susz and his coworkers[17c,d] found that in aprotic solvents hindered benzoyl chlorides (2,6-dimethyl- and mesitoyl) gave infrared spectra, when mixed with aluminum trichloride or titanium tetrachloride, indicative of a triple bond stretching frequency (~2200 cm^{-1}). Nonhindered acid chlorides gave much lower frequencies. These results were considered consistent with a resonance hybrid possessing considerable acylium ion character. Recent work with antimony pentafluoride, fluorosulfonic acid, and sulfur dioxide media involved the demonstration of free oxocarbonium ion (CH_3CO^+)[18b] via NMR techniques.

The transfer reactions of the imidoyl acyl group have recently been shown to involve the E–A mechanism (eq 7).[18b-i]

$$R{-}C(NR')X \xrightarrow{-X^-} R{-}\overset{+}{C}{=}NR' \xrightarrow{+Y^-} RC(NR')Y \quad (7)$$

B. Carbamic Acid Derivatives

Hydrolysis of dimethylcarbamoyl chloride appears to be SN1 as judged by the small positive entropy of activation, lack of reactivity to hydroxide ion, and trapping by added nucleophiles which do not increase the rate yet yield trapped products. *N,N*-Dimethylcarbamoylpyridinium chloride, however, hydrolyzes probably via an A–E mechanism in water consistent with the absence of a mass law effect in pyridine buffers, large negative entropy of activation, a moderate solvent isotope effect, and a linear free-energy relationship with 4-nitrophenyl acetate reactivity with nucleophiles including water.[19a] Similar evidence was marshalled[19b] to show that diphenylcarbamoyl chloride and other carbamoyl chlorides[19c] and the corresponding pyridinium derivative hydrolyzed via SN1 and A–E mechanisms, respectively.

The aminooxonium ion has been demonstrated as an entity in antimony pentafluoride–fluorosulfonic acid solutions.[19d]

C. Phosphoramidates

N,N,N',N'-Tetramethyldiaminophosphorochloridate hydrolyzes in water faster than diisopropyl phosphorochloridate consistent with an SN1 mechanism. The rate of hydrolysis has a small negative entropy of activation and is unaffected by hydroxide ion, 3-cresolate ion, or pyrrolidine.[20a] Probably the situation is better stated as an early cleavage of the P–Cl bond compared to bond formation between phosphorus and the nucleophile.[20b]

D. Aminosulfonates

It was proposed that dimethylaminosulfonyl chloride hydrolyzed via an SN1 process because of the lack of effect of added nucleophiles.[21] Mercuric chloride, a reagent known to promote SN1 reactions by electrophilic catalysis, increased the hydrolysis rates of dimethylcarbamoyl, dimethylaminosulfonyl, tetramethyldiaminophosphoryl, and benzoyl chlorides consistent with an acylium ion intermediate.[22]

E. Phosphinates

Comparison of relative rates with the hydrolysis of *tert*-butyl chloride in different media indicates that diisopropylphosphinyl chloride probably hydrolyzes via an A–E mechanism, but di-*tert*-butylphosphinyl chloride, where an associative mechanism is suppressed by steric hindrance, goes via an SN1 pathway.[23] Cryoscopic studies with 100% sulfuric acid gave no indication of *stable* phosphinylium ion formation from phosphinic acids.

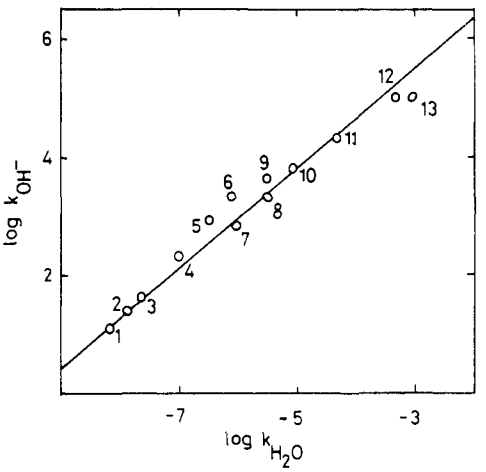


Figure 3. Plot of the logarithm of the second-order rate constants for reaction of hydroxide vs. water with esters: $XCO_2(2\text{-}NO_2C_6H_4)$, where X is (1) C_2H_5, (2) CH_3, (3) $C_6H_5CH_2$, (4) $C_2H_5SCH_2$, (5) $-CO_2^-$, (6) $(CH_3)_3N^+CH_2-$, (7) $C_6H_5OCH_2-$, (8) $NCC(CH_3)_2-$, (9) $BrCH_2-$, (10) $ClCH_2-$, (11) $C_5H_5N^+CH_2-$, (12) C_2H_5OCO-; (13) Cl_2CH-. The figure is redrawn from Figure 3 in B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, **91**, 2982 (1969).

III. E1cB Mechanisms

A. Carboxylic Acid Derivatives

1. Ketenes and Ketenimines

Ketene and ketenimine synthesis from acid chlorides[24-27] and imine chlorides[28-31] with tertiary amines is a well-known preparative route (eq 8, X = O, NR) and presumably owes its success to the absence of protonic species in the solvent. Acylammonium ions could be involved (eq 9)[25] in the mecha-

$$R{\cdot}R_2CHC(X)Cl + NEt_3 \rightleftharpoons R_1R_2C{=}C{=}X + NHEt_3^+Cl^- \quad (8)$$

$$CH_3COCl \longrightarrow CH_3\overset{+}{C}ONR_3\,Cl^- \longrightarrow CH_2{=}C{=}O + NHR_3^+Cl^- \quad (9)$$

nism, and the observation that ketene itself is not hydrolyzed exceptionally quickly in water[31b] makes ketene intermediates in acyl transfers in water seem not unexpected (in retrospect).

2. Comparison with Addition–Elimination Reactions

The hydrolysis of 2-nitrophenyl esters of monosubstituted acetic acids in water was found to be related to the rate constant for hydroxide attack on these esters;[32] hydroxide had 0.84 the selectivity to change in structure of the acid as the water rate (Figure 3) and 2-nitrophenyl acetates not falling on the regression line were judged to have the hydroxide reaction not proceeding via an A–E path because the line is defined for esters which must involve such mechanisms. Acetate itself fits the line and the hydroxide reaction is therefore A–E. The pK_a of the "α proton" of 2-nitrophenyl acetate is unknown but must lie between 14 and the pK_a of ethyl acetate (~25) so that preference for the A–E mechanism probably resides in the concentration of the anion being too low to support an E1 reaction competitive with the A–E path; the rate of proton removal is also most likely low for the acetate esters as well.

Enhancements in the hydroxide term occur with cyanoacetate (100-fold),[33] dimethylsulfonioacetate (10-fold),[33] ethyl malonate (8×10^3-fold),[34a] and ethyl α-methylmalonate (2×10^2-fold)[34a] where the mechanisms are proposed to be E–A, borderline, E–A, and E–A, respectively. The pK_a of the "α

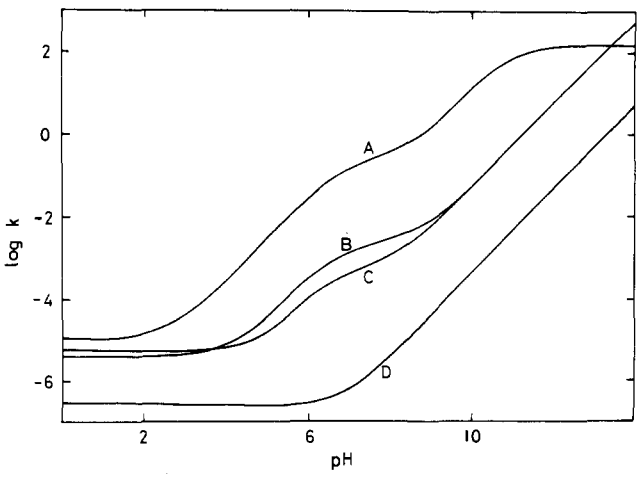


Figure 4. Plots of the pseudo-first-order rate constant for hydrolysis at zero buffer concentration of (A) 2-nitrophenyl ethyl malonate, (B) 2-nitrophenyl ethyl α-methylmalonate, (C) 4-nitrophenyl ethyl α-methylmalonate, (D) 2-nitrophenyl ethyl α,α-dimethylmalonate. The figure is redrawn from Figure 1 in B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, **91**, 2993 (1969).

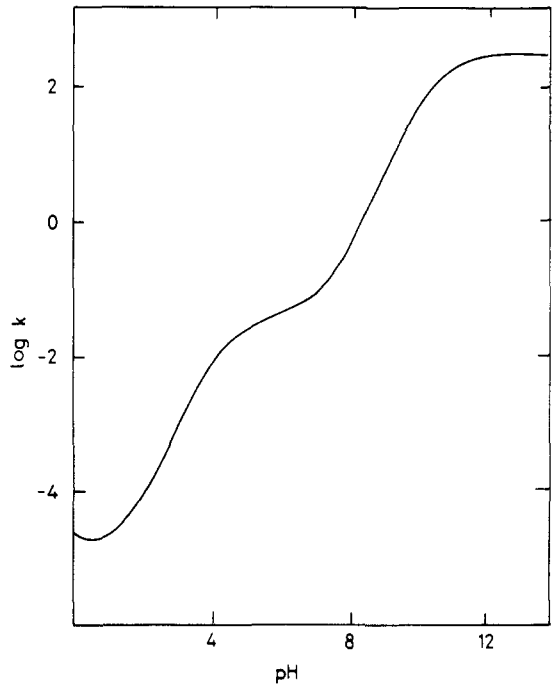
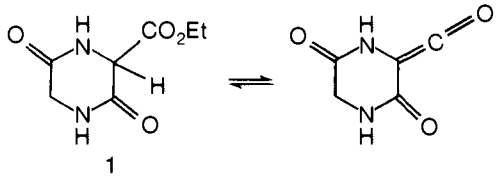


Figure 5. Plot of the pseudo-first-order rate constant for hydrolysis of 4-nitrophenyl acetoacetate at zero buffer concentration. The figure is redrawn from Figure 1 of R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 5956 (1970).

protons" in these esters is low; thus there is sufficient carbanion to sustain an E–A mechanism where this occurs. We shall see later, however, that an E1cB mechanism is not necessarily attendant on a low pK_a for the α proton. An ester with a labile "α proton" which undergoes rapid exchange is ethyl 2,5-piperazinedione-3-carboxylate,[34b] and it is possible that this involves an E1cB process (eq 10).



+ EtOH (10)

1

The use of models which cannot react via an E–A mechanism is also exemplified by the arguments[34c] against the E–A

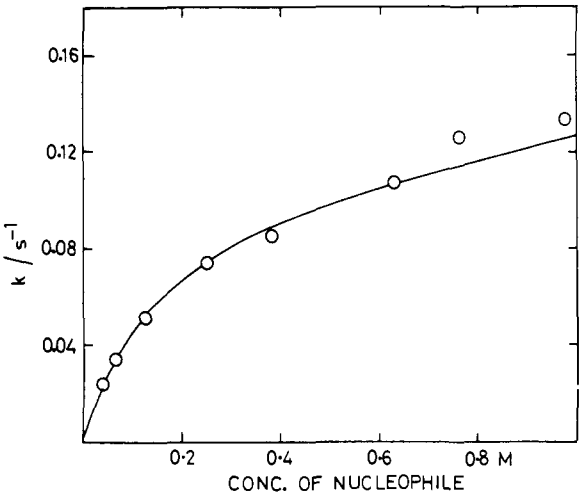
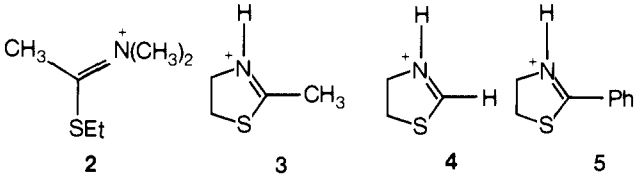


Figure 6. Effect of changing *N*-ethylmorpholine buffer concentration at pH 8.43 on the rate of release of 2-nitrophenol from 2-nitrophenyl ethyl α-methylmalonate; rates are corrected for background hydrolysis. An A–E mechanism involving attack of the amine on the acyl carbon contributes to the reaction. The figure is redrawn from Figure 3 in B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, **91**, 2993 (1969).

hydrolysis of *S*-ethyl *N,N*-dimethylthioacetimidate (**2**). The thiazolines (**3**, **4**, and **5**) hydrolyze in alkali with approximately similar rate constants[34d] as expected for an A–E mechanism, and it is therefore unlikely that the acetimidate hydrolysis is E–A.



2 3 4 5

3. Proton Transfer

The pH dependencies for the pseudo-first-order rate constant for hydrolysis of a number of substituted phenyl esters possess inflections (Figures 4 and 5) which do *not* correspond to the pK_a's of any carbon acid grouping in the substrate (2-nitrophenyl[34a] and 4-nitrophenyl[35] ethylmalonate, 2- and 4-nitrophenyl ethyl α methylmalonate,[34a] 4-nitrophenyl acetoacetate,[35] and 4-nitrophenyl *S*-ethyl thiomalonate[35]). The hydrolyses are catalyzed by base,[34-36] and the catalytic effect levels off as the buffer concentration increases (Figure 6). The pH dependencies and curved buffer catalyses can be accommodated by eq 11;[34] in the absence of buffer at low pH's

$$\mathrm{SH} \underset{k_{HB}[HB]}{\overset{\substack{k_B[B] \\ k_1[H_2O] \\ k_2[OH^-]}}{\rightleftharpoons}} \mathrm{S^-} \xrightarrow{k_3} \text{products} \qquad (11)$$
$$k_{-1}[H_3O^+] \quad k_{-2}[H_2O]$$

$k_{-1}[H_3O^+] > k_3$; thus $k_{obsd} = (k_1k_3/k_{-1})[H_2O]/[H_3O^+]$, and the pH dependence has positive slope equal to unity. The k_1 term becomes rate limiting as the pH rises ($k_{obsd} = k_1[H_2O]$) because $k_{-1}[H_3O^+]$ falls below k_3; the $k_2[OH^-]$ term becomes dominant as pH increases further, but when all substrate is converted to conjugate base, k_3 is rate limiting. "Curved" buffer catalysis can be explained by a change in rate-limiting step caused by $k_{HB}[HB]$ becoming greater than k_3[34] as seen in the *partial* kinetic equation (eq 12) omitting

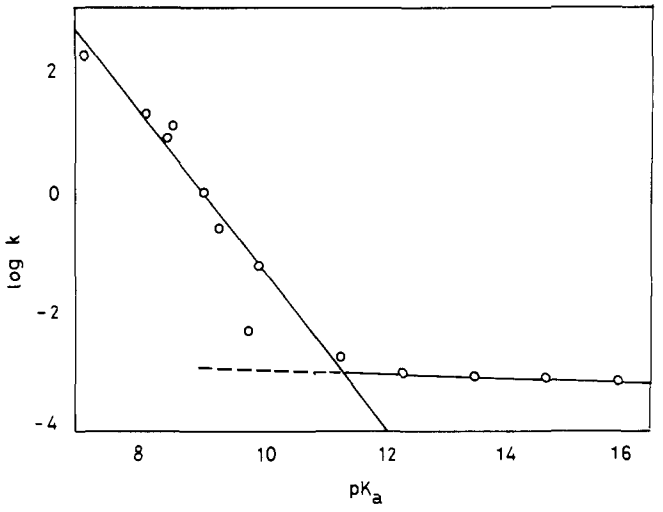


Figure 7. Effect of changing the leaving group on the hydrolysis of acetoacetate esters. Points above pK_a = 10 represent alkyl leaving groups; those below, phenol and oxime leaving groups. The parameter plotted (log k') is that defined in eq 3; the concave relationship indicates a change in mechanism. The figure is redrawn from Figure 3 in R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 5956 (1970).

