the stability of the OH⁻ at the active site is increased even more by long-range hydrogen-bonding interactions between the active (nucleophilic) H_2O and components of what has been termed the "water chain" in the active site, indicating again the importance of residues around but not in the active site.

Quantum and molecular mechanical calculations have thus provided insights into rate-enhancing factors in enzyme catalysis. Long-range electrostatic and hydrogen-bonding effects are crucial. It will be of interest to investigate these in a systematic manner to discover where the major portion of electrostatic stabilization energy in charge separation processes is centered. It will be further desirable to develop methods to calculate reaction paths so that reliable energies of activation can be computed to allow accurate estimates of rate enhancements of enzyme-catalyzed reactions over the corresponding nonenzymatic ones. Finally, it will be of value to combine the conformational energy and quantum mechanical approaches so that, of the favorable binding modes calculated in the ground state, we can predict which of these modes will be catalytic or productive ones.

Direct Observation of Simple Tetrahedral Intermediates

Brian Capon,* Ashim K. Ghosh, and Duncan McL. A. Grieve

Department of Chemistry, Glasgow University, Glasgow G12 8QQ, Scotland, United Kingdom

Received April 17, 1981

Many reactions are thought to pass through transient intermediates which have not been detected but whose incursion is inferred on the basis of indirect evidence. The potential energy–reaction coordinate diagram for such a reaction may be written as shown in Figure 1. For reactions of polyatomic molecules, this is a cross section of a potential energy surface in a multidