General Acid Catalysis of Acetal, Ketal, and Ortho Ester Hydrolysis

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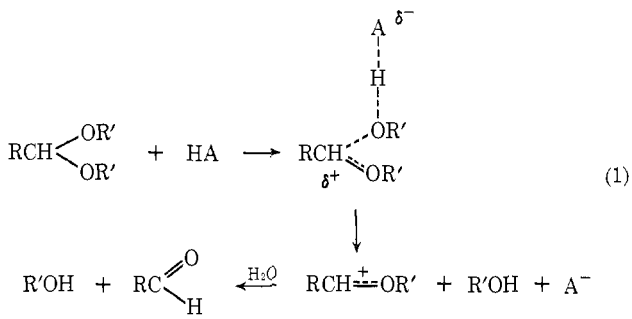
Prior to 1967, general acid catalysis by buffer acids involving proton transfer as part of the rate-determining step (eq 1) had never been conclusively ob-



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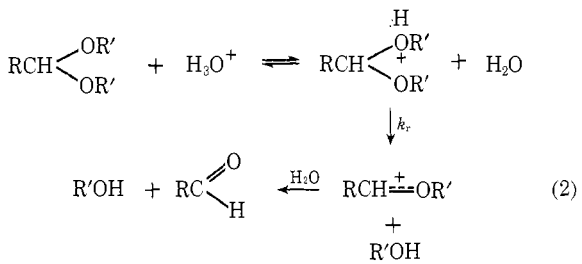
served in the hydrolysis reactions of acetals and ketals, although it had been sought by a number of investigators over a period of many years.[1-3] An impressive array of experimental evidence[4] pointed to an A-1 mechanism in which preequilibrium protonation of the acetal or ketal was followed by rate-limiting breakdown of the protonated substrate to an alcohol and a resonance-stabilized carbonium ion (eq 2).



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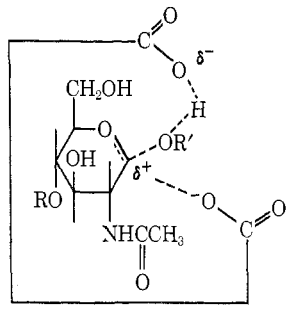
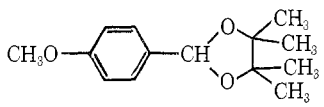
Interest in the mechanism of acetal and ketal hydrolysis received new impetus in 1965 when the three-dimensional structure of the glycosidic enzyme lysozyme was determined by X-ray crystallographic analysis.[5] Earlier the complete amino acid sequence had been elucidated.[6] Lysozyme catalyzes the hydrolysis of the glycosidic (1–4) linkages of polysaccharides made up of repeating *N*-acetylglucosamine and *N*-acetylmuramic acid residues. Carboxyl groups from glutamic acid-35 and aspartic acid-52 are presumably located in the active site of the enzyme. Several mechanisms have been proposed to explain the action of lysozyme,[7-9] all of which involve general acid catalysis by glutamic acid-35. In the example shown below, general acid catalysis by glutamic acid-35 occurs along with electrostatic stabilization of a developing carbonium ion by the aspartate carboxylate anion. Finding general acid catalysis of acetal hydrolysis in simple chemical systems and elucidating the



structural features in the acetal that would facilitate such catalysis became important therefore not only to physical organic chemists but also to enzymologists.

The first report of buffer catalysis in the hydrolysis of an acetal[10] dealt with 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (**1**). Its hydrolysis is weakly



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catalyzed by formic acid in H_2O. The observed buffer catalysis and other criteria of mechanism were not typical of a normal A-1 reaction, and suggested that water might be involved in the critical transition state of the hydronium ion catalyzed reaction. An A-2 mechanism involving attack of water on the protonated acetal was proposed, as in eq 3. An A-2 reaction is by definition one in which preequilibrium

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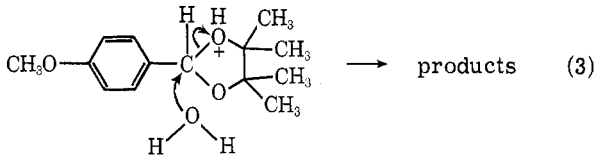
(1) J. N. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).
(2) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 3146 (1955).
(3) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).
(4) E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).
(5) C. C. F. Blake, D. F. Koenig, G. A. Mair, A. C. T. North, D. C. Phillips, and V. R. Sarma, *Nature (London)*, **206**, 757 (1965); L. N. Johnson and D. C. Phillips, *ibid.*, **206**, 761 (1965).
(6) P. Jolles, *Angew. Chem., Int. Ed. Engl.*, **3**, 28 (1964); R. E. Canfield, *J. Biol. Chem.*, **238**, 2699 (1963).
(7) D. C. Phillips, *Sci. Amer.*, **215**, 78 (1969).
(8) G. Lowe, G. Sheppard, M. L. Sinnott, and A. Williams, *Biochem. J.*, **104**, 893 (1967).
(9) M. A. Raftery and T. Rand-Meir, *Biochemistry*, **7**, 3281 (1968).
(10) T. H. Fife, *J. Amer. Chem. Soc.*, **89**, 3228 (1967).



protonation by hydronium ion is followed by rate-determining attack of water on the protonated substrate. The $\Delta S^{\pm}$ values (−15 eu) are slightly less negative and the $k_{D_3O^+}/k_{H_3O^+}$ ratio (2.4) is larger than generally assumed for an A-2 reaction.[11] However, the values generally assumed stem primarily from acid-catalyzed ester hydrolysis reactions where a relatively large number of water molecules are involved,[12] with water possibly acting as a proton transfer agent. These limits need not apply to an A-2 acetal hydrolysis reaction. An A-2 mechanism is supported by the fact that substitution of a methyl group at the reaction center decreases the rate of hydrolysis 540-fold.[13]

The tetramethyl substitution in the dioxolane ring of **1** is undoubtedly responsible for the observed mechanism change, since corresponding diethyl and ethylene glycol acetals hydrolyze by the normal A-1 mechanism.[3,14] Such substitution would enhance reclosure of the ring if a carbonium ion intermediate were being formed. If ring closure were exceedingly rapid, the reaction might proceed most readily to products if reaction with a water molecule occurred before bond breaking was complete, that is, without formation of a carbonium ion as a discrete intermediate. It should be noted that **1** hydrolyzes 1030 times more slowly than the corresponding ethylene glycol acetal and 40,000 times more slowly than the corresponding diethyl acetal.[10] Alternatively, the carbonium ion intermediate might be formed readily but reversibly, with the equilibrium lying far to the left and reaction of the carbonium ion with water rate determining. Capon and Page[15] recently found evidence for an A-2 mechanism of the type of eq 3 in the hydrolysis of another 1,3-dioxolane.

As will be seen later, none of the structural features in an acetal that give rise to general acid catalyzed hydrolysis is present with the tetramethyl-1,3-dioxolanes. The mechanism of the buffer-catalyzed reaction is presumed to follow a course similar to that of the hydronium ion catalyzed reaction, involving either attack of formate ion on the protonated acetal or trapping of a carbonium ion intermediate by formate ion. Intramolecular nucleophilic attack by carboxylate anion has been observed by Anderson and Capon in the hydrolysis of phthalaldehydic acid diethyl acetal in aqueous dioxane.[16]

Intermolecular General Acid Catalysis. A fundamental question was how true general acid catalysis

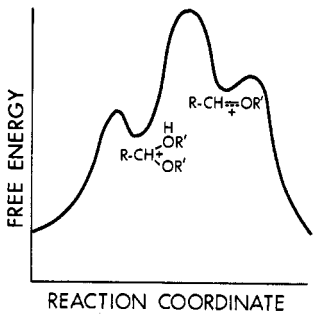
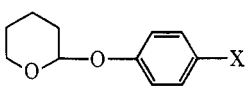


Figure 1. A free-energy *vs.* reaction-coordinate diagram for acid-catalyzed hydrolysis of a simple acetal proceeding by an A-1 mechanism.

might be observed in acetal hydrolysis reactions. In Figure 1, an energy profile for hydronium ion catalyzed A-1 hydrolysis of a simple acetal (eq 2) is presented. Protonation could become partially rate determining if the height of the peak for the protonation step were increased by reducing basicity or if the height of the peak for the bond-breaking step were reduced by increasing the ease of C–O bond breaking.

With these thoughts in mind, the hydrolysis reactions of a series of 2-(substituted phenoxy)tetrahydropyrans, in which electron withdrawal by substituents in the leaving group would both lower basicity and



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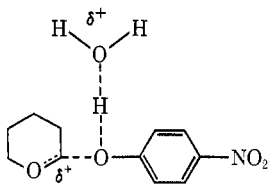
promote bond breaking, were investigated. In 50% dioxane–H_2O at 30°, the ratio $k_{D_3O^+}/k_{H_3O^+}$ decreases progressively as electron withdrawal increases, and $\Delta S^{\pm}$ becomes progressively more negative.[17] The values for 2-ethoxytetrahydropyran are characteristic of an A-1 mechanism ($k_{D_3O^+}/k_{H_3O^+}$ = 2.82; $\Delta S^{\pm}$ = +7.9 eu). For such a mechanism, the D_2O solvent isotope effect is generally in excess of 2.7 and $\Delta S^{\pm}$ is generally positive.[3,18] In contrast, the values for 2-(*p*-nitrophenoxy)tetrahydropyran are not consistent with an A-1 mechanism, but indicate solvent involvement in the critical transition state ($k_{D_3O^+}/k_{H_3O^+}$ = 1.33; $\Delta S^{\pm}$ = −7.6 eu). The most likely mechanism is protonation by hydronium ion concerted with C–O bond breaking.



Unmistakable general acid catalysis was observed with the nitro derivative in both H_2O and 50% dioxane–H_2O.[17,19] The Brønsted coefficient α for cataly-

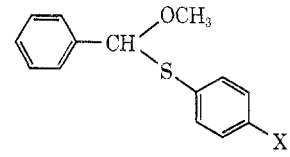
(11) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Amer. Chem. Soc.*, **79**, 2362 (1957); F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).
(12) T. H. Fife and D. M. McMahon, *J. Amer. Chem. Soc.*, **91**, 7481 (1969).
(13) T. H. Fife and L. H. Brod, *J. Org. Chem.*, **33**, 4136 (1968).
(14) T. H. Fife and L. Hagopian, *ibid.*, **31**, 1773 (1966).
(15) B. Capon and M. Page, *Chem. Commun.*, 890 (1971).
(16) Discussed by B. Capon, *Chem. Rev.*, **69**, 436 (1969).
(17) T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, **90**, 4081 (1968).
(18) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).
(19) T. H. Fife and L. H. Brod, *J. Amer. Chem. Soc.*, **92**, 1681 (1970).

sis by chloroacetic, formic, and acetic acids in H_2O is 0.5, while that for catalysis by dichloroacetic, chloroacetic, formic, and acetic acids in 50% dioxane–H_2O is 0.65. The point for hydronium ion appears to fit well on these Brønsted plots. Second-order rate constants for general acid catalysts are considerably less in D_2O than in H_2O. For example, with formic acid as the catalyst the ratio k_{HA}/k_{DA} is 2.65, indicating that proton transfer occurs in the transition state. These were the first examples of general acid catalysis of acetal hydrolysis. That general acid catalysis is observable with phenoxytetrahydropyrans but not with corresponding phenyl glycosides[20] is presumably due to reduced carbonium ion stability with the glycosides owing to inductive electron withdrawal by the ring hydroxyl groups. As an indication of this difference in stability, it has been estimated that 2-methoxytetrahydropyran hydrolyzes 3.1×10^7 times faster than methyl α-D-glucopyranoside.[21]

If protonation were strictly rate determining, it would be expected that the proton would lie closest to the weakest base in the transition state. In view of the large differences in pK_a of the catalyst and the substrate (a reasonable estimate of the pK_a of the nitro derivative would be −10), the proton should be largely transferred in the transition state. A Brønsted coefficient of 0.5, implying that the proton is about halfway between catalyst and substrate, must therefore mean that basicity is increased in the transition state. This could be achieved by partial breaking of the C–O bond. Consequently, the reaction is best considered to be a concerted process.

With formic acid as the catalyst in hydrolysis of the unsubstituted, *p*-chloro-, and *p*-nitrophenoxytetrahydropyran derivatives, a plot of log k_{HA} *vs.* σ, the Hammett substituent constant,[22] was linear with a slope, ρ, of +0.9, showing that electron withdrawal in the leaving group facilitates general acid catalysis. This positive ρ value can be contrasted with the value of −0.9 for hydronium ion catalyzed hydrolysis of these compounds. Since the influence of electron withdrawal on basicity will cause a more negative ρ value, ease of bond breaking must be relatively more important in the general acid catalyzed reaction than in the hydronium ion catalyzed reaction. This is reasonable since protonation is more difficult when a weak acid is the catalyst and C–O bond breaking should consequently have progressed further in the transition state. Also, ease of bond breaking must be of greater importance in facilitating general acid catalysis than basicity considerations. In a later study, Anderson and Capon[23] reported that benzaldehyde methyl phenyl acetals were also subject to general acid catalyzed hydrolysis. The same structural features responsible for general acid catalysis with the phenoxytetrahydropyrans are undoubtedly also of importance in that series. Again, when substituent groups were varied in the phenolic leaving group, the ρ value was positive in the acetic acid catalyzed reaction.

In order to define more fully the relative importance of low basicity and ease of bond breaking in giving rise to general acid catalysis, the hydrolysis of thioacetals was studied. Replacement of oxygen by sulfur will, of course, reduce basicity greatly. General acid catalysis could not be observed in the hydrolysis of benzaldehyde-1,3-oxathiolanes and benzaldehyde methyl *S*-phenyl thioacetals **3**.[24] In the latter series



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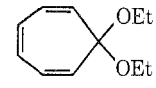
it was shown that the C–S bond is initially broken in the reaction. This series is of particular interest because with the exactly analogous oxygen acetals general acid catalysis is observed. Thus, although basicity is lower with the thioacetals, general acid catalysis is not observed since bond breaking is not sufficiently easy. Ease of bond breaking is thereby again indicated as the critical feature in allowing general acid catalysis to occur.

While general acid catalysis had been found with phenolic acetals giving rise to moderately stable carbonium ions, it was important to demonstrate such catalysis with acetals and ketals having poor leaving groups of relatively high basicity since the natural substrates for lysozyme are of that type. General acid catalysis in water by weak buffer acids was observed in the hydrolysis of tropone diethyl ketal (**4**).[25]



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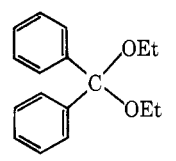
With this ketal the intermediate oxocarbonium ion, being a tropylium ion, is of extreme stability so that bond breaking is easy even though the leaving group is poor. Tropone diethyl ketal hydrolyzes very rapidly; the rate constant for hydronium ion catalysis at 15° is $1.5 \times 10^5\ M^{-1}\,sec^{-1}$.

The degree of oxocarbonium ion stability necessary for general acid catalysis to be observable with acetals and ketals of aliphatic alcohols was determined in a series in which the intermediate oxocarbonium ion stability progressively increases.[26] This series included benzophenone diethyl ketal (**5**), 2,2-(*p*-methoxyphenyl)-1,3-dioxolane (**6**), ferrocenecarboxaldehyde dimethyl acetal (**7**), 2,3-diphenylcyclopropenone diethyl ketal (**8**), tropone diethyl ketal, and tropone ethylene ketal. Buffer acid catalysis could not be detected with any of the compounds except the tropone ketals.[26]

(20) D. Piszkiewicz and T. C. Bruice, *J. Amer. Chem. Soc.*, 89, 6237 (1967).
(21) E. Dyer, C. P. J. Glaudemans, M. J. Koch, and R. H. Marchessault, *J. Chem. Soc.*, 3361 (1962).
(22) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1940, Chapter VII.
(23) E. Anderson and B. Capon, *J. Chem. Soc. B*, 1033 (1969).
(24) T. H. Fife and E. Anderson, *J. Amer. Chem. Soc.*, 92, 5464 (1970).
(25) E. Anderson and T. H. Fife, *ibid.*, 91, 7163 (1969).
(26) T. H. Fife and E. Anderson, *J. Org. Chem.*, 36, 2357 (1971).



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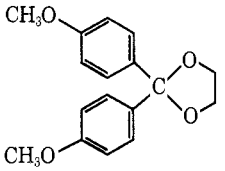

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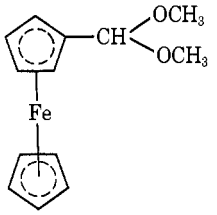

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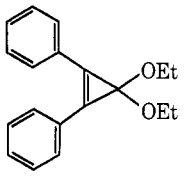

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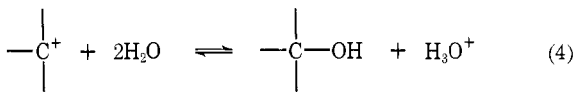
The observation of general acid catalysis is at the present time the only conclusive evidence for a mechanism change in these reactions. It would therefore appear preferable to consider reactions in which buffer acid catalysis cannot be observed as proceeding by the well-established A-1 mechanism rather than by a borderline A-Se2 mechanism. Thus, in terms of oxocarbonium ion stability, the boundary between the A-1 mechanism and one involving partially rate-determining protonation by hydronium ion with general acid catalysis by buffer acids must lie between the oxocarbonium ion intermediates derived from 2,3-diphenylcyclopropenone diethyl ketal (**8**) and the tropone ketals. An indication of the relative stabilities of the oxocarbonium ions can be obtained from pK_R^+ values for a series of related carbonium ions. The pK_R^+ is the negative logarithm of the equilibrium constant for the reaction of eq 4. These values become more positive in the series diphenylmethyl (−13.3),[27] bis(*p*-methoxyphenyl)methyl (−5.71),[27] 2,3-diphenylcyclopropenyl (−0.67),[28] and tropylium (+4.7).[29] It can be concluded that, for general acid catalysis of acetal and ketal hydrolysis to be detectable when the leaving group is poor, the intermediate carbonium ion must have great stability, approaching that of an alkoxy tropylium ion; *i.e.*, bond breaking must be quite easy.



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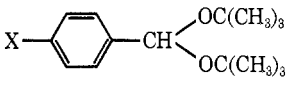
Bond breaking could also be facilitated by the introduction of steric strain into the ground state of the molecule, if such strain were relieved in the transition state. It has been suggested, from examination of models constructed from coordinates obtained in X-ray crystallographic studies, that a feature of the lysozyme reaction might be distortion of the hexose unit adjacent to the bond undergoing cleavage, from the stable chair conformation to a half-chair conformation resembling that of an oxocarbonium ion.[7-9] Such steric strain in the ground state should facilitate formation of the transition state and might explain general acid catalysis in the enzymatic reaction.

Relief of ground-state strain does lead to an enhancement of the rate and to general acid catalysis in the hydrolysis of para-substituted benzaldehyde di-*tert*-butyl acetals (**9**).[30] General acid catalysis had



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been sought previously in the hydrolysis of similarly substituted benzaldehyde diethyl acetals[3] and could not be detected. Considerable restriction of rotation is evident from inspection of Stuart–Briegleb models of the di-*tert*-butyl acetals so substantial ground-state strain should be present. General acid catalysis might also arise if basicity were markedly less than for structurally simpler acetals. Lower basicity would, however, slow the hydronium ion catalyzed reaction greatly, whereas it is in fact enhanced, the second-order rate constant for hydronium ion catalysis of benzaldehyde di-*tert*-butyl acetal being 15 times greater at 25° than that for benzaldehyde diethyl acetal at 30°. Thus, while bond breaking and basicity considerations are possibly both important, the facilitation of bond breaking by relief of steric strain in the ground state is most likely the predominant feature leading to general acid catalysis in this series. If basicity is lowered by the *tert*-butyl groups, the actual facilitation of bond breaking may be many times the observed difference in the rates of hydrolysis in comparison with benzaldehyde diethyl acetal.

If ground-state strain is not relieved in the transition state, an enhanced rate of hydrolysis will not be observed. 2,6-Dichlorobenzaldehyde di-*tert*-butyl acetal hydrolyzes relatively slowly, and general acid catalysis is barely detectable. The large ortho substituents should restrict groups in the ground state, but if, in addition to the electronic effects exerted by the chloro substituents, groups are also restricted in the transition state, the observed slowness of hydrolysis can be explained. Two chloro substituents will reduce basicity to a greater extent than with the other compounds studied. Consequently, the lack of significant general acid catalysis with the dichloro compound shows that it is not low basicity that is giving rise to general acid catalysis.

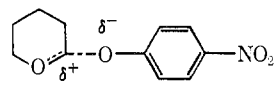
Giudici and Bruice[31] have shown that ground-state planarity will not by itself lead to general acid catalysis of acetal hydrolysis. Of the possible effects on mechanism produced by binding of substrate to lysozyme, the introduction of strain into the substrate must therefore be of greatest importance.

From these studies of acetal hydrolysis it can be concluded that general acid catalysis by buffer acids will be detectable if the leaving group is good (a phenol),

(27) N. C. Deno and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3051 (1955); N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *ibid.*, **77**, 3044 (1955).
(28) R. Breslow, H. Hover, and H. W. Chang, *ibid.*, **84**, 3168 (1962).
(29) W. von E. Doering and L. H. Knox, *ibid.*, **76**, 3203 (1954).
(30) E. Anderson and T. H. Fife, *ibid.*, **93**, 1701 (1971).
(31) T. A. Giudici and T. C. Bruice, *Chem. Commun.*, 690 (1970).

basicity of the acetal is low, and a moderately stable carbonium ion is formed as an intermediate. Also, general acid catalysis will result when the leaving group is poor (an aliphatic alcohol) if the carbonium ion intermediate is exceedingly stable (an alkoxytropylium ion) or if there is great steric strain in the ground state which is relieved in the transition state; that is, the C–O bond breaking process must be easy.

pH-Independent Hydrolysis. In the hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran, a pH-independent reaction is observable from pH 4 to alkaline pH values (0.01 *M* NaOH) in either 50% dioxane–H_2O or H_2O.[19] Such a reaction had never been observed previously in the hydrolysis of simple acetals. Plateau regions in the pH–rate constant profiles had been seen in the hydrolysis of various types of glycosides, but with those compounds neighboring groups are present which participate in the reaction.[20] The evidence pointed to an uncatalyzed unimolecular decomposition in the hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran. Thus, the reaction proceeds at essentially the same



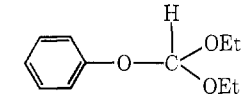
rate in D_2O as in H_2O ($k_{D_2O}/k_{H_2O} = 0.9$); if water were acting as a general acid, the reaction should be much slower in D_2O. The entropy of activation calculated from the pH-independent rate constant is +2.2 eu; water involvement in the transition state should give a highly negative $\Delta S^{\ddagger}$. The rate of the reaction is highly dependent on the nature of the solvent, being about 50 times greater in H_2O than in 50% dioxane–H_2O, suggesting considerable charge development in the transition state. Finally, the most convincing piece of evidence for a unimolecular mechanism is the fact that if the reaction were considered to involve general acid catalysis by water, the point for water on the appropriate Brønsted plot would lie many log units above the regression line. A unimolecular reaction is intelligible in terms of the good leaving group and the reasonably stable oxocarbonium ion intermediate; both features facilitate C–O bond breaking. A pH-independent reaction has also been observed in hydrolysis of the acylal γ-ethoxy-γ-butyrolactone, where similar structural features (a good leaving group and a stabilized carbonium ion intermediate) are present.[32] Similar solvent effects and D_2O solvent isotope effects were observed in that reaction.

Hydrolysis of tropone diethyl ketal was found to proceed by a pH-independent pathway at pH values greater than 10, again with a ratio k_{D_2O}/k_{H_2O} of 0.9.[25] As carbonium ion stability is increased, the rate of the hydronium ion catalyzed reaction will increase as well as the rate of the pH-independent reaction, although not necessarily to the same extent, thereby explaining why the pH-independent reaction is not observed until pH 10 with tropone diethyl ketal, whereas it becomes predominant at pH values greater than 4 with 2-(4-nitrophenoxy)tetrahydropyran.[17,19] Benzaldehyde methyl *S*-(2,4-dinitrophenyl) thioacetal hydrolyzes in a pH-independent reaction across almost the entire pH scale, hydronium ion catalysis not being detectable until a concentration of 0.3 *M* is reached.[24]

It is striking that pH-independent reactions are observed with 2-(*p*-nitrophenoxy)tetrahydropyran and tropone diethyl ketal because hydrolysis of these compounds is susceptible to general acid catalysis. The reactions are mechanistically related in that the C–O bond is breaking in both cases, general acid catalysis being effected by partial protonation of oxygen in a concerted process. Ease of C–O bond breaking is certainly the cause of the unimolecular reaction; it must therefore be a key factor leading to general acid catalysis.

Ortho Ester Hydrolysis. A brief consideration of structurally related ortho esters is informative since it shows the generality of the conclusions derived from the study of acetals. The hydrolysis of certain types of ortho esters has been considered to be general acid catalyzed since the work of Brønsted in 1929.[1] It had been found that the rates of hydrolysis of ethyl orthoacetate, ethyl orthopropionate, and ethyl orthocarbonate were dependent on buffer concentration.[1] DeWolfe later claimed that hydrolysis of ethyl orthoformate is general acid catalyzed in 70% dioxane–H_2O as the solvent but not in H_2O,[33] and the work of Price and Kwart on methyl orthobenzoates indicated that hydrolysis of those compounds is general acid catalyzed in 70% methanol–H_2O.[34] However, it has recently been suggested that these results were due to specific salt effects in the mixed solvents.[35,36] The general acid catalysis that had been observed in ortho ester hydrolysis was fairly weak, and it was considered that the Brønsted coefficient would generally be high.[4] Values of about 0.7 had been found.[1,34,37]

Considering the structural features responsible for general acid catalysis in acetal and ketal hydrolysis, an ortho ester having a good leaving group and from which a reasonably stable oxocarbonium ion intermediate would be produced ought to show pronounced general acid catalysis with a relatively low Brønsted coefficient. This prediction has been fulfilled. The hydrolysis of diethyl phenyl orthoformate (**10**) in 50%



10

dioxane–H_2O at 25° proceeds with pronounced general acid catalysis and with a Brønsted coefficient of 0.47 (correlation coefficient 0.993 for a correlation including six carboxylic acids and cacodylic acid).[38] This value

(32) T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 271 (1965).

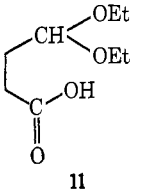
(33) R. H. DeWolfe and R. M. Roberts, *ibid.*, **76**, 4379 (1954).
(34) H. Kwart and M. B. Price, *ibid.*, **82**, 5123 (1960).
(35) M. Lahti and A. Kankaanpera, *Acta Chem. Scand.*, **24**, 706 (1970).
(36) P. Salomaa, A. Kankaanpera, and M. Lahti, *J. Amer. Chem. Soc.*, **93**, 2084 (1971).
(37) A. J. Kresge and R. J. Preto, *ibid.*, **87**, 4593 (1965).
(38) E. Anderson and T. H. Fife, *J. Org. Chem.*, **37**, 1993 (1972).

is considerably less than any previously determined. In hydrolysis of **10**, phenol is the leaving group. Specific salt effects cannot be responsible for the observed buffer effects since the second-order rate constants determined at high salt concentration, held constant with KCl, or with $NaClO_4$, were slightly greater at the higher ionic strengths where the contribution of the buffer anion to the total ionic strength is small. Therefore, the observed effects represent genuine general acid catalysis.

In contrast, the second-order rate constants for buffer acid catalysis of the hydrolysis of diphenyl ethyl orthoformate are less at 45° than those for diethyl phenyl orthoformate at 25°, and the Brønsted coefficient is considerably higher, 0.68.[38] Diphenyl ethyl orthoformate possesses the same phenol leaving group, but the oxocarbonium ion intermediate is less stable. Basicity is also less, due to the electron-withdrawing ability of phenoxy relative to an ethoxy group.[39] Thus, even though basicity is less, general acid catalysis is less favorable, illustrating again that the critical feature in facilitating general acid catalysis is oxocarbonium ion stability and the ease of C–O bond breaking. When the intermediate oxocarbonium ion is further stabilized in the diphenyl ethyl system in the case of diphenyl ethyl orthoacetate, the rate constants become larger as expected and the Brønsted coefficient diminishes (0.49).

Intramolecular General Acid Catalysis. In the design of chemical models which mimic the action of enzymes, molecules possessing functional groups that might catalyze the particular reaction intramolecularly have assumed large importance. This is because of the analogy between an intramolecular reaction and an enzyme-catalyzed reaction proceeding through an enzyme–substrate complex in which the substrate is held in close proximity to the appropriate catalytic groups in the active site.[40]

Intramolecular catalysis of acetal hydrolysis was studied before the successful demonstration of bimolecular buffer acid catalysis. We had measured the rates of hydrolysis of γ,γ-diethoxybutyric acid (**11**)



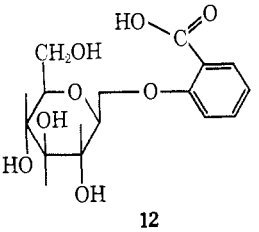
11

in both H_2O and 50% dioxane–H_2O and had found that carboxyl group participation, if any, was quite small.[41] This is because the structural features responsible for general acid catalysis in bimolecular reactions are absent, the leaving group being poor and the carbonium ion intermediate not highly stabilized.

(39) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556.
(40) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966.
(41) T. H. Fife, unpublished work.

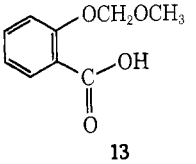
Bruice and Pizkiewicz[42] later investigated an extensive series of substituted 1,3-dioxolane ketals where in certain cases a substituent carboxyl group was held much more rigidly in respect to the ketal function than in **11**, but again carboxyl group participation could not be demonstrated.