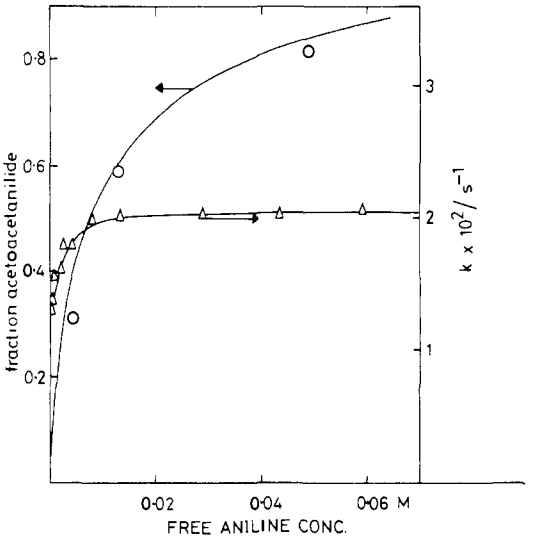
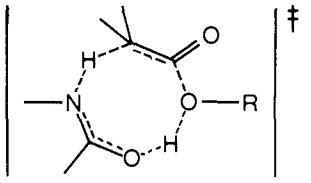


Figure 8. Trapping an intermediate in the reaction of 4-nitrophenyl acetoacetate with aniline and water at pH 4.6. Above 0.01 *M* aniline concentration the rate of 4-nitrophenol release is constant, but the fraction of acetoacetanilide in the product still increases considerably. The figure is redrawn from Figures 4 and 5 of R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 5956 (1970).

$$k_{obsd} = k_B[B]/(k_{HB}[HB]/k_3 + 1) \qquad (12)$$

water and hydroxide as effective species. Linear catalysis at high concentration of buffer is consistent with a pathway involving attack at the ester carbonyl.[34]

Concerted acid–base catalysis of acylation by ketene[37a,b] has been suggested for the catalytic action of amides, and presumably a pathway exists for concerted acid–base catalysis via a ketene for ester exchange; the only real evidence which exists for this suggestion is the absence of catalysis by *N,N*-disubstituted amides. Simple acid–base catalysis of acyl-



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ation by ketene could involve either formation of an intermediate reactive acyl compound[37b] (CH_3COB^+) or facilitation of proton transfer in an addition–elimination type mechanism

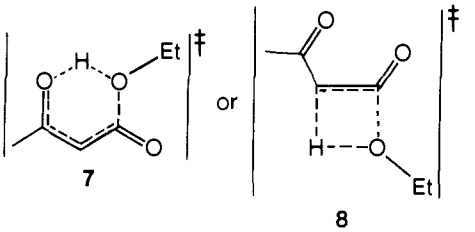
$$CH_2C(O^-)NH^+ \xrightarrow{\text{acid-base}} CH_3CON$$

4. Deuterium Oxide Solvent Isotope Effects

This effect has been utilized to attempt to distinguish between E–A and A–E mechanisms in hydroxide catalyzed reactions.[38] For the plateau region the E–A mechanism gives $k_{obsd} = k_1$ and the A–E process gives $k_{obsd} = k_2K_w/K_a$ (see eq 3), and it has been assumed[38b] that k_1 has little or no isotope effect. The method was tested for 5-nitrocoumaranone where k'(D/H) = 0.58. The effect on k_2, K_w, and K_a (D/H, 1.22, 0.15, H/D, 3.5, respectively) is available in the literature[38a] or can be estimated;[38b] thus k'(D/H) is calculated to be 0.65 for the A–E mechanism in agreement with the observed value. Unfortunately, this criterion is not now as clear-cut as it was hoped because other bona fide E1 reactions have been studied and have k_1(D/H) varying from unity to 0.69.[35] This result is not surprising since dispersal of charge from ground to transition state in E1 reactions would be expected to depend heavily on solvation.

5. Leaving Group

The alkaline plateau rate constant for hydrolysis of substituted phenyl acetoacetates has a Hammett ρ value of +2.8, and the dependence is on σ^-, consistent with considerable C–O cleavage in the transition state of the rate-limiting step. A wider range of leaving groups can be included if the correlation is with the pK_a of the leaving hydroxyl function. Such a Bronsted-type plot (Figure 7) is meaningful provided the leaving atoms and their charge type are identical. The results were interpreted as a change in mechanism[35] (strongly indicated by the sharp break in the Bronsted plot from low to high slope as the pK_a is decreased) from E–A type for the phenyl esters to A–E type for the alkyl esters. The cause of this change probably resides in the greater sensitivity of E1 reactions to the leaving group than A–E reactions. Although alkyl acetoacetates undergo hydrolysis in alkali via the A–E mechanism, catalysis could still promote transfer via an E–A mechanism: cyclic transition states have been proposed for alcoholysis of alkyl acetoacetates leading to a ketene intermediate.[39] Evidence for this involves a rate constant independent of alcohol concentration and a small negative entropy of activation independent of solvent change. The formation of ket-



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enes has been postulated in the use of malonates in providing thermally labile cross links for cotton modification.[40]

6. Trapping

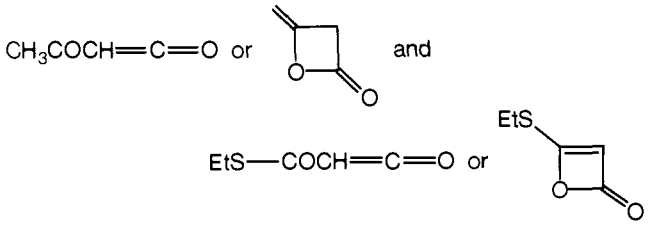
Formation of acetoacetanilide from 4-nitrophenyl acetoacetate in aniline buffers was found to increase significantly over a range of aniline concentration where the rate constant for 4-nitrophenol release was invariant (Figure 8). This result is consistent with a mechanism involving release of 4-nitrophenol *prior* to aniline attack. The absence of nucleophilic at-

TABLE I. Reactions where Elimination Intermediates Have Been Demonstrated in Basic Solution

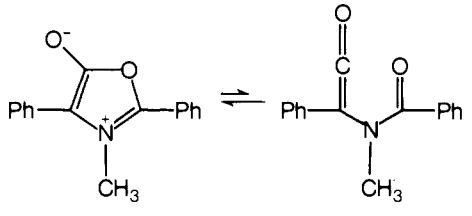
Reactants	Intermediates	Ref
$NH_2C(NH)NH_2$	NH_2CN	46, 47
R'NHCON(NO)R	$RCHN_2$, R'NCO	*h*, 48, 49
$NH(NO_2)C(NH)N(NO)CH_3$	CH_2N_2, $N(NO_2)C(NH)$	*e*
NH_2CSNHR	NCS^-, RNCS	*c*, 50
$RNHCON_3$	N_3^-, RNCO	*g*
RNHC(NH)SR'	R'SH, RNHCN	51, 52
RNHCOSR'	NCO^-, R'SH	*d*, 53
$RNHCS(S^-)$	RNCS	*a*, 54
RNHCSSCOOEt	RNCS	*a*, 54
$NH_2CS(OR)$	NCS^-	55
$RNHC(NH)NH_2$	NH_2CN	56
NH_2COOR	NCO^-	57
NH_2CONHR	NCO^-	*b*, *e*, *f*, 58, 59
$NH_2CONHNO_2$	NCO^-, NH_2NO_2	*i*
$PhCONHC(NH)(C_2H_2N_3)$	PhCONHCN	52

[a] J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, **21**, 204 (1956); M. G. Ettlinger and J. E. Hodgkins, *J. Am. Chem. Soc.*, 77, 1833 (1955); **78**, 1952 (1956); A. Kjaer and R. Gmelin, *Acta Chem. Scand.*, **10**, 1193 (1956); 11, 906 (1957); A. Kjaer, R. Gmelin, and R. B. Jensen, *ibid.*, **10**, 26,432 (1956); A. Kjaer and R. B. Jensen, *ibid.*, **10**, 141 (1956); D. L. Garmaise, R. Schwartz, and A. F. McKay, *J. Am. Chem. Soc.*, **80**, 3332 (1958); L. M. Dowling, and G. R. Stark, *Biochemistry*, **8**, 4728 (1969); J. von Braun, *Chem. Ber.*, **42**, 4568 (1909); **45**, 1563 (1912); J. von Braun and G. Manz, *Justus Liebigs Ann. Chem.*, **468**, 258 (1929); J. von Braun, W. May, and R. Michaelis, *ibid.*, **490**, 189 (1931). [b] W. H. R. Shaw and B. Grushkin, *J. Am. Chem. Soc.*, **82**, 1022 (1960). [c] W. H. R. Shaw and D. G. Walker, *ibid.*, **78**, 5769 (1956); **79**, 2681, 3683, 4329 (1957); **80**, 5337 (1958). [d] G. R. Stark, W. H. Stein, and S. Moore, *J. Biol. Chem.*, **235**, 3177 (1960); U. Weiss, *J. Am. Chem. Soc.*, **69**, 2684 (1947); G. Frerichs and P. Foerster, *Justus Liebigs Ann. Chem.*, **371**, 227 (1909); H. Bechurts and G. Frerichs, *J. Prakt. Chem.*, 66, 172 (1902); J. D. Ravel, J. J. McCord, C. G. S. Skinner, and W. Shire, *J. Biol. Chem.*, **232**, 159 (1958). [e] G. D. Vogels, F. E. De Windt, and W. Bassie, *Recl. Trav. Chim. Pays-Bas.*, **88**, 940 (1969); G. D. Vogels and C. Van Der Drift, *ibid.*, **88**, 951 (1969). [f] A. A. R. Sayigh, J. N. Tilley, and H. Ulrich, *J. Org. Chem.*, **29**, 3344 (1964). [g] T. Curtius and A. Burkhardt, *J. Prakt. Chem.*, **58**, 205 (1898); E. Oliveri-Mandala and F. Noto, *Gazz. Chim. Ital.*, **43**, 514 (1913); E. Oliveri-Mandala, *ibid.*, **44**, 662 (1914). [h] E. R. Garrett, S. Goto, and J. F. Stubbin, *J. Pharm. Sci.*, **54**, 119 (1965). [i] G. L. Boivin and P. A. Boivin, *Can. J. Chem.*, **29**, 478 (1951); T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1797 (1929); B. Boopsingh and J. M. Briody, *J. Chem. Soc., Perkin Trans. 2*, 1487 (1972).

tack by aniline at the ester carbonyl is confirmed by the absence of an effect, on the rate constant for 4-nitrophenol release, of increasing the aniline concentration (see Figure 8). An intermediate was observed using ultraviolet spectroscopy (at 325 nm) and fast reaction equipment in the hydrolysis of 4-nitrophenyl *S*-ethyl malonate, but it is likely that this intermediate is the carbanion rather than the ketene. Although there seems to be little doubt about the existence of an intermediate after the carbanion in the transfer of some of these reactive esters, there is a shadow of doubt about the precise nature of these intermediates:[41a]



An interesting example of intramolecular trapping was described recently[41b] where the trapped ketene cannot be stabilized further by proton transfer:



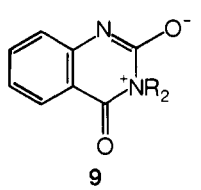
7. Biological Aspects

So far as we are aware there is no evidence for a ketene as an intermediate in biochemical pathways although there are many instances such as in the biosynthesis of lipids which could involve such species. Recently D amino acid oxidase has been found to be inhibited by 4-nitrophenyl glycinate but not by ethyl glycinate.[42] Although the free glycinate certainly ought to transfer via an A–E mechanism, the formation of a protonated imine could lower the pK_a of the "α proton" sufficiently to support an E–A mechanism for the 4-nitrophenyl ester. The poor leaving ability of the ethyl ester presumably ensures its unreactivity as an inhibitor.

B. Carbamic Acid Derivatives

1. Trapping

The intermediate in transfer reactions of the parent carbamate, isocyanic acid, is stabilized by proton transfer as the conjugate base and is therefore effectively trapped. Table I summarizes reactions where an intermediate has been demonstrated; carbodiimides and cyanamide from iminocarbamates are also usually sufficiently stable in water to have at least a transient existence. Intramolecular trapping of isocyanate (**9**)[43a] and carbodiimide (**10**)[43b] functions has been reported; the absence of labile protons prevents stabilization via proton transfer.



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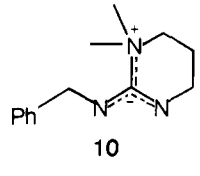

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2. Heavy Atom Isotope Effects

The deuterium oxide solvent isotope effect has been used to diagnose an E1cB mechanism for the alkaline hydrolysis of 4-nitrophenyl *N*-methylcarbamate.[38c] The value for k_{OH}-(D/H) = 1.8 is larger than expected for nucleophilic attack at the carbonyl carbon (1.22)[44a] but is compatible with preequilibrium formation of an anion.[44b] Primary heavy atom isotope effects are more definitive, but only a few relevant to this discussion have been reported. Hydrolysis of urea in acidic solution gave carbon primary isotope effects ($^{12}C/^{14}C$) = 1.101

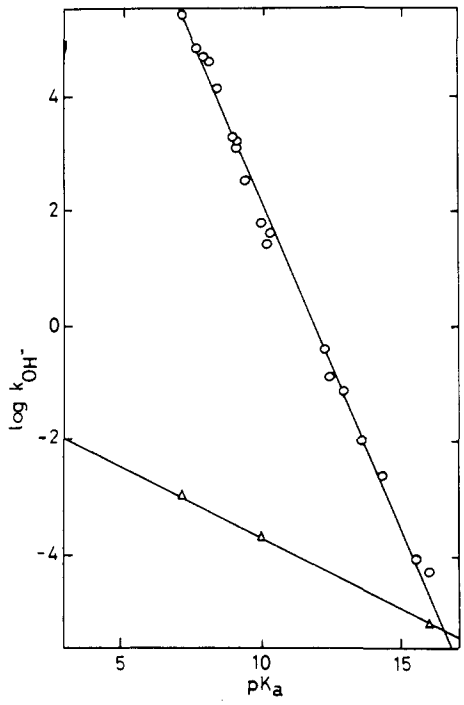


Figure 9. Dependence of k_{OH} on the pK_a of the leaving hydroxyl group for alkyl and phenyl esters of (Δ) *N*-methyl-*N*-phenylcarbamic acid and (O) *N*-phenylcarbamic acid. Alkyl esters are those with pK_a > 10; the figure is redrawn from Figure 1 of A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1244 (1973).

± 0.005 and ($^{12}C/^{13}C$) = 1.055 ± 0.003.[45] These values indicate considerable N–C bond cleavage in the transition state of the rate-limiting step consistent with an E–A mechanism. Change in bond order from trigonal planar to tetrahedral in the N–C bond in an A–E mechanism could yield an isotope effect,[45c] but this is likely in any case to be small. The bond order change effect has been considered by other workers for other systems to be relatively small.[45d-g]

3. Leaving Group

Intermediate isolation is not useful for *N*-substituted carbamates, and linear free-energy relationships involving leaving group variation have been successfully employed as diagnostic tools.[41a,60-63] The reaction of hydroxide with substituted phenyl *N*-phenylcarbamates possesses a high Hammett ρ (~3)[41a,61] with σ^- dependence consistent with considerable C–O cleavage in the transition state of the rate-determining step. An A–E mechanism is characterized by low ρ and a σ dependence.[64] A Bronsted type relationship (Figure 9) holds for alkyl and phenyl esters of *N*-phenylcarbamic acid[60] suggesting an E–A mechanism over the whole range of pK_a up to the pK_a of ethanol. Probably a change in mechanism to A–E occurs for leaving groups slightly less acidic than ethanol. *N*-4-Nitrophenylcarbamates change mechanism when the pK_a of the leaving group is about 13.[61] This result could be due to the lower thermodynamic stability of the intermediate 4-nitrophenyl isocyanate compared with the unsubstituted compound.

Small entropies of activation for the alkaline hydrolysis of phenyl *N*-phenylcarbamates argue for an E1cB mechanism,[65] but the ethyl esters have a relatively large negative value (−25.5 eu/mol) although the Bronsted-type plot suggests an E–A mechanism. The discrepancy is in part due to the fact that k_{OH} for a hydrolysis passing through an E1cB mechanism is composite and represents k_1K_a/K_w (see eq 2 and 3). The "Bronsted" data suggest that in any case a considerable proportion of the hydrolysis of the ethyl ester proceeds via the A–E pathway.

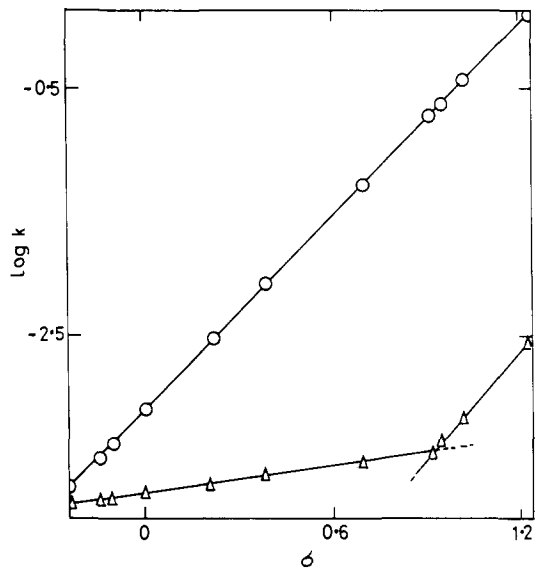
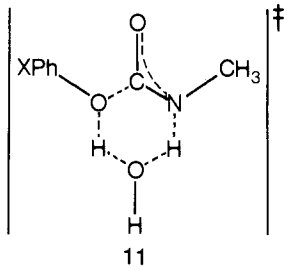


Figure 10. Effect of leaving group on the pseudo-first-order rate constants at pH 4 (Δ) and 8 (O) for the hydrolysis of aryl *N*-methylcarbamates. The circles represent the E1cB mechanism for alkaline hydrolysis; the triangles represent the neutral hydrolysis and a change in mechanism occurs as the electron withdrawing power of the substituent increases. The figure is redrawn from Figure 2 of T. Vontor and M. Večeřa, *Collect. Czech. Chem. Commun.*, **38**, 516 (1973).

The hydrolysis of substituted phenyl *N*-methylcarbamates involves a water term (plateau region of the pH profile) which has a Hammett dependence with a "break" diagnostic of a change in mechanism (Figure 10).[66,67] Substituents with low σ values possess a low ρ value (0.36), whereas high σ substituents involve a high ρ value (3.04), and these results are indicative of a change in mechanism with increasing electron-withdrawing power of the aryl group. However, the authors[66,67] equate a solvent deuterium oxide isotope effect (k_D/k_H) of 1.4, a high Hammett slope, and a large negative entropy of activation for the most reactive species with a cyclic transition state (**11**). The low slope, solvent deuterium oxide isotope effect (D/H) 0.29, and lower negative entropy are associated with a simple A–E mechanism involving attack of water at the carbonyl in the least reactive series. These interpretations are clearly open to criticism, especially the allocation of Hammett slopes; before one can be satisfied as to the cause of the nonlinear Hammett plot, further work will be necessary.



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4. Water Attack on Conjugate Base

The term k_1 of eq 4 for the hydrolysis of an acidic substrate refers to the decomposition of the conjugate base *prior* to water attack. The k_3 term refers to water attack on the conjugate base prior to release of the leaving group. The rate constants clearly are for limiting cases of a general mechanism: k_1 where C–O bond cleavage is complete; k_3 where C–O bond fission is incomplete when bond formation is advanced between water and carbon. Bearing these definitions

TABLE II. Rate Enhancements for Substrates with Blocked and Unblocked α Atoms[a]

Ester[b]	Ratio $k_{OH}^{H}/k_{OH}^{CH_3}$	Ref
$C_6H_5N(H)COOpNp$	7.3×10^4	41a, 61
$CH_3N(H)COOpNp$	6.9×10^6, 1.46×10^6	63, 68
$N(H_2)COOpNp$	6.25×10^8	63
$C_6H_5N(H)COOC_6H_5$	1.05×10^6	61
$4\text{-}NO_2C_6H_4N(H)COOC_6H_5$	7.99×10^4	61
$C_2H_5OCOC(CH_3)(H)COOoNp$	6.77×10^3	34a

[a] Other examples of this approach come in the appropriate sections for other acyl transfers. [b] Proton in parentheses is to be blocked by CH_3; pNp = 4-nitrophenyl; oNp = 2-nitrophenyl.

TABLE III. Steric Effect of "α Substituent" on Rate[a]

Substrate[b]	k_{OH} ($1/M^{-1}$ min^{-1})	Substrate	k_{OH} ($1/M^{-1}$ min^{-1})
RNHCOOpNp		$R_2NCOOpNp$	
CH_3	1.3×10^5	CH_3	2×10^{-2}
C_2H_5	1.6×10^5	C_2H_5	3.6×10^{-4}
$n\text{-}C_3H_7$	1.6×10^5	$n\text{-}C_3H_7$	1.7×10^{-4}
$i\text{-}C_3H_7$	1.9×10^5	$i\text{-}C_3H_7$	5.1×10^{-6}

[a] Values are taken from ref 68; temperature 22°; water solvent. [b] pNp = 4-nitrophenyl.

in mind we can distinguish experimentally between the extremes for the hydrolysis of phenyl *N*-phenylcarbamate.[41a] If all the reaction went via the k_3 pathway (see eq 4), the observed first-order rate constant $k_{obsd} = k_3K_a/(K_a + a_H)$; the phenyl ester has a $pK_a > 12$ and, since $a_H > K_a$ for the pH range studied (pH <12), then $k_{obsd} = k_3K_a[OH]/K_w$. Thus a hydroxide term k_{OH} can be experimentally determined by plotting k_{obsd} vs. [OH] and $k_3 = k_{OH}K_w/K_a$. Since $k_{OH} = 54.2$ M^{-1} sec^{-1}, the term k_3 has a value in excess of 0.542 sec^{-1} ($54.2 \times 10^{-14}/10^{-12}$). If this is so, then a rate constant less than 0.542 sec^{-1} should never be observed assuming that the neutral species (unionized carbamate) will react faster with water in an A–E mechanism than does the anion; at pH 9 a rate constant of 0.000548 sec^{-1} was measured. Thus a mechanism involving considerable bond formation between water and the anion in the transition state (k_3) is not involved.

5. Comparison with Addition–Elimination Reactions

Blocking the labile "α proton" by methyl substitution should provide a rate constant for hydroxide attack approximating to that for the A–E mechanism in the unblocked substrate. For definitive conclusions any rate enhancement of the unblocked over blocked substrate should be large, but it is difficult and probably unwise to put an exact lower limit to this figure although the values given in Table II are probably definitive. Table II illustrates enhancements for some reported systems.

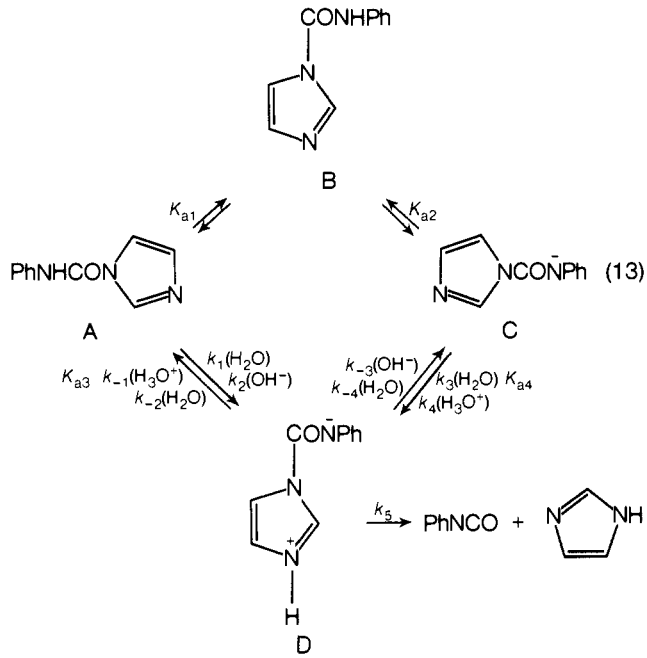
6. Substituents on the α Atom

In principle the effect of substituents on the α atom on the rate constant can diagnose the mechanistic type in a hydrolytic process apart from the complete blocking already described. Table III shows that dependence of k_{OH} on the substituent does not vary substantially with increasing steric effect for a known E1cB reaction. A dramatic variation is observed with a bona fide A–E process, the alkaline hydrolysis of the N,N-disubstituted esters of carbamic acid. The E–A mechanism has less steric requirements for its rate-limiting steps (the ionization and the E1 processes) than the A–E mechanism involving the approach of a relatively bulky group to the acyl carbon. A better model would probably be the alkaline hydrolysis of substituted acetate esters because the disubstitution in the present case over-accentuates steric effects.

Electronic effects of the N-substituent provide evidence for an E–A mechanism.[61] The Hammett ρ for alkaline hydrolysis of phenyl (N-substituted)phenylcarbamates is +0.64; this value may be compared with the sensitivity of phenyl (*N,N*-methyl-substituted)phenylcarbamates to attack of the hydroxide ion (calculated from ref 61 to be +2.1).

7. Proton Transfer

The need for proton transfer in an E–A reaction with carbamates only gives rise to general acid–base catalysis under certain circumstances because proton transfer to or from electronegative atoms is usually diffusion controlled. Catalysis will only occur when proton transfer is necessary to or from an intermediate which has such a fast formation or decomposition step that the diffusion (proton transfer) step is rate limiting and the general base or acid is more efficient than bulk water. The hydrolysis of *N*-(*N'*-phenylcarbamoyl)imidazole has been shown to involve general acid–base catalysis[69] consistent with an E1cB mechanism (eq 13). The buffer catal-



(13)

ysis approaches zero as buffer concentration increases, consistent with a change in the rate-determining step. When the proton transfer steps are not rate limiting (at high buffer concentration) and the various species of eq 13 are in equilibrium with one another, a bell-shaped pH profile would be expected for the hydrolysis (dotted line in Figure 11); however, at zero buffer concentration two maxima are obtained. Assuming a steady-state concentration of the zwitterion (D), an equation relating k_{obsd} with a_H may be obtained (eq 14); values for

$$k_{obsd} = \frac{k_5(k_1 + k_2[OH^-]a_H/K_{a1} + k_5(k_3 + k_4a_H)K_{a2}/a_H}{k_{-1}a_H + k_{-2} + k_{-3}[OH^-] + k_{-4} + k_5} \times \frac{a_HK_{a1}}{a_H + a_HK_{a1} + K_{a1}/K_{a2}} \quad (14)$$

pK_{a3} and pK_{a4} may be calculated from the experimental data and come close to the expected values when k_{-1} and k_{-3} are taken as the diffusion rate constant (10^{10} M^{-1} sec^{-1}). As yet there are not enough data to construct an Eigen type plot[70a] for the system.

The reverse of the hydrolysis of urea, namely synthesis via

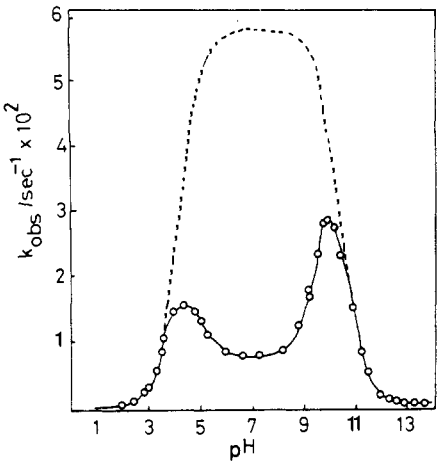


Figure 11. Effect of pH on the hydrolysis of *N*-(*N'*-phenylcarbamoyl)-imidazole (30°, 1 *M* ionic strength). The solid line represents the hydrolysis at zero buffer concentration; the dashed line is for higher buffer concentration. The figure is redrawn from Figure 1 of A. F. Hegarty, C. N. Hegarty, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1258 (1974).

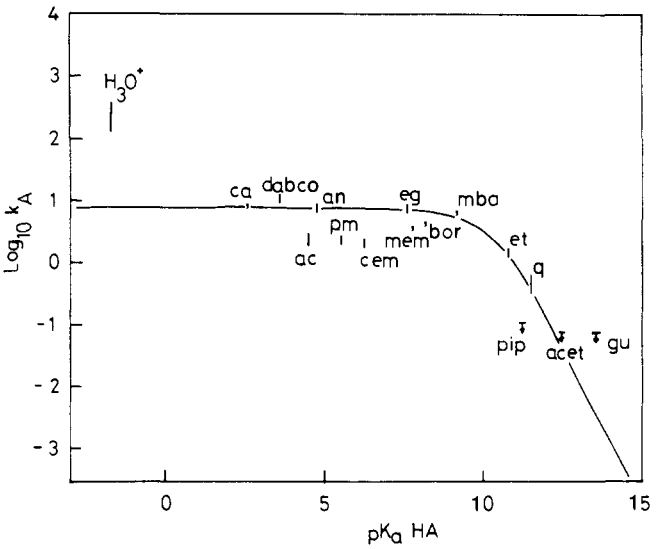
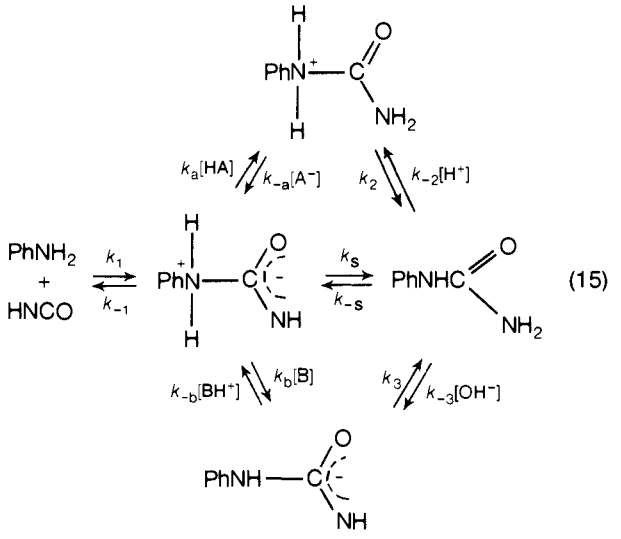
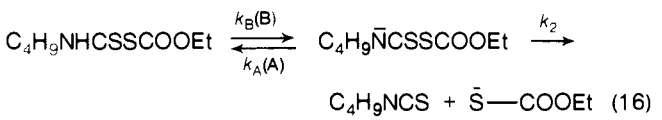


Figure 12. The Bronsted plot of k_A of the acid for the acid-catalyzed reaction of aniline with cyanic acid (25°, 1 *M* ionic strength). Legend: ca, chloroacetic acid; dabco, triethylenediamine dication; an, anilinium ion; pm, *N*-propargylmorpholinium ion; cem, *N*-2-chloroethylmorpholinium ion; mem, *N*-methylmorpholinium ion; eg, ethylglycine (protonated); bor, boric acid; mba, methyl β-alaninate (protonated); et, ethylammonium ion; q, quinuclidinium; pip, piperidinium; acet, acetamidinium; gu, guanidinium. The figure is redrawn from ref 71b.