The lack of intramolecular catalysis in these systems was striking, especially since Capon had reported[43] that *o*-carboxyphenyl β-D-glucoside (**12**) hydrolyzed



12

at 95° considerably more rapidly at moderate pH values than did the corresponding *p*-carboxyl isomer. The pH–rate constant profile for hydrolysis was characterized by a plateau that suggested participation by the carboxyl group. It was reported from the same laboratory[44] that *o*-methoxymethoxybenzoic acid (**13**) also hydrolyzed with participation by the *o*-carboxyl group. Although intramolecular general acid catalysis was later preferred as the mechanism in both cases,[45] information that would offer a conclusive choice between the kinetically equivalent possibilities of intramolecular general acid catalysis and hydronium ion catalyzed hydrolysis of the anionic species was not offered.



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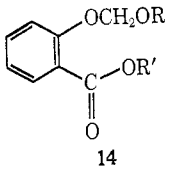
Dunn and Bruice[46] studied a series of *o*-methoxybenzoic acids substituted in the benzene ring. Catalysis by a second carboxyl group in 2-methoxymethoxyisophthalic acid was no greater than could be explained as a steric effect, permitting the conclusion that electrostatic stabilization of a developing carbonium ion was not important. Of interest was a Brønsted coefficient, α, for intramolecular catalysis of 1.0. While this value was based on only two compounds (**13** and the 5-nitro derivative), it did suggest that the proton was completely transferred in the transition state, an interpretation strongly supported by a study of the formals **14** where both the R and R′ substituents were varied.[47] Values of ρ^* for hydronium ion catalyzed hydrolysis are −3.0 regardless of the nature of the R′ group (methyl or hydrogen). This is inconsistent

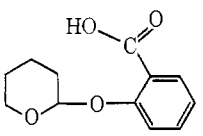
(42) T. C. Bruice and D. Piszkiewicz, *J. Amer. Chem. Soc.*, **89**, 3568 (1967).
(43) B. Capon, *Tetrahedron Lett.*, 911 (1963).
(44) B. Capon and M. C. Smith, *Chem. Commun.*, 523 (1965).
(45) B. Capon, M. C. Smith, E. Anderson, R. H. Dahm, and G. H. Sankey, *J. Chem. Soc.*, 1038 (1969).
(46) B. Dunn and T. C. Bruice, *J. Amer. Chem. Soc.*, **92**, 2410 (1970).
(47) B. Dunn and T. C. Bruice, *ibid.*, **93**, 5725 (1971).



14

with a transition state in which the proton is intermediate between the two oxygens in the case of the carboxyl-substituted compound, since the amount of oxocarbonium ion character in the transition state should be different if the proton is only partially transferred, as compared with the ester where the mechanism is A-1. A difference in transition-state structure would be reflected in a different ρ^* value. Dunn and Bruice reason that the mechanism must be A-1 in all cases and that the neighboring carboxyl group probably stabilizes the proton on the acetal oxygen electrostatically. They point out that an A-1 mechanism is reasonable since buffer acid catalysis is *not* observed in the hydrolysis of analogous formals without carboxyl group substitution.

In view of the problem of kinetic equivalence in intramolecular reactions, it was important to study carboxyl-substituted acetals where buffer acid catalysis is observed in hydrolysis of the unsubstituted compounds. In such cases, the mechanisms of the inter- and intramolecular reactions should be the same. Therefore, kinetically equivalent possibilities would not be such serious obstacles to interpretation as in the previous cases, and assessment of the relative efficiency of intramolecular catalysis would be possible. Consequently, the hydrolysis reactions of 2-(*o*-carboxyphenoxy)tetrahydropyran (**15**) and benzaldehyde



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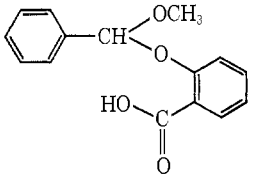


16

methyl *o*-carboxyphenyl acetal (**16**) were investigated.[48]

The pH–rate constant profile shown in Figure 2 was obtained for hydrolysis of **15** in 50% dioxane–H_2O at 15°. A large plateau in the profile will be noted. As in the other cases of intramolecular catalysis, kinetically equivalent possibilities exist, and the curve in Figure 1 can be calculated from either eq 5 or eq 6 with

$$k_{obsd} = [k_0 + k_1 a_H]\left[\frac{a_H}{K_a + a_H}\right] \quad (5)$$

$$k_{obsd} = k_1 a_H\left[\frac{a_H}{K_a + a_H}\right] + k_2 a_H\left[\frac{K_a}{K_a + a_H}\right] \quad (6)$$

appropriate values of the rate constants, where k_1 is the second-order rate constant for hydronium ion catalyzed hydrolysis of the un-ionized acetal, k_2 is the second-order rate constant for hydronium ion catalyzed hydrolysis of the ionized species, k_0 is the rate constant for intramolecular general acid catalysis, and K_a is the

(48) T. H. Fife and E. Anderson, *J. Amer. Chem. Soc.*, **93**, 6610 (1971).

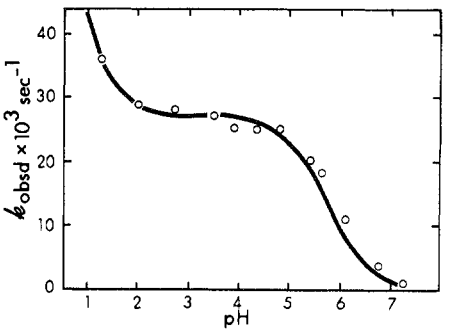
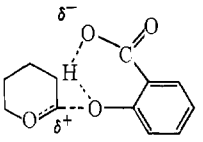


Figure 2. Plot of k_{obsd} for hydrolysis of 2-(*o*-carboxyphenoxy)-tetrahydropyran in 50% dioxane–H_2O at 15° *vs.* pH.

dissociation constant of the carboxyl group. The neighboring carboxyl group greatly accelerates hydrolysis. The value of k_2 is 6.1 × 10^5 greater than $k_{H_3O^+}$ for the corresponding ethyl ester and 3.8 × 10^5 greater than $k_{H_3O^+}$ for the unsubstituted compound. These are the maximum differences in k_{obsd} for hydrolysis of these compounds at any pH. The k_2 value for the *p*-carboxyl-substituted compound could not be determined since its rates of hydrolysis are much too slow to measure accurately at the required pH at 15°. However, from the measured value of k_1 and a reasonable assumption as to the difference between k_1 and k_2, based on the known ρ value for hydronium ion catalyzed hydrolysis of 2-(4-substituted phenoxy)-tetrahydropyrans and the σ values for COOH and COO^-, it could be calculated that k_2 (para) must be only 1.6 × 10^{-6} the magnitude of k_2 (ortho). These differences in the rate constants are many times larger than expected on the basis of inductive effects.

Determination of the rate constants in D_2O would give ambiguous results.[42] However, it is reasonable that the mechanism does involve intramolecular general acid catalysis (eq 5) in view of the intermolecular buffer acid catalysis observed with the unsubstituted compounds. General acid catalysis should therefore be favored in the intramolecular reaction.

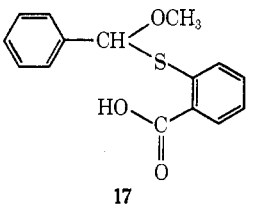


The ratio of rate constants for intramolecular general acid catalysis of the hydrolysis of **15** and intermolecular formic acid catalyzed hydrolysis of 2-phenoxytetrahydropyran is 580 *M*, a minimum value since the intramolecular reaction was studied at 15° while the bimolecular reaction was studied at 50°. The ratio would be considerably larger if comparisons were made at the same temperature. The calculated ratio represents the concentration of formic acid in the bimolecular reaction that would be required to give a pseudo-first-order rate constant comparable to that obtained in the intramolecular reaction. It is evident that intramolecular catalysis is greatly favored, and that an increase in local concentration of the carboxylic acid catalyst cannot explain the great efficiency of the reaction relative to intermolecular

catalysis. The ratio of 580 M may reflect the nearly optimal geometry of the system in **15** for proton transfer between the two oxygen atoms.

The magnitude of the rate constant k_2 for hydrolysis of benzaldehyde methyl *o*-carboxyphenyl acetal ($1.2 \times 10^7\ M^{-1}\ \text{sec}^{-1}$) rules out nucleophilic attack of a carboxylate anion on the protonated substrate, or any mechanism involving a completely transferred proton, if the basicity of the acetal is normal. It can be calculated that k_{-1}, the rate constant for transfer of a proton from the conjugate acid of the substrate to H_2O, would then necessarily have to be greater than that for a diffusion-controlled process. If basicity has been increased with this compound by the presence of the neighboring carboxylate anion, then in order to account for the rapid rate of hydrolysis a decrease of 10^5 in the dissociation constant of the conjugate acid would be required since k_2 for **16** is 1.9×10^5 greater than $k_{H_3O^+}$ for the corresponding methyl ester. As in the case of **15**, the most likely mechanism involves intramolecular general acid catalysis.

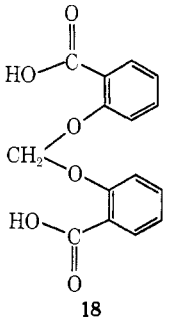
With the exactly analogous thioacetal, benzaldehyde methyl *S*-(*o*-carboxyphenyl) thioacetal (**17**), carboxyl



17

group participation cannot be conclusively observed, there being a difference of only 30 between k_1 and k_2. This supports the contention that the same structural features will permit both intramolecular catalysis and buffer acid catalysis because, in contrast with the oxygen acetals, buffer acid catalysis is not observed in hydrolysis of the corresponding thioacetals.[24] In view of the low basicity of sulfur, either intramolecular general acid catalysis or carboxyl group, electrostatic stabilization of a proton on sulfur might have been expected to be a favorable process. A most important feature of these reactions must be that the salicyl anion is a better leaving group than the thiosalicyl anion.

Disalicyl acetals with two suitably located carboxyl groups (**18** and **19**) show very large rate enhancements



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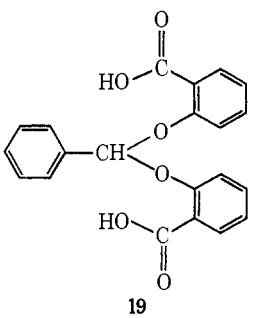


19

in both H_2O and 50% dioxane–H_2O, in comparison with the corresponding methyl esters (3×10^9 in the case of **19** in 50% dioxane–H_2O).[49] The pH–rate

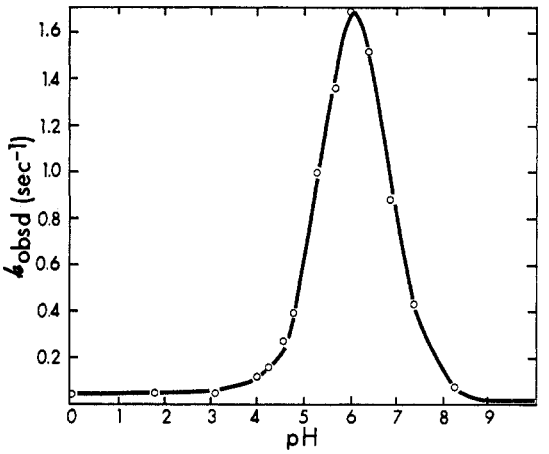
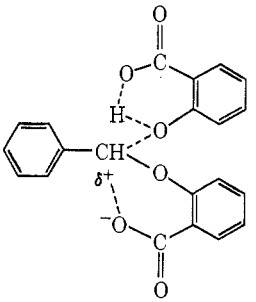


Figure 3. Plot of k_{obsd} *vs.* pH for hydrolysis of benzaldehyde disalicyl acetal in 50% dioxane–H_2O at 25°.

constant profiles are bell-shaped, as shown in Figure 3 for **19**, but with both **18** and **19** it is possible that only one carboxyl group actually participates in the reaction, with the other exerting mainly a substituent effect. In the case of **19** the rate constant for intramolecular general acid catalyzed hydrolysis of the monoanion calculated from the data in Figure 3 is only 65-fold greater than that for the un-ionized species. This is slightly greater than expected from a substituent effect, so it is possible that some electrostatic carbonium ion stabilization is occurring, but the carboxylate anion can be giving only a small increase in the rate constant. Thus, bifunctional catalysis by



two carboxyl groups as postulated for lysozyme has not been demonstrable, even though nucleophilic attack or electrostatic stabilization of a developing carbonium ion would be expected to be most favorable when the carbonium ion intermediate is fairly unstable, as is the case with **18** especially. If the ionized species reaction involves intramolecular general acid catalysis, as is most probable, this mechanism is capable of giving rate enhancements of the magnitude seen in enzymatic reactions without assistance from other functional groups.