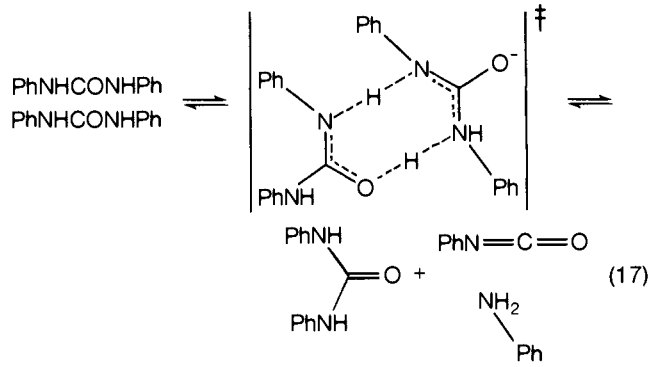
isocyanic acid and amine, has been shown to involve[71a,b] diffusion limiting proton transfer in the decomposition of the zwitterion intermediate (eq 15). Evidence for a change in rate-limiting step from decomposition of the zwitterion to its formation is a nonlinear Bronsted type plot of amine reactivity vs. ammonium ion pK_a and the existence of a saturation effect in the buffer catalysis of the reaction of weakly basic amines with isocyanic acid. Strongly basic amines with k_1 rate limiting do not exhibit buffer catalysis. The Bronsted plots for acid and base catalysis are nonlinear as in the (now classical) Eigen plot[70a] (e.g., Figure 12).



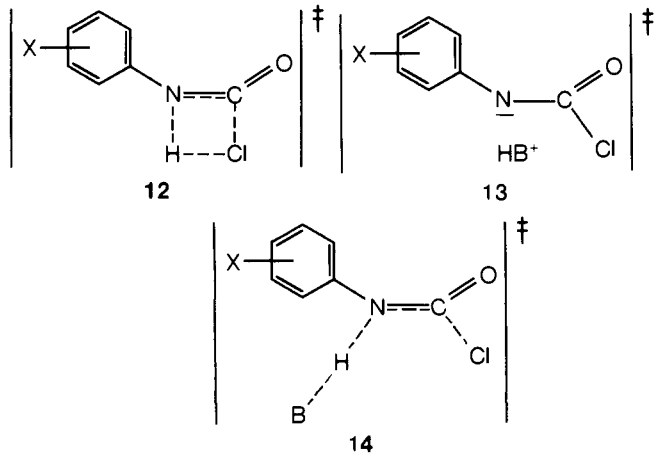
Another example of a change in rate-limiting step caused by increasing buffer concentration for reaction of a carbamate type compound has been reported by Hodgkins.[54a] The catalysis of the formation of isothiocyanate from dithiocarbamates in pyridine buffers exhibits a saturation effect consistent with the mechanistic scheme of eq 16.



Catalysis by products in the reaction of isocyanates with amines and catalysis of this reaction by amides and acids has led to the suggestion that in nonaqueous solvents a concerted catalytic path is involved (eq 17).[71b-d] Consistent with this suggestion is the absence of catalysis by such amides as *N,N*-dimethylacetamide. In aqueous solutions the observation of catalysis in isocyanate formation from ureas or the reverse reaction is not usual owing to the swamping effect of water.



The decomposition of carbamoyl chlorides in weakly basic nonaqueous solvents is relatively insensitive to substituent on the *N*-phenyl group ($\rho = -0.50$)[71e] consistent with a concerted mechanism (**12**). In the presence of a tertiary aniline the



12 **13** **14**

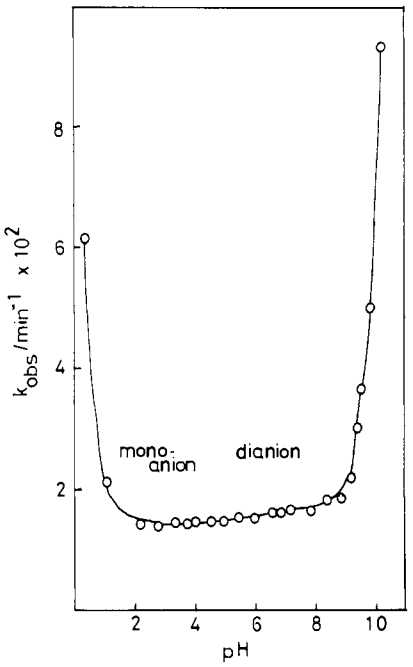


Figure 13. Hydrolysis of carbamoyl phosphate as a function of pH (37°, 0.6 *M* ionic strength). The figure is redrawn from Figure 2 of C. M. Allen and M. E. Jones, *Biochemistry*, **3**, 1238 (1964).

Hammett plot is biphasic with relatively high slope (ρ = 0.9) for electron-withdrawing substituents (where k_H/k_D is low); for electron-releasing substituents (with k_H/k_D of about 4) the Hammett slope is 0. These data were considered to be consistent with transition states **13** and **14**, respectively.

8. Carbamoyl Phosphate

The hydrolysis of carbamoyl phosphate has been the subject of a number of investigations,[72] and interest in reactions of this ester have been stimulated by its important role in the urea cycle in primary metabolism, in pyrimidine biosynthesis, and by the possibility of its playing a role in the urease mechanism. Maximal oxygen-18 incorporation into the phosphate product follows the pH profile (Figure 13) for monoanion concentration indicating P–O cleavage for this species. Neutral and dianion hydrolysis and reaction of hydroxide with dianion gave C–O cleavage.[72a] Trapping experiments with azide ion show that carbamoyl azide accumulates, but no rate enhancement occurs; small negative entropy of activation, lack of deuterium oxide solvent isotope effect, and lag in initial ammonia release are consistent with an E–A mechanism. Alternatively[72b] the results were considered consistent

$$NH_2COOPO_3^{2-} \longrightarrow NCO^- + H_2PO_4^- \qquad (18)$$

with an SN1 mechanism (eq 19), and although later workers[72a] ascribed trapping by azide to action on cyanic acid the fast deprotonation of the amino oxocarbonium ion could in effect be the trapping step. Both hydroxide attack on dianion

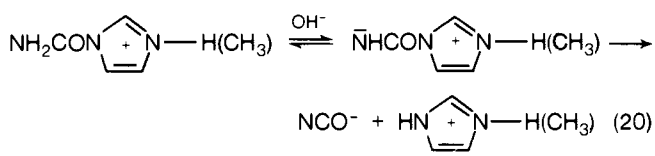
$$NH_2COOPO_3^{2-} \longrightarrow \overset{+}{N}H_2CO + PO_4^{3-} \qquad (19)$$

and on monoanion (effectively dianion hydrolysis in the pH region of dianion concentration) yield rate constants which fit a linear free energy relationship between k_{OH} and pK_a of leaving alcohol constructed from ethyl and substituted phenyl carbamate data[73] consistent with an E1cB mechanism for these phosphate species and confirming the earlier conclusions. Azide trapping experiments indicate[72c] the absence of isocyanate intermediates in the hydrolysis of *N*-4-nitrophenylcarbamoyl phosphate dianion showing that an E–A type mechanism is not operative. P–O cleavage occurs with the dianion, but with the monoanion a small incursion of an E1cB mechanism is shown by the azide trapping experiments. However, the hydroxide rate constant for *N*-phenylcarbamoyl phosphate dianion hydrolysis (2.73 × 10^{-2} M^{-1} sec^{-1})[72d] agrees with that (8.56 × 10^{-2} M^{-1} sec^{-1}) calculated from the equation: log k_{OH} = 15.2 − 1.34pK_a[60] for *N*-phenylcarbamates (pK_a is the that of the leaving alcohol, and the pK_a of the conjugate acid of the leaving trianion is taken as 12.3) consistent with an E1cB mechanism involving phenyl isocyanate. The value of k_{OH} for *N*-phenylcarbamoyl phosphate monoanion hydrolysis with hydroxide (calculated from the first-order rate constant for dianion hydrolysis, pK_a for the phosphate, and K_w) comes to 3.17 × 10^4 M^{-1} sec^{-1} close to the value (7.42 × 10^5 M^{-1} sec^{-1}) calculated from the equation using as pK_a for the conjugate acid of the leaving dianion 7.2. Evidence favoring at E1cB mechanism for the *N*-phenylcarbamoyl phosphate hydrolysis is that tris(hydroxymethylamino)methane does not accelerate the hydrolysis, but product analysis indicates significant fractions of the corresponding trapped urea.[72d]

Carbamoyl phosphate is involved in a number of biological carbamoylation processes, but there is no definite evidence that carbamoylation proceeds via an E–A mechanism. The more important systems are: aspartate transcarbamoylase, ornithine transcarbamoylase (citrulline synthetase),[74] β-alanine transcarbamoylase,[75] oxamic acid transcarbamoylase,[76a] and biotin biosynthesis.[76b] Transfer of iminocarbamate occurs in argininosuccinate[77] and guanylic acid synthetase.[78]

Heavy atom (carbon and anhydride oxygen of carbamoyl phosphate) effects suggest that the anhydride bond is unaffected on passage to the transition state, but that bonding to the carbon changes in the aspartate transcarbamoylase reaction;[79] these results are consistent with the formation of a tetrahedral intermediate rather than with an E1cB mechanism. The absence of ^{32}P incorporation into carbamoyl phosphate from inorganic phosphate except in the presence of aspartic acid and the absence of ^{18}O uptake into carbamoyl aspartate or carbamoyl phosphate from enriched water are not consistent with a stepwise process involving a carbamoyl enzyme.[80] It was concluded that the enzymatic process involved simultaneous action of carbamoyl phosphate and aspartic acid in the synthesis of carbamoyl aspartate. Although the model work with carbamoyl phosphate involves the E–A mechanism of nucleophilic substitution, the later work on analogs indicates that A–E pathways may predominate under certain conditions, and it is likely that the more efficient intramolecular situation at the enzyme-active site promotes the A–E process.

Experiments with *N*-carbamoylimidazole[74] showed that it was not a good carbamoylating species and probably not involved in ornithine transcarbamoylase as an acyl-enzyme intermediate. The pH dependence for its hydrolysis is sigmoid,[81] and it was proposed that the plateau region involved hydroxide and cation rather than the equivalent neutral species (eq 20); cyanate is the hydrolysis product.[74,81] A test



(20)

of this mechanism was to synthesize the *N*-carbamoyl-*N'*-methylimidazolium ion and measure its hydroxide-catalyzed hydrolysis. Similarity of the two rate constants is judged to be evidence that eq 20 is correct.[71b] Moreover the rate constant is only tenfold larger than that for the hydrolysis of 4-nitrophe-

nyl carbamate (imidazole and 4-nitrophenolate have conjugate acids with similar pK_a's).

9. Diazoalkane Synthesis

N-Nitrosourea decomposition in alkoxide solutions was thought to proceed via an A–E mechanism because alkyl carbamates were isolated as product.[82] However, the observation that lithium or potassium cyanates are obtained by reaction of *N*-nitroso-*N*-methylurea with butyllithium or potassium *tert*-butoxide provides evidence for an E1cB mechanism.[49,83]

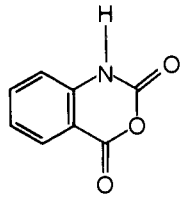
$$R_2CHN(NO)CONH_2 \rightleftharpoons R_2CHN(NO)\overline{C}ONH \longrightarrow R_2CHNNO^- + HNCO \quad (21)$$

10. Carbamate Protecting Groups

The extreme sensitivity of some carbamates to mild hydrolytic conditions has prompted the use of this group as a protecting agent. Peptide[84a] and protein[84b] thiols, sugars,[84c,d] and protein tyrosines[84e] have been protected in this way.

11. Cyclic Anhydrides of Carbamic Acid Derivatives

The following heterocyclic compounds could decompose via E–A mechanisms. Isatoic anhydride (**15**) forms ureido products with amines but N-methylation of the anhydride destroys this reaction, consistent with isocyanate formation.[85]



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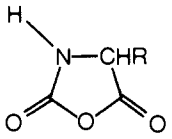

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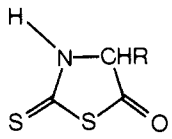

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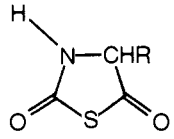
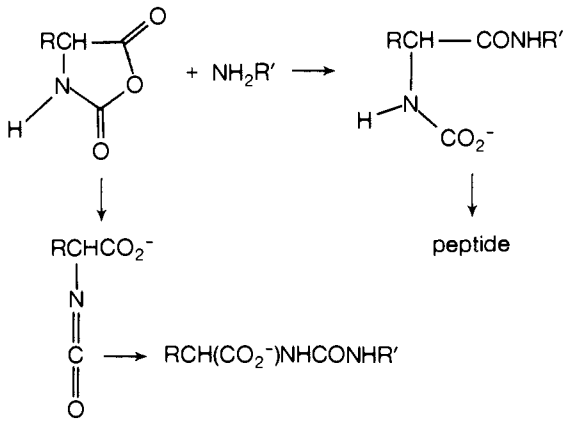


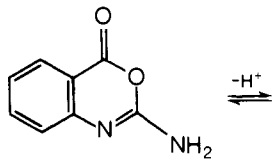
18

Hydrolysis of *N*-carboxyamino acid anhydrides (**16**) involves an isocyanate intermediate according to infrared evidence, but it is uncertain whether this lies on the main hydrolytic pathway.[86] Peptide and polypeptide synthesis with *N*-carboxyamino acid anhydrides (**16**) and analogs (**17** and **18**)[87] could involve isocyanate formation as a competing pathway among other possibilities (see eq 22).



(22)

A carbodiimide intermediate has been demonstrated in the hydrolysis of 2-amino-4,5-benzo-6-oxo-1,3-oxazine (**19**)[88] but is probably a blind-alley intermediate. The substrate is a



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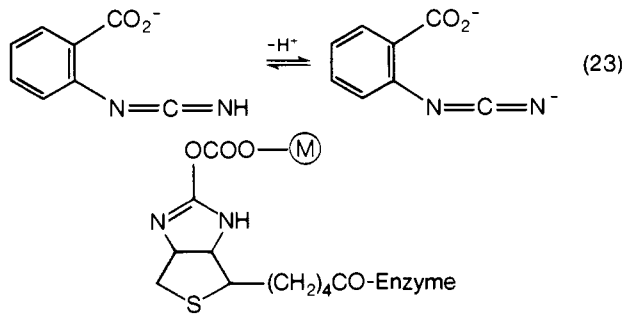


(23)

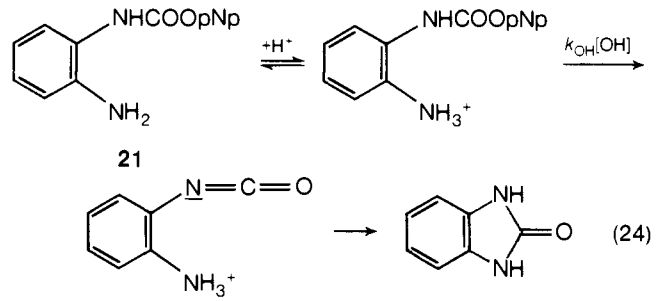
20

model for *O*-carboxybiotin complexes (**20**); steric requirements preclude a carbodiimide intermediate in the hydrolysis of this derivative; not only would the diimide be strained, say 60° from linearity, but the allene-like stereochemistry would be destroyed by forcing the intermediate to be planar.

12. Intramolecular Reactions

Reactions of carbamates where an intramolecular nucleophilic attack can occur are illustrated in Table IV; it is to be expected that the possibility of an intramolecular nucleophilic attack reduces the possibility of an E–A mechanism, and the results of the following studies show that control of mechanism is very sensitive to the nature of the intramolecular nucleophile.

Cyclization of 4-nitrophenyl *N*-(2′-aminophenyl)carbamate (**21**)[61] yields initially the isocyanate which is trapped by the amino function. This mechanism is consistent with unit slope of the pH profile for cyclization between pH 5 and 8 which indicates that attack of free amine is not a rate-determining step and with trapping experiments with 4-chloroaniline which do not enhance the rate yet give substantial quantities of the competing product urea. Trapping experiments from pH 5 upwards do not say anything about the mechanism involving a shoulder in the pH profile corresponding to a pK_a of 3.87: a mechanism giving rise to the shoulder could involve hydroxide attack (E–A) on the ammonium ion as in eq 24. The value of

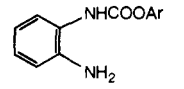
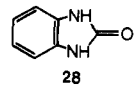
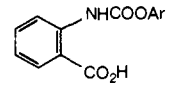
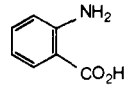
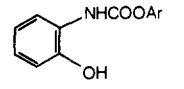
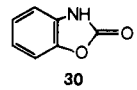
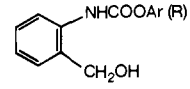
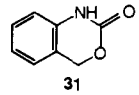
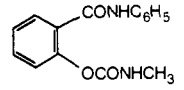
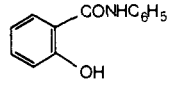
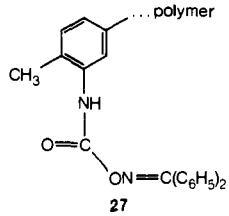
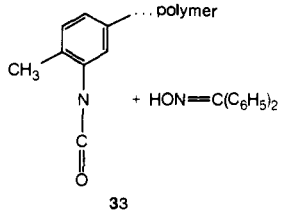


(24)

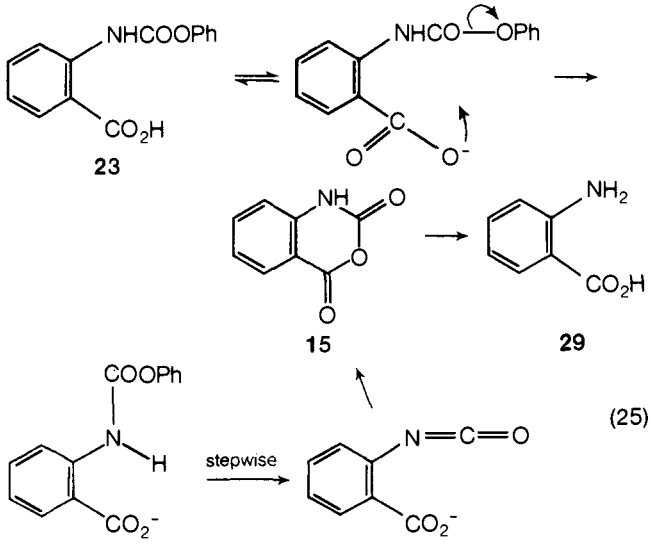
k_{OH} for this process (3.34 × 10^6 M^{-1} sec^{-1}) may be calculated from the Hammett equation[61] and σ = 1.7;[90] the apparent hydroxide ion rate constant ($k_2'K_{a1}'$ in ref 61) has a value 6.3 × 10^6 M^{-1} sec^{-1}, in good agreement with the calculated value assuming the isocyanate mechanism.

Reaction of phenyl (*N*-2-carboxyphenyl)carbamate (**23**) at neutral pH's to yield anthranilic acid (**29**) proceeds via isatoic anhydride.[89] The pH dependence of the decomposition is sigmoidal with a hydroxide term above pH 11 and inflection at the pH corresponding to carboxyl ionization. In the region of

TABLE IV. Intramolecular Transfer of the Carbamate Group

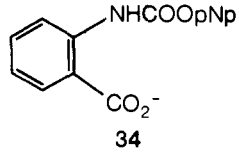
Reactant	Product	Mechanism	Ref
 22	 28	Hydroxide term E–A Neutral term E–A	61
 23	 29	Hydroxide term, possibly E–A Anionic term A–E	89
 24	 30	Hydroxide term, possibly E–A Anionic term A–E	91
 25	 31	Hydroxide term A–E for R; E–A for Ar	92
 26	 32	Possibly involves MeNCO	93
 27	 33		94

pH 2–9 the *N*-methyl analog of **23** does not hydrolyze at a significantly different rate from that for the parent, and together with the deuterium oxide solvent isotope effect (H/D = 1.2) an A–E mechanism is probable.



(25)

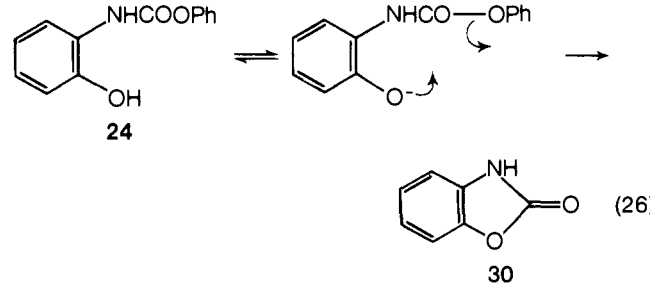
The value of σ for CO_2^- is uncertain[90] and could be zero or 0.31; we can calculate, using the Hammett relationship for 4-nitrophenyl (N-substituted)phenylcarbamates,[61] the value of k_{OH} for isocyanate formation from **34.** Using the Hammett ρ selectivity of +2.86 for change of substituent on the leaving phenol group, we can then estimate the k_{OH} value for phenyl



34

N-(2′-carboxyphenyl)carbamate (anion), and this is 63.4 or 100 M^{-1} sec^{-1} depending on the σ value employed. The observed value of 1.0 M^{-1} sec^{-1} [89] is low, but the 100-fold difference does not rule out the intermediate formation of isocyanate in the alkaline range of pH; trapping experiments were not carried out in this pH range, and it is quite conceivable that a change in the mechanism should occur.

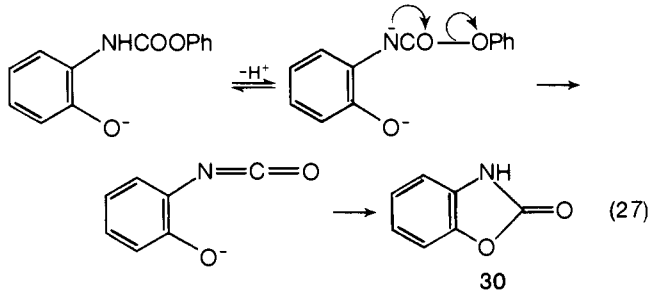
Intramolecular nucleophilic attack by the phenoxide group to yield 2-benzoxazolinone (**30**) from phenyl *N*-(2-hydroxyphenyl)carbamate (**24**) is consistent with intramolecular nucleophilic substitution.[91] The pH dependence is sigmoid with an inflection at the pK_a of the phenol and a hydroxide term predominating above pH 12. The plateau rate constant for the corresponding *N*-methyl analog is about tenfold greater, consistent with the A–E mechanism (eq 26); the slightly larger



(26)

value for the *N*-methyl analog is possibly due to steric interactions between methyl and ortho hydrogens altering the conformation of the carbonyl group.[91] The hydroxide term for the hydrolysis of the anionic species can be calculated assuming the mechanism involves isocyanate using the rate constant for phenyl *N*-phenylcarbamate under similar conditions (54.2 M^{-1} sec^{-1}) from ref 41a, the ρ value for substituents on the *N*-phenyl ring (+0.64),[61] and a σ value of −1.00[90] for the oxyanion at the ortho position; the resulting value (12.6 M^{-1} sec^{-1}) is close to the observed value of k_{OH} (5.14 M^{-1}

sec^{-1}) consistent with an isocyanate intermediate in the alkaline region of pH (eq 27). As in the carboxylate participation,



(27)

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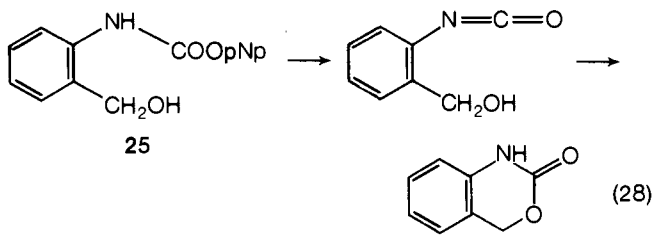
intermolecular hydroxide attack via the E–A mechanism competes successfully with the intramolecular A–E mechanism at high basicity.

Cyclization of esters of 2-hydroxymethylcarbanilic acid (**25**) and the *N*-methyl analog gives relatively stable benzoxazin-2-ones (**31**).[92] The pH profile for phenol release shows hydroxide terms but no inflections, and the 4-nitrophenyl ester has a rate constant similar to the hydrolysis of 4-nitrophenyl *N*-phenylcarbamate but about 10^4-fold larger than the cyclization of the *N*-methyl analog; the ethyl ester cyclizes some 10^6-fold faster than the hydrolysis of ethyl *N*-phenylcarbamate (which is known to involve as rate-determining step the formation of isocyanate),[60] and the ethyl ester of the *N*-methyl analog (of the acid of **25**) has a cyclization rate constant similar to the parent. It was proposed[92] that whereas the cyclization of the 4-nitrophenyl ester (**25**) involves an isocyanate intermediate (eq 28), the ethyl ester possesses an A–E mechanism (eq 29).



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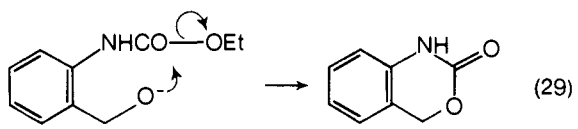
25 31



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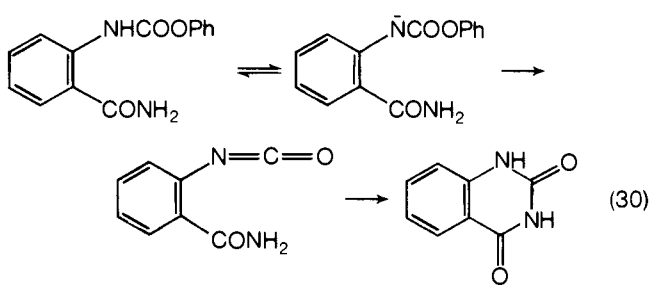
The hydrolysis of salicylanilide carbamates (**26**)[93] in alkali gave salicylanilide and in ethanol–water mixtures ethyl *N*-methylcarbamate; the formation of the latter strongly suggests methyl isocyanate as an intermediate, and the ratio of hydroxide ion rate constants for monomethyl- and dimethylcarbamoyl salicylanilides (see structure **26** in Table IV) in excess of 10^6-fold is consistent with this conclusion. In a related paper[93b] the formation of quinazolinediones (**35**) proceeds via trapping of the isocyanate by the amide rather than via initial nucleophilic attack of amide on the carbamate. Distinction between the two mechanisms was made by comparing the hydroxide ion rate constants for the *N*-methyl carbamate and the parent—some 100-fold difference.

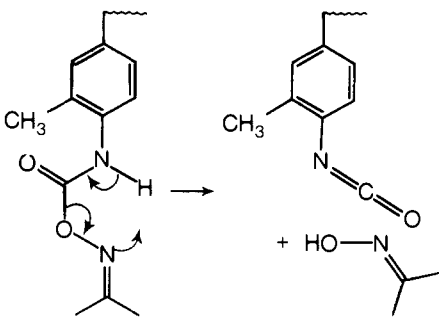


(30)

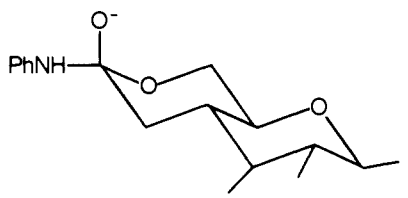
35

An interesting example of intramolecular catalysis involves the formation of isocyanates for cross-linking in polymers by using carbamate monomers possessing a basic function (**27** → **33**).[94]

Migration from the 4- to the 6-hydroxyl in *N*-phenylcarbamoyl protected carbohydrates is postulated to involve an A–E mechanism possessing a tetrahedral adduct (**36**).[84c]



27 33



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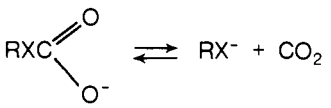
C. Carbonic Acid Derivatives

1. Decarboxylation

Carbonic acid derivatives of which a carboxylic acid is a special case decompose to yield carbon dioxide (or its analog), and the elimination mechanism (eq 31) has never been

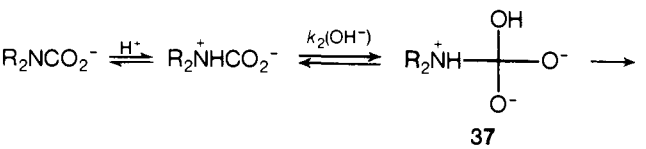


(31)

seriously questioned. The subject of decarboxylation of carboxylic acids where RX^- is a stabilized carbanion comes under this heading; this topic has been the subject of extensive reviews[95] and will not be treated here.

2. Carbamic Acids

A recent kinetic study[96] has disposed of the A–E mechanism for *N*-arylcarbamate decomposition (eq 32); the value of



37

$R_2NH + HCO_3^-$ (32)

k_2 was estimated to be 6×10^9 M^{-1} sec^{-1} assuming this mechanism for 2-ethoxyphenylcarbamic acid and is many orders of magnitude larger than the rate constant for attack of hydroxide ion on 4-nitrophenyl *N,N*-dimethylcarbamate (3×10^{-4} M^{-1} sec^{-1}). Attack of hydroxide ion on the neutral carbamic acid (eq 33) can be similarly eliminated.