In summary, intramolecular general acid catalysis is observed with acetals having good leaving groups and giving rise to relatively stable oxocarbonium ions so that buffer acid catalysis can be detected in hydrolysis of the unsubstituted compounds. In these reactions the efficiency of intramolecular catalysis is great, and rate enhancements of 10^5–10^9 take place in com-

(49) E. Anderson and T. H. Fife, *Chem. Commun.*, 1470 (1971).

parison with suitable derivatives in which carboxyl group participation is not possible. Bifunctional catalysis by two suitably placed carboxyl groups has not been observed, even though in the case of methoxymethoxyisophthalic acid[46] and the disalicyl acetals **18** and **19** the conditions for demonstration of electrostatic stabilization of a developing carbonium ion appear to be optimal.

Lysozyme. The foregoing information on the chemical hydrolysis of simple acetals can be applied to the mechanism of action of glycosidic enzymes and, in particular, lysozyme. If it is assumed that glutamic acid-35 is involved in the catalytic action of lysozyme and that the enzyme acts in accord with the principles established in the chemical model studies, then two points are clear.

(1) The key problem of general acid catalysis in the enzymatic reaction is explainable if the substrate is distorted during the binding process and if the resulting strain is relieved during the hydrolytic reaction, thereby making C–O bond breaking more facile, in analogy to hydrolysis of the benzaldehyde di-*tert*-butyl acetals. Since with natural substrates for lysozyme the leaving group is poor and the intermediate carbonium ion is relatively unstable, the bond-breaking process *must* be sufficiently enhanced for general acid catalysis to take place. As noted previously, relief of ground-state strain produced by distortion of the substrate has been an integral feature of postulated mechanisms for lysozyme,[7–9] although there is no conclusive evidence that it occurs.

(2) From the lack of bifunctional catalysis in the hydrolysis of dicarboxyl-substituted acetals, regardless of the stability of the intermediate carbonium ion, it is possible that aspartic acid-52 may not be directly involved in the catalytic process in the lysozyme reaction. The bell-shaped pH–rate profile for lysozyme[50] most likely indicates that ionization of two groups is important, but this does not necessarily imply direct involvement of aspartic acid-52 in the reaction. A possibility is that this group is important in stabilizing a particular conformation of the enzyme. A bell-shaped pH–rate constant profile is also obtained with disalicyl acetals such as **19** where participation by one carboxyl group causes most of the observed rate enhancement which is of the magnitude observed in enzyme-catalyzed reactions. Consequently it is not necessary to involve bifunctional catalysis to explain the kinetic behavior of lysozyme. The chemical studies on acetal hydrolysis have therefore set forth the possibilities by which lysozyme exerts its catalytic effect and have led to explanations of the problem of general acid catalysis.

It is hoped that the continuation of such physical–organic work in conjunction with studies of the enzyme itself will finally give a clear picture of how lysozyme is exerting its catalytic effect.

I wish to thank all my coworkers for their contributions to this work. I am particularly grateful to Dr. Edwin Anderson for many stimulating discussions. This work was supported by research grants from the National Institutes of Health and the National Science Foundation.

(50) J. A. Rupley, *Proc. Roy. Soc., Ser. B*, **167**, 416 (1967); J. A. Rupley and V. Gates, *Proc. Nat. Acad. Sci. U. S.*, **57**, 496 (1967); T. Osawa and Y. Nakasawa, *Biochim. Biophys. Acta*, **130**, 56 (1966).

[10]Annulenes and Other $(CH)_{10}$ Hydrocarbons

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A limited number of organic compounds expressable in terms of simple molecular formulas have attracted the interest of organic chemists almost since the inception of this science. The annulene series could probably be described in this way. These are fully conjugated, monocyclic polyenes; the number of CH moieties in the ring is indicated by an arabic numeral in brackets.

Aromatic chemistry, guided by the simple "$(4n + 2)$ rule" of Hückel,[2] developed along an interesting course;[3] [6]annulene (benzene) was well known, and [8]annulene (cyclooctatetraene) yielded to synthesis in 1911.[4] However, the next major breakthrough in annulene chemistry was not the isolation of the next higher homolog, [10]annulene, but rather the synthesis of [18]annulene, by Sondheimer in 1959.[5] This was largely due to the discovery that macrocyclic polyacetylenes

Professor Masamune received his Ph.D. from University of California, Berkeley, in 1957. After several years at the University of Wisconsin, first as a postdoctoral fellow, then as a lecturer, he became a fellow at Mellon Institute. In 1964 he moved to the University of Alberta. His research interests fall into three main categories: the synthesis of natural products, extremely strained systems, and cyclic π-electron systems.

Nicholas Darby is a doctoral candidate working with Professor Masamune on planar ten-π-electron systems.

(1) F. Sondheimer and R. Wolovsky, *J. Amer. Chem. Soc.*, **84**, 260 (1962).

(2) E. Hückel, *Z. Phys.*, **70**, 204 (1931).

(3) Omitted from this Account are charged species [*e.g.*, cyclopropenyl cation: (a) R. Breslow, J. T. Groves and G. Ryan, *J. Amer. Chem. Soc.*, **89**, 5048 (1967); (b) D. G. Farnum, G. Mehta, and R. G. Silberman, *ibid.*, **89**, 5048 (1967); cyclononatetraenide: (c) T. J. Katz and P. J. Garratt, *ibid.*, **86**, 5194 (1964); (d) E. A. LaLancette and R. E. Benson, *ibid.*, **87**, 1941 (1965)], bridged annulenes [*e.g.*, (e) E. Vogel, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, **12**, 215 (1968)], and derivatives of annulenes.

(4) R. Willstätter and E. Wase, *Ber.*, **44**, 3423 (1911).