TABLE V. Decomposition of Alkyl Hydrogen Carbonates

ROH	pK_a	K_{eq}/M	k_{decomp}/min^{-1}	Ref
Allyl	15.52	$10^{1.61}$	$10^{-2.23}$	102a
Glycol	14.77	$10^{1.44}$	$10^{-2.2}$	102b
2-Chloroethyl	14.31	$10^{2.05}$	$10^{-1.5}$	102b
Triethanolamine		$10^{1.0}$	$10^{-2.14}$	102g
2-Tetrahydrofurfuryl		$10^{1.64}$	$10^{-2.13}$	102h
Furfuryl	15.54[a]	$10^{1.93}$	$10^{-1.27}$	102h
Methyl	15.54	$10^{1.08}$	$10^{-2.62}$	102a
Ethyl	16.00	$10^{1.36}$	$10^{-2.99}$	102c, 102j
Glycerol	14.4	$10^{1.35}$	$10^{-2.89}$	102k
Benzyl	15.08[a]		$10^{-1.85}$	102a
Cyclohexyl			$10^{-3.39}$	102e
n-Butyl	16.06		$10^{-3.05}$	102i
Isobutyl	16.25[a]		$10^{-3.52}$	102i
sec-Butyl			$10^{-3.72}$	102i
n-Propyl	16.00		$10^{-3.14}$	102f, 102d
Isopropyl	16.57[b]		$10^{-3.44}$	102f

[a] Calculated using $pK_a = 15.9 - 1.42\sigma^*$ (P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960). [b] Calculated by S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971).

$$R_2NCO_2^- \overset{H^+}{\rightleftharpoons} R_2NCO_2H \overset{k_4(OH^-)}{\rightleftharpoons} R_2N(OH)_2O^- \longrightarrow R_2NH + HCO_3^- \quad (33)$$

Decarboxylation of *N*-arylcarbamates is oxonium ion catalyzed, and the pH dependence exhibits a plateau at low pH's; the rate constants possess a Bronsted type relationship[96,97] with the pK_a of the ammonium ion which exhibits two linear portions consistent with a changeover in rate-determining step (Figure 14). Carbamates from weakly basic and strongly basic amines decarboxylate with general acid and specific acid catalysis, respectively,[96-98] consistent with a mechanism where carbamates from weakly basic amines involve rate-limiting proton transfer while strongly basic amines involve rate-limiting decarboxylation (eq 34); urea synthesis from isocyanic acid and amines exhibits strikingly similar behavior.[71a,b]

$$R_2NCO_2^- \underset{OH^-, H_2O, B}{\overset{H^+, H_2O, A}{\rightleftharpoons}} R_2\overset{+}{N}HCO_2^- \longrightarrow R_2NH + CO_2 \quad (34)$$

3. Dithiocarbamic Acids

Dithiocarbamic acid decomposition is acid catalyzed but becomes pH independent at low pH's,[99] consistent with the neutral or zwitterionic species being the reactant. Some workers prefer the zwitterion as the active species (eq 35),[100] while others[101a] argue for an intramolecular proton

$$R_2NCS_2^- \overset{H^+}{\rightleftharpoons} R_2\overset{+}{N}HCS_2^- \longrightarrow R_2NH + CS_2 \quad (35)$$

transfer in a neutral species (eq 36). If the mechanism is to

$$R_2N{-}CS_2^- \overset{H^+}{\rightleftharpoons} R_2N{-}C(H)(S)=S \rightleftharpoons R_2NH + CS_2 \quad (36)$$

be distinguished from that of eq 35, the proton transfer must be included in some form of four-center transition state. The

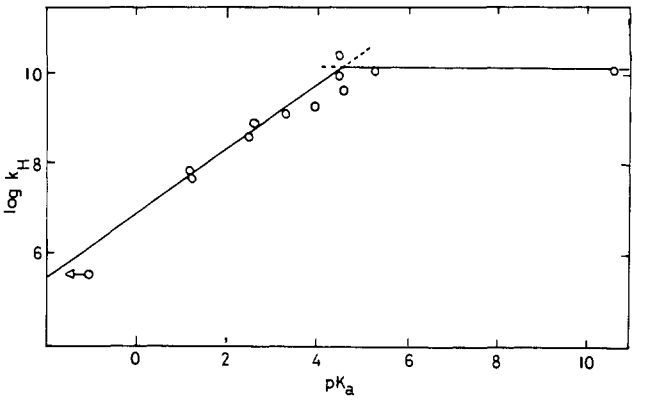


Figure 14. Effect of structure on the rate of hydronium ion catalyzed decarboxylation of N-substituted carbamic acids in water at 25°. All amines are aromatic except the one at high pK_a (cyclohexylamine) and at low pK_a (imidazoline). The figure is redrawn from Figure 5 of S. L. Johnson and D. L. Morrison, *J. Am. Chem. Soc.*, **94**, 1323 (1972).

stability of dithiocarbamic acids in nonpolar solvents tends to favor the zwitterionic mechanism.[101b] An interesting review on dithiocarbamates has been published.[101c]

4. Carbonic Acid Half Esters

Faurholt and his coworkers[102] have studied in detail the decomposition of carbonate half esters; Table V collects some of the data which indicate that the unimolecular decomposition of the half ester is strongly related to the pK_a of the departing alcohol (a β_{lg} for the departure of the alcoholate may be calculated from Faurholt's data) consistent with a transition state with extensive C–O-alkyl fission. Although Faurholt's work yields data close to the presently accepted values, it was obtained over a period of about 30 years and apparently not with the view of obtaining Bronsted coefficients; more recent work with this aim (unpublished observations of Professor C. K. Sauers at Rutgers, 1973) provides better values for the Bronsted coefficients in the reaction of alkoxide ions with carbon dioxide (eq 37) (β_{nuc}, forward direction, 0.3; β_{lg}, reverse direction, −1.1; β, overall equilibrium, +1.4). The apparent charge on the various atoms in the transition state may be calculated from Sauers' values and from this follows a knowledge of the extent of bond fission (**37**).

$$RO^- + CO_2 \rightleftharpoons \left| RO\overset{-0.79}{\cdots}C\overset{-0.21}{\cdots}O \right|^{\ddagger} \rightleftharpoons ROCO_2^- \quad (37)$$

37

Mechanisms similar to eq 35 and eq 36 have been proposed for the decomposition of neutral *O*-alkyl dithiocarbonate esters.[103b,c]

D. Sulfuric Acid Derivatives

1. Sulfates

The hydrolysis of monosulfate esters (X = OR in eq 38) is

$$XSO_3H \xrightarrow{H_2O} H_2SO_4 + HX \quad (38)$$

part of a large class of reactions which includes the hydrolysis of Bunte salts (X = SR),[104] thiosulfate ion (X = S^-),[105] halosulfonic acids (X = Hal), acyl sulfates (X = RCO–), sulfamic acids, hydroxylamine *N*- and *O*-sulfonates,[106] and the exchange of the oxygens of the sulfate ion in aqueous solution.[107] The pH dependencies of the hydrolyses, often com-

TABLE VI. Structure–Function Relationships for Reactions of Sulfate Derivatives

Substrate	Conditions	T/°C	pK_a range	β_{lg}	Ref
		Leaving Group Variation			
$XC_6H_4OSO_3H$	N/24 HCl	48.6	7.0–10.3	−0.25[c]	121[b]
		78.7	7.0–10.3	−0.21[c]	121[b]
	1.03 M HCl	45	4.0–8.4	−0.22	115
		25	4.0–8.4	−0.26	115
$RSSO_3H$	0.4 M $HClO_4$	69.7	5.0–10.3	+0.12	104[b]
$XC_6H_4NHSO_3H$	0.09 M HCl	45	3.8–5.4	−0.27[a]	e[b]
		75	3.8–5.4	−0.36	e[b]
$RNHSO_3H$	1.41 M HCl	99.96	4.6–10.6	−0.57	f[b]
$XC_6H_4OSO_3^-$	Neutral	100	4.0–8.4	−1.2	115
	Cyclodextrin at pH 10	50.3	2 points	−1.5	132
$C_6H_5SO_2OC_6H_4X$	Alkaline	50	7.0–10.2	−0.93	g[b]
		Nucleophile Variation			
				β_{nuc}	
4-Nitrophenyl-sulfate	Amines	35	3.0–12	+0.13	108[e]
	Thiophenols in DMF	90	6.0–7	+0.05[d]	120[b]

[a] Imprecise, Brønsted scattered. [b] Calculated from data in the reference. [c] Ortho groups deviate. [d] Since these reactions were carried out in DMF at 90° the ionic states of the equimolar reactants used are unknown and the interpretation of β_{nuc} unclear. [e] F. L. Scott and W. J. Spillane, *Chem. Ind. (London)*, 1999 (1967). [f] J. D. Capps and M. D. Bentley, *J. Org. Chem.*, **33**, 1295 (1968). [g] R. V. Vizgert, *Zh. Obshch. Khim.*, **28**, 1873 (1958).

plex, usually exhibit portions due to a spontaneous reaction of the monoanion and an acid-catalyzed limb.[108] The spontaneous reaction is usually characterized by S–O cleavage, while the acid reactions are complicated by C–O fission.[108]

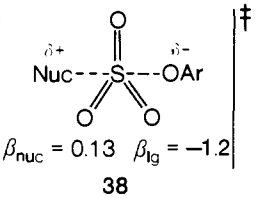
Mechanistic insight into this area is important to the chemistry of both sulfonation and biological sulfate transfer. The former has been thoroughly reviewed by Gilbert[109] and examples are the use of sulfur trioxide complexes of organic bases (e.g., pyridine-*N*-sulfonate), halosulfonates, and sulfamic acid in the sulfonation of steroids.[110] Sulfate esters play an important role in sulfate transfer,[111] in the biological reduction of sulfite,[111d,112] in steroid isolation,[113] and in carbohydrate chemistry.[114]

Monoanion Solvolysis. Solvolysis of the monoanion in neutral solution has been studied extensively only for aryl sulfate monoesters[115,116] and is observable only for substrates with powerful leaving groups—a consequence of the high Bronsted exponent for leaving group variation (β_{lg} = −1.2, see Table VI). No spontaneous reaction for sulfamate ions has been observed since the leaving species would be R_2N^-, but the neutral solvolyses of tertiary amine–sulfur trioxide adducts have been extensively studied.[117]

The magnitude of β_{lg} is consistent with a markedly E1 transition state. The slow solvolysis of fluorosulfate ion,[118a,b] due presumably to the strength of the S–F bond, is the basis of the fluoride inhibition of some sulfate reactions[117c] and its use in trapping reactive sulfate intermediates;[119] in addition, it indicates that factors other than the pK_a of the conjugate acid of the departing leaving group can control reactivity.

Nucleophilic attack of water on the monoanion has been excluded by specific electrolyte studies,[115] but it has several times been noted that the difference between powerful aquation of a transition state and weak nucleophilic interaction of water with the monoanion may be semantic rather than real.[115,116] Markedly negative entropies of activation and a positive deuterium oxide solvent isotope effect (H/D = 1.26) for solvolysis of the 4-nitrophenyl sulfate monoanion indicate considerable differential solvation of ground and transition states. The low Bronsted exponent for amine attack on the 4-nitrophenyl ester (β_{nuc} = 0.13; see Table VI) indicates weak interaction with nucleophile. Similar low dependence on base strength was observed for the attack of thiophenols.[120]

Catalysis. We have seen that the transition state for monosulfate hydrolysis involves advanced bond fission but minimal interaction with the nucleophile; that is, the transition state approximates sulfur trioxide plus phenolate ion (**38**). Thus ca-



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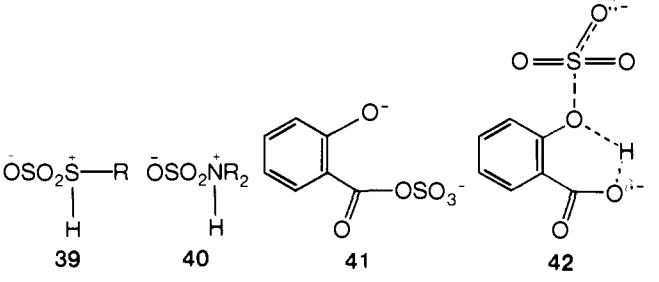
talysis may be expected from influences which stabilize the transition state (i.e., products) or improve the leaving group; little catalysis would be expected from activating the nucleophile.

Acid catalysis in the hydrolysis of aryl monosulfates has been explained by an A1 mechanism involving zwitterion formation.[108b-d,115,121-125] This provides both an internal nucleophile in the form of an oxyanion and an activated leaving group. Such a scheme (eq 39) is supported by the small posi-

$$HOSO_2OAr \rightleftharpoons \bar{O}SO_2\overset{+}{O}Ar \rightleftharpoons SO_3 + HOAr \qquad (39)$$
$$\qquad\qquad\quad |$$
$$\qquad\qquad\quad H$$

tive or zero entropies of activation,[121,124] the inverse deuterium oxide solvent isotope effect,[125] and the steric effects of bulky ortho groups.[121,124] The overall sensitivity to the basicity of the leaving group is low (β_{lg} = −0.23)[121,125] since the Bronsted exponent is composite. Bunte salts[104] and sulfamic acids[126] may also hydrolyze in acid via zwitterions (**39** and **40**), and the latter hydrolyses have been recently reviewed.[126] Aryl selenates solvolyze via an A2 route.[127]



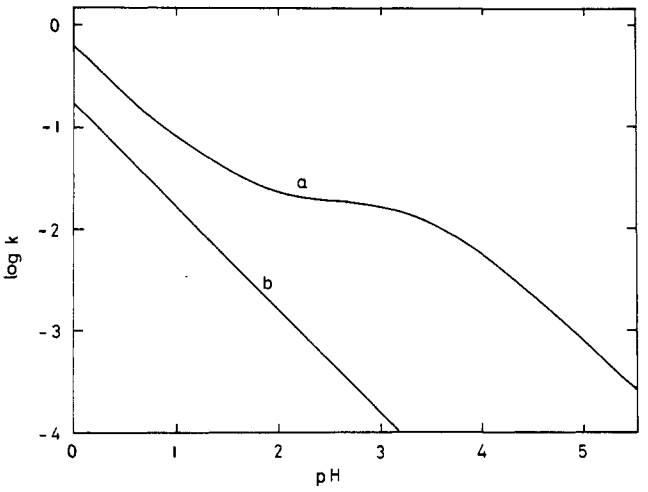
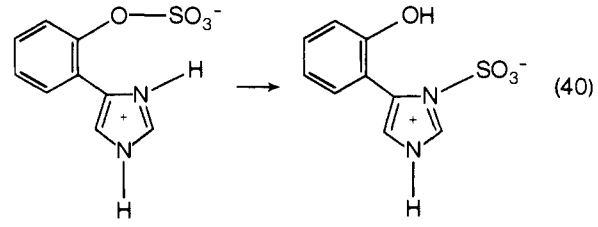


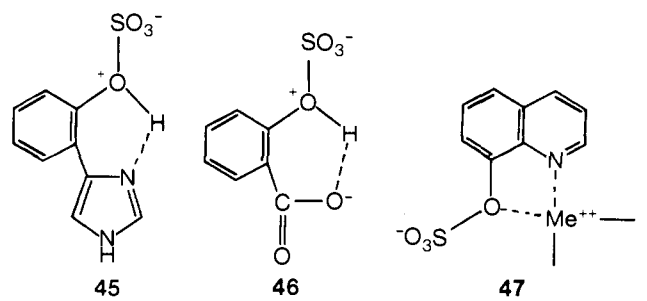
Figure 15. The pH–rate profiles (35°) for the hydrolysis of (a) salicyl sulfate and (b) 4-carboxyphenyl sulfate. The figure is redrawn from Figure 2 of S. J. Benkovic, *J. Am. Chem. Soc.*, **88**, 511 (1966).

Acid catalysis may also be provided intramolecularly: the carboxylic acid moiety of salicyl sulfate provides catalysis to expel the phenol and leave sulfur trioxide (Figure 15); the para isomer shows no such catalysis.[125] An acyl sulfate intermediate (**41**) was excluded using a hydroxylamine trapping experiment,[128] and the mechanism appears to involve intramolecular general acid catalyzed phenol expulsion (**42**). Comparison of trapping experiments with salicyl sulfate and sulfur trioxide in mixed alcoholic solvents was not definitive as to mechanism.[129] A similar case is the hydrolysis of 2-(4(5)-imidazolyl)phenyl sulfate.[130] A mechanism involving the *N*-sulfate (eq 40) is not absolutely ruled out because the rate constant for



43 44 (40)

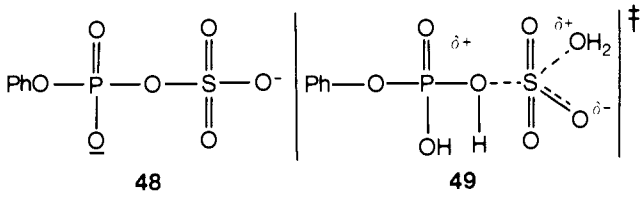
N-sulfate hydrolysis is larger than the hydrolysis rate for the starting ester (**43**). Fluoride ion does not trap any intermediate as fluorosulfonate in the hydrolyzing mixture but does trap the synthesized *N*-sulfate (**44**). Although fluoride ion is known to trap *N*- but not *O*-sulfate,[117c] it has a low efficiency compared with water in trapping *N*-sulfonates. It is therefore only possible to place a limit on the amount of reaction proceeding via the *N*-sulfate (<50%). Catalysis of the hydrolysis of 8-hydroxyquinoline *O*-sulfate by intramolecular acid catalysis and by metal ions has been observed.[123] In none of the above cases is the nature of the electrophilic catalysis clear; the neighboring acid group may serve to aid proton transfer to the leaving group or to stabilize a zwitterionic transition state (**45**, **46**, **47**).



45 46 47

Other modes of catalysis investigated have been micellar[117b,131] and cyclodextrin induced.[132] The former case may be due to ground-state destabilization or transition-state stabilization depending on the conditions. It is interesting that the acid catalysis of sulfate hydrolysis becomes more pronounced in solvents of low polarity, especially ethers.[108b,c] Moist dioxane increases the rate of hydrolysis of alkyl sulfates 10^7-fold relative to water[108c] possibly because of specific solvation of the zwitterionic transition state; sulfur trioxide, which resembles the transition state (see structure **38**), is well known to give etherate complexes.[133]

Acyl Sulfates. The sulfate donor in some biological transfers (e.g., formation of chondroitin sulfate, cerebrosulfatides, and phenolic sulfates)[134] has been shown to be 3′-phosphoadenosine 5′-phosphosulfate (PAPS). Model studies[135] on phenyl phosphosulfate (**48**) have indicated that the S–O fission process of the mono- and dianions and neutral species involve transition states with marked sulfur trioxide character (structures **49**, **50**, and **51**) and that **48** acts to sulfylate‡ rather than phosphylate only by a factor of 10.[135a] Acetyl sulfate transfers the acetyl group as shown by the predominance of C–O cleavage; no sulfylation is observed with this ester.[135a]



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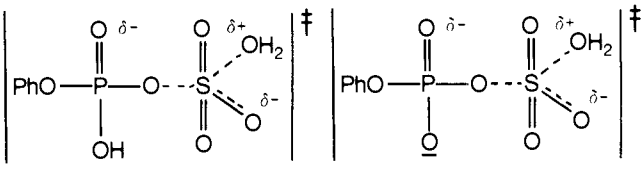


50 51

Biological Implications. The transition states for cyclodextrin catalyzed and aryl sulfate hydrolyses have been shown to approximate the normal solvolytic transition state with appreciable sulfur trioxide character.[132] In addition, the rates of sulfylation of *Aspergillus* aryl sulfatase by aryl sulfates correlates with the corresponding acid catalysis rates, again pointing to a "sulfur trioxide" transition state.[136] Such observations indicate that implications drawn from aqueous sulfate chemistry may be a fair guide to sulfate chemistry at biological sites. The low Bronsted coefficient for nucleophile variation indicates that an active site may play little part in enzyme mediated sulfate transfer. The high dependence on leaving group hints that activation may be in this portion of the system.

The evidence indicates that the metabolism of selenium in the cell may share some of the enzymic paths of sulfur metabolism.[137] In view of this the observed A1 reaction of sulfates under acid conditions of catalysis[108b-d,115,121-125] contrasts sharply with the A2 reactions of the corresponding selenates.[127]

2. Amino Sulfonates

Until recently there was but little kinetic activity in this area and elimination–addition routes had been observed only for highly activated N-monosubstituted sulfamoyl chlorides in nonaqueous solutions. Thus, *N*-ethylsulfonylamine (EtN=SO_2), produced by dehydrohalogenation of ethylsulfamoyl

‡ We use "sulfylate" here by analogy with the general term coined for all "acylations" involving phosphorus acids (namely "phosphylate"). The use of "yl" denotes the transfer of an acyl function.

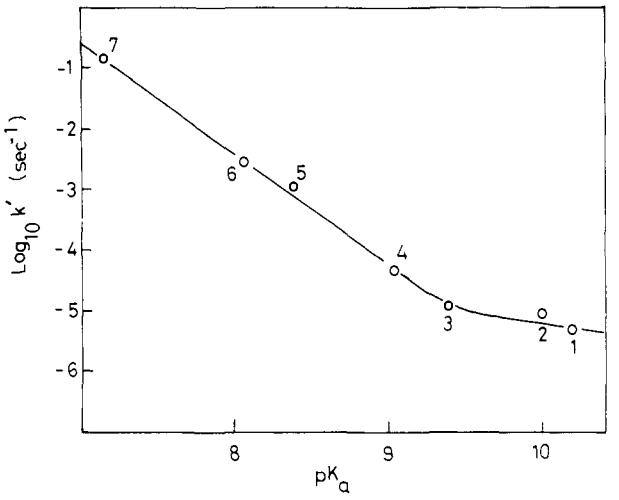


Figure 16. Dependence of k' (see eq 12) on pK_a of the phenol leaving group (60°, 50% ethanol–water). Legend: (1) 4-methoxyphenyl, (2) phenyl, (3) 4-chlorophenyl, (4) 3-chlorophenyl, (5) 3-nitrophenyl, (6) 4-acetylphenyl, (7) 4-nitrophenyl. The figure is redrawn from Figure 2 of ref 71b.

chloride, was trapped rapidly either by nucleophiles or by cycloaddition.[138] Other similar dehydrohalogenations have been reported[139,140] and sulfamoyl chloride itself reacts with aniline in the presence of sodium hydroxide to form the sulfanilide.[141] The pronounced acidity of the N–H group in monosubstituted aminosulfonates ($RNHSO_2X$) was indicated by salt formation (e.g., $EtO_2\bar{N}SO_2N^+Et_3$,[138] $NH_2SO_2\bar{N}SO_2N^+Et_3$,[139] and $Ar\bar{N}$-$SO_2N_3{\cdot}R_3N^+H$[142]) and opened the possibility of the E1cB route for hydrolysis (eq 41). The apparent pK_a's of some sub-

$$RNHSO_2X \overset{K_a}{\rightleftharpoons} R\bar{N}SO_2X \xrightarrow{k'(-X^-)} RN{=}SO_2 \xrightarrow{H_2O} RNHSO_3H \quad (41)$$

stituted phenyl *N*-methylaminosulfonates in 50% aqueous ethanol are predictable from a Hammett relationship (ρ = 2.54);[143] the pK_a of the 4-nitrophenyl ester fits the value derived kinetically from eq 42. Since k' (the "alkaline" plateau

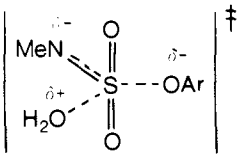
$$k_{obsd} = k_{H_2O} + k'/(1 + K_W/K_a[OH]) \quad (42)$$

rate constant) is 1000-fold larger than k_{H_2O}, it is unlikely that k' reflects attack of water on the conjugate base of the ester.[143] The rates of hydroxide catalysis for aryl esters of benzene- and 4-phenylbenzenesulfonic acids correlate with Hammett σ values and possess ρ values of +2.75 and 2.56, respectively.[144] However, the alkaline plateau rate constants for aryl *N*-methylaminosulfonates show high correlation slopes with Hammett σ^- constants ($\rho_{k'} = +4.04$)[143] and the ρ value for the apparent reaction of hydroxide with the neutral esters ($k_{OH^-} = k'K_a/K_w$) is 6.58 (corresponding to a Bronsted β_{lg} of −2.3). Such high selectivity for departing species and σ^- dependence is typical of an E1cB pathway. The lower value of β_{lg} (~−1.03) and approximately 10^8-fold decreased reactivity toward hydroxide ion for aryl *N,N*-dimethylaminosulfonates supports this assignment. Absence of an effect of amine nucleophiles on the rate of release of phenol from the monomethyl derivative while yielding totally the amide product also supports the E1cB path.[143] The Bronsted exponent (β_{lg}) for aryl methylaminosulfonates changes sharply when the pK_a (lg) exceeds 9.4 (Figure 16), and this could be due to a changeover in mechanism to stronger participation of the nucleophile water in the transition state for phenolate expulsion.[52] Such an explanation is consistent with the phenols of higher pK_a needing extra driving force for their expulsion than the active phenols.[143b]

TABLE VII. Rate Constants for Reaction of Hydroxide Ion with $RNHSO_2N_3$[a]

R	$k_{OH}/(M^{-1}\ sec^{-1}) \times 10^{-6}$
Methyl	2.40
n-Propyl	2.63
Isopropyl	1.87
Isobutyl	2.20
tert-Butyl	4.80

[a] Data taken from ref 142.



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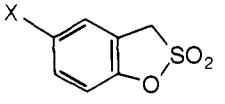
The base-catalyzed hydrolysis of some hypotensive sulfamoyl azides was suggested[142] to involve an E1cB mechanism, and in view of the results of the work on the methylamino esters[143] this interpretation is probably correct. Results of the work on N-substituted azides[142] can be interpreted[143] as evidence for the E–A process in hydrolysis: the absence of a substituent effect (Table VII) is not consistent with an A–E mechanism. The slight acceleration of the *tert*-butyl over the methyl substituent may reflect steric release in the E1cB transition state although differences in the solvation cannot be dismissed.

3. *Alkanesulfonate Derivatives* (R_2CHSO_2X)

In this section a mechanistic view will be presented of sulfyl transfers of alkanesulfonate esters, halides, and sultones; brief mention will also be made of some analogous processes from other regions of sulfur chemistry. Reviews of arenesulfonate esters,[144] fluorosultones,[145] sultones,[146] and sulfenes[147] have appeared but the kinetic data available are not extensive. Reactions of alkyl esters of sulfonic acids will not be included since solvolysis is via C–O fission.[148]

Sulfonyl derivatives command relatively important roles in bioorganic chemistry. Thus, α-toluenesulfonyl fluoride has been used to modify the active sites of serine proteases,[149] and 2-hydroxy-5-nitro-α-toluenesulfonic acid sultone (**53**, X = NO_2) sulfonylates several enzymes with 1:1 stoichiometry[150,151] and is a useful active-site titrant.[152] The large (>10^5-fold) cyclic/acyclic rate ratio for alkaline hydrolysis of **53** (X = H) and phenyl α-toluenesulfonate[153] demands de-



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R_2CHSO_2X

54

tailed mechanistic consideration. When hydroxyl and amino groups cannot be sulfonylated with aromatic sulfonyl chlorides (e.g., in some oximes,[154] and in *N-tert*-butoxycarbonyl-2-(2-hydroxythiazolidine) in Woodward's cephalosporin-C synthesis[156]), mild, rapid, introduction via sulfenes may be possible.

The marked lability of hydrogen atoms α to the sulfonyl group (e.g., in **53** and **54**) is fundamental to the chemistry of these compounds. Salts have been isolated (e.g., $CH_3SO_2\bar{C}H$-$SO_2N^+Et_3$,[147] $CF_3\bar{C}FSO_2C_5H_6N^+$ [146]) but only where the carbanion is highly stabilized. Many studies of exchangeability with solvent deuterons[146,157-164] have been made and the C–H pK_a's of **53** (X = H) and phenyl α-toluenesulfonate in dimethyl sulfoxide are 15.6 and 18.0, respectively.[165] Such

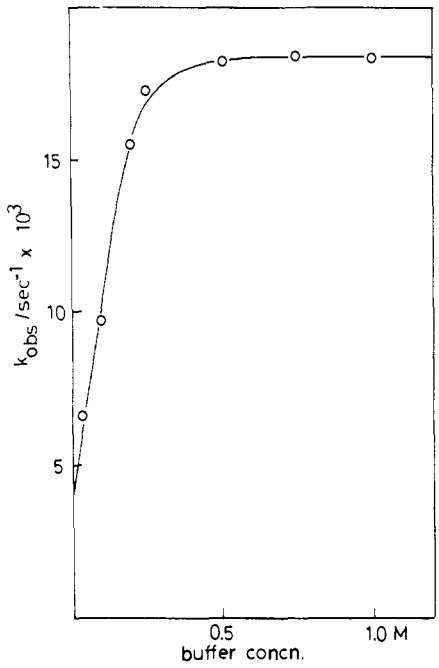


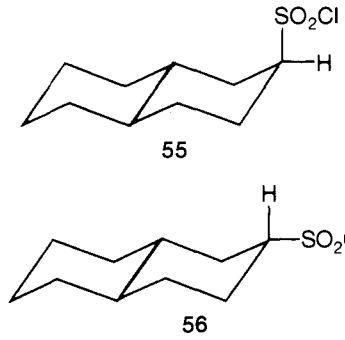
Figure 17. Rate constants for the release of 4-nitrophenol from 4-nitrophenyl toluene-α-sulfonate as a function of buffer concentration: buffer, diethylamine; fraction of base, 0.2; pH, 10.26; ionic strength, 1 *M*; 25°. The figure is redrawn from Figure 2 of ref 173.

work led to suggestions of elimination–addition routes via sulfenes (eq 43). Full discussions of the sulfene-mediated base

$$R_2CHSO_2X \longrightarrow R_2C{=}SO_2 \xrightarrow{YH} R_2CHSO_2Y \qquad R_2C{=}SO_2 \xrightarrow{YD} R_2CDSO_2Y \qquad (43)$$

solvolysis of sulfonyl halides are already available (notably from the groups of King[159-161] and Truce[162,163]) and only a brief summary follows. The most powerful argument for sulfene intermediates in these reactions is formation of mono- but no polydeuterated products in deutero alcohols.[160-163] In the absence of base, esterification of phenylmethanesulfonyl chloride proceeds slowly with no H–D exchange. Nucleophilic substitution at sulfur would yield undeuterated product, and, if a non-obligatory carbanion were formed, polydeuteration of the α position would be expected. The extent of exchange is strongly dependent on the nature of the exchanging carbon center (2-octanesulfonyl chloride exchanges less readily[166] than ethanesulfonyl chloride[160-161]), the leaving group (2-octanesulfonyl azide shows no reaction under the conditions used for the chloride),[166] and the structure of the catalytic base.[157,167] Thus, less bulky bases lead to monoexchange, but multiexchange becomes more pronounced as amine base size increases.[157]

It is believed that E–A substitution with an E-2 step to sulfene occurs in the solvolyses of sulfonyl halides[159,168] in view of the base size effect, variation of k_D/k_H with base, the dependence of the rates of pyridine-catalyzed chloride expulsion from substituted phenylmethanesulfonyl chlorides on σ^- Hammett constants (ρ^- = 2.35) and the observation that **55** reacts more slowly by a factor of 15 than **56** in the absence of base but more rapidly by a factor of 71 in the presence of triethylamine.[159] King[159] excludes the E1cB mechanism (as opposed to E2) since the rates of exchange and hydrolysis are incompatible on such a basis. Considering the discussions now taking place concerning the validity of the concerted elimination reaction in general,[5] an E1cB mechanism for the



above solvolyses could adequately account for the experimental observations if the proton transfer step were essentially rate controlling. An E1cB mechanism has been proposed, however, for the hydrolysis of dichloromethanesulfonyl chloride since $k_{exchange}$ is greater than $k_{hydrolysis}$.[169] Although distinction between E2, E1cB, or rate-controlling proton transfer in E1cB is not made, an E–A mechanism has been postulated to account for the higher base lability of α hydrogen containing fluoroalkanesulfonyl fluorides than their substituted analogs (CF_3CHFSO_2F and $CF_3CFClSO_2F$).[170]

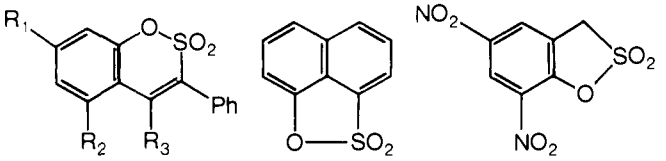
Vizgert has reported studies on aryl esters of substituted sulfonic acids, $RSO_2OC_6H_4X$,[171] and ρ values for hydroxide hydrolysis are (at 50° in 70% v/v dioxane water): 2.53, 2.48, 2.56, and 2.46 for R = $CH_2{=}CHCH_2{-}$, $CH_2{=}CMeCH_2{-}$, CH_3, and *n*-Pr, respectively. Since these values are close to those for aryl benzenesulfonates,[144] the E–A mechanism should remain hypothetical for these compounds although monodeuterated compounds are formed. Although the authors claimed a correlation with Hammett σ^- values, we could find no evidence of the use of substituents for which σ and σ^- values would differ significantly. Recent independent work from the laboratory of King[172] and from this laboratory[173] has clarified the mechanism for aryl phenylmethanesulfonate transfer reactions. The most convincing evidence for an E1cB mechanism involving an intermediate is the nonlinear dependence of rate on buffer concentration (Figure 17). At high buffer concentration the absence of a concentration effect is consistent with rate-controlling decomposition of the carbanion to sulfene, and the buffer dependence at low concentration corresponds to rate-controlling proton transfer (eq 44). Further evidence consistent with the E1cB mechanism

$$PhCH_2SO_2OAr \underset{k_A(A)}{\overset{k_B(B)}{\rightleftharpoons}} \bar{C}HSO_2OAr \xrightarrow[-OAr^-]{k_2} PhCH{=}SO_2 \qquad (44)$$

comes from the 1000-fold larger rate constant for hydroxide hydrolysis of the 4-nitrophenyl ester compared with the corresponding benzenesulfonate, trapping experiments with amines, a large primary deuterium isotope effect in the low buffer concentration region and a low effect in the high buffer concentration region,[174] and the high selectivity to Hammett substituents[172,173] which are σ^-.[173] Further work from this laboratory[174] shows that as the leaving group ability of the phenol is increased a change in rate-determining step from the E1 reaction to the proton transfer occurs.

Although the chemistry of five- and six-membered sultones has been reviewed,[146] it is only recently that extensive kinetic studies have been undertaken.[151] Alicyclic sultones generally react with nucleophiles via C–O fission;[175,176] however, **53** (X = H) hydrolyzes in base with only S–O cleavage.[177] Pathways leading to S–O cleavage could involve either attack at sulfur in an A–E mechanism or a sulfene route with prior elimination of the leaving group. The latter possibility is made more real by the low reactivity of sultones of type **57** toward base cleavage,[178] the similarity of the pK_a of **53** (X = H) to those

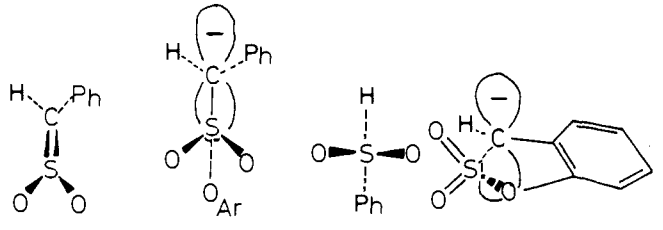
expected of carbamate esters ($pK_a > 14$) which follow an E1cB path, and the fact that the acyclic analog of **53** has a bona fide E1cB hydrolytic pathway. On the other hand, the large rate increase (10^5–10^6-fold) shown by five-membered ring sultones relative to their acyclic analogs[153] need not be due to the incursion of an E1cB route since **58** shows a similar rate acceleration,[179] and comparable ring size effects are observed for cyclic sulfites[180] and sulfates.[181] Moreover,



57 **58** **59**

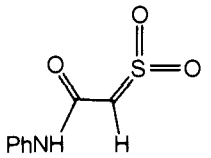
X-ray crystallographic studies have indicated considerable ring strain in five-membered sultones.[182] Definitive evidence against the E1cB mechanism for the basic hydrolysis of esters of the type **53** was obtained in Kaiser's laboratory: the hydrolysis of **59** in deuterated base yields greater than 50% of the unlabeled sulfonic acid on recovery from the product mixture.[183] Further evidence was the reisolation of the calculated amount of unlabeled sultone (**53**, X = H) on hydrolysis (partial) in deuterated base.[183] The ρ value of +1.23 for a series of sultones (**53**)[184] is also very low for an E1cB process.

It remains to account for the apparent anomaly that esters of type **53** hydrolyze in base via an A–E mechanism whereas the acyclic analogs (eq 44) possess an E–A mechanism. Sulfenes probably have the planar configuration (**60**) as their most stable form so it is likely that the transition state for the E1 reaction will also be planar or very nearly so for those atoms constituting the sulfene intermediate (**61**). This is supported by recent theoretical calculations which indicate that the planar sulfene CH_2SO_2 is more stable by some 35 kcal/mol than the "perpendicular" form, the parent of **62**.[185] Although the benzylic proton of the sultone **53** is labile and could readily expel the phenoxide consideration of the transition state for such a mechanism, **63** shows that the incipient sulfene is in a "perpendicular" conformation and not the more stable planar form.[173]



60 **61** **62** **63**

The unusual reactivity of the sulfonyl center in sulfoacetic acid derivatives has been explained by the intermediacy of a π-stabilized sulfene (**64**).[186] Iminosulfenes, $R_2C{=}S(O){=}NX$, have been proposed in the base-catalyzed alcoholysis of alkaneiminosulfonyl chlorides.[187]



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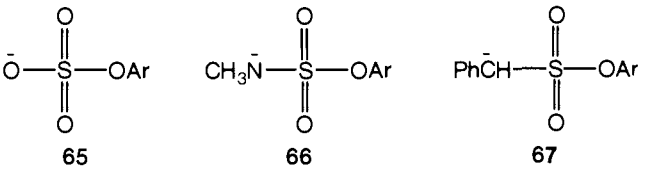
4. *Role of the pK_a of the α Proton*

We are now in a position to discuss the role of the pK_a of the α proton: in the series of anions **65**, **66**, and **67**, we are fairly sure that weak participation by the nucleophile water is needed to expel the aryl oxide in the sulfate half ester, but this necessity only arises in the aminosulfonate case (**66**)



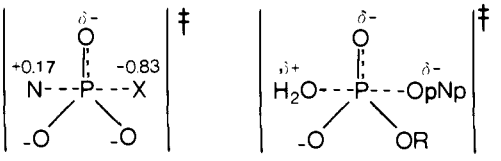
65 **66** **67**

when the leaving group becomes weak, for example, with phenol.[143b] With the carbanion no water assistance is necessary. The ratio of pK_a's of the α protons is **65** < **66** < **67**. At high pK_a in a given substrate the concentration of anion may not be sufficient to support an E1cB process in competition with an A–E mechanism. At low pK_a, although the concentration of anion is relatively large, the driving force for expulsion of the leaving group may not be sufficient for the E1 process to compete. Since the E1 process is in a sense an internal nuclephilic displacement we shall speak of "internal nucleophilicity" when discussing the power of the anion to expel a leaving group. When the transition-state for the elimination is close to products the internal nucleophilicity is strongly dependent on the stability of the intermediate.

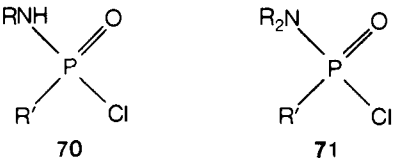
E. Phosphoric Acid Derivatives

1. *Phosphates*

The hydrolysis and transfer of monophosphate esters and derivatives in chemical and biochemical systems have been the subject of authoritative reviews,[188] and for this reason we only wish to mention the conclusions of these reviews and the most recent advances not incorporated. It has been concluded that extensive P–X cleavage occurs in the transition state **68** with little bond formation between nucleophile and phosphorus[189a] although there is doubt as to the extent of bond formation in the hydrolysis of the dianion. In monoanion hydrolysis there is presumably proton transfer to the leaving group, and a stepwise process or a concerted cyclic mechanism involving water as a bridge has been postulated for this. Recent evidence involving the observation of an ^{18}O isotope effect (1.0204 ± 0.0044) in the hydrolysis of 2,4-dinitrophenyl phosphate at neutral pH's confirms the existence of a transition state (**68**) with considerable "metaphosphate" character. While the isotope effect does not rule out mechanisms which do not involve rate-determining P–O cleavage such as A–E processes, a preliminary study indicated no isotope effect in the hydrolysis of dibenzyl 2,4-dinitrophenyl phosphate.[190]



68 **69**



70 **71**

In contrast with the dianions of monophosphates which hydrolyze via the above mechanism,[190,191] phospho diesters with good leaving groups involve an A–E mechanism for monoanion hydrolysis[192] with considerable bond formation in the transition state (**69**). The change in mechanism from E–A to

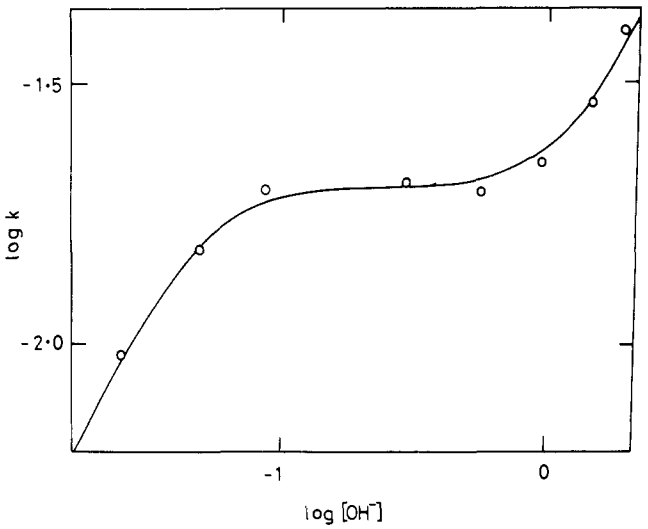


Figure 18. Dependence on hydroxide ion concentration of the rate constant for the hydrolysis of 4-nitrophenyl *N,N'*-diphenylphosphorodiamidate (58.3°, 50% ethanol–water). The figure is redrawn from Figure 5 of A. Williams and K. T. Douglas, *J. Chem. Soc., Perkin Trans. 2*, 318 (1973).

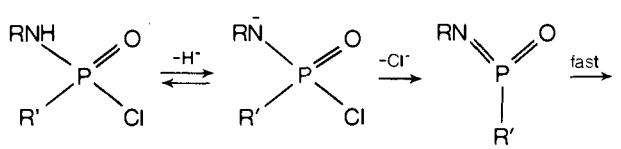
A–E as the phosphate is esterified is related to the lower "internal nucleophilicity" of the α atom in the diester case ($pK_a \simeq 1$) compared with those in the monoester dianion (pK_a's $\simeq 1$ and 6). A statistical factor is also involved in providing extra driving force for leaving group expulsion in the mono ester case.

2. Phosphoramidate

The large difference in alkaline rate constants between mono- and disubstituted nitrogen esters and halides was originally attributed to steric inhibition of the approach of hydroxide ion in an A–E mechanism. Later[193] it was attributed to hydrogen bonding of the hydroxide ion to the NH of the substrate. Westheimer[194] was the first to suggest the operation of an E–A mechanism of hydrolysis to account for the large rate constant differences. Further work showed that the reactions of nucleophiles other than hydroxide are not activated consistent with the proposed mechanism. Also, 2,6-lutidine catalyzes the hydrolysis of *N,N'*-diethylphosphoramidic chloride but not that of diethylphosphoryl chloride.[195]

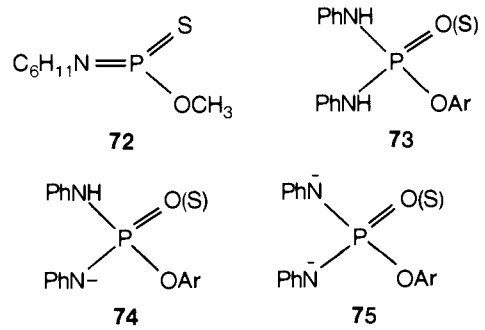
Hydrogen peroxide accelerates the rate of release of 4-nitrophenol from 4-nitrophenyl *N,N'*-diphenylphosphorodiamidate and the corresponding *N,N'*-dimethyl analog[196] in accord with an A–E mechanism for hydroperoxide attack and an E1cB mechanism for hydroxide attack. The changeover in mechanism is presumably caused by the powerful α-nucleophile effect of the hydroperoxide.

Stereochemical diagnosis of mechanism is possible with phosphoramidate hydrolyses; the alkaline hydrolysis of asymmetric methyl *N*-cyclohexylphosphorothioic chloride gives a



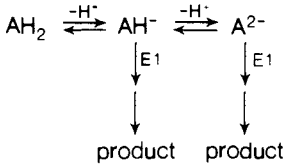
products (45)

racemic product in accord with a planar intermediate, the metaphosphorimidate (**72**).[197] The products of alkaline hydrolysis of the 4-nitrophenyl ester are optically active. While the evidence for the planar intermediate is difficult to assign to any other process the evidence for the 4-nitrophenyl ester



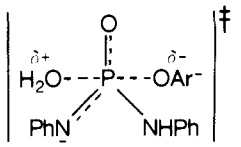
could fit either A–E or E–A mechanisms. A solvolysis study using methanol/water solvents for the chloride revealed a preference for reaction with methanol,[198] and it was concluded that hydrolysis did not involve free metaphosphorimidate.

Hydrolysis of substituted phenyl *N,N'*-diphenylphosphorodiamidates and the analogous thio ester revealed pH dependencies similar to Figure 18.[199] The observed rate law fitted a



(46)

scheme where both dianion and anion decomposed to metaphosphorimidate intermediates. The Hammett sensitivities for the apparent hydroxide rate constants are too large to accommodate a simple A–E mechanism.[199] None of the results so far obtained distinguish between the formation of free metaphosphorimidate and a transition state involving weak bond formation between nucleophile and phosphorus (**76**).



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Hydrolysis of phosphoramidates with expulsion of alkyl leaving groups could proceed via an E1cB mechanism.[200]

IV. Appendix. Elimination–Addition Mechanisms of Acyl Group Transfer

Recent work has included a novel application of solid-phase techniques to the problem of intermediate trapping. Rebek and his coworkers attach the acyl group donor to a polymer molecule and the acceptor or trapping nucleophile to another polymer. If the intermediate is sufficiently stable in free solution, it migrates to the acceptor where the product is detected by normal analytical methods. The technique, called the "three-phase test", is clearly a positive test: if no transfer is observed, then the intermediate could be nonexistent or too labile to exist long enough in solution to migrate. Addition–elimination must be very rare between polymer acceptors and donors. The method has been applied to carbamate,[201] β-ketoacyl,[201] and phosphoramidate[202] transfer and has provided the first convincing demonstration of the elusive metaphosphate (PO_3^{2-}) intermediate in monophosphate transfer.[203]

Sulfene chemistry has been the subject of an important review,[204] and an E2 mechanism for hydrolysis of phenylmethanesulfonate esters of very acidic phenols has been demonstrated to have a carbanion-like transition state involving very little S–O bond cleavage.[205]

Trapping experiments with *N*-methylaniline acceptor have been used to infer the existence of monomeric metaphosphates in the pyrolysis of methyl 2-butenylphostonate.[206] Metaphosphorimidates were postulated as intermediates in the photolysis in methanol of *cis*- and *trans*-1-azido-2,2,3,4,4-pentamethylphosphetane 1-oxide to explain the identity of the ratio of cis and trans methyl esters.[207] Recently three-coordinate five-valent phosphorus compounds ($R_2NP(NR)_2$ and $R_2NPS(NR)$) have been isolated from the corresponding azides; these unsaturated intermediates have stabilizing groups such as *tert*-butyl or trimethylsilyl attached to the nitrogen.[208]

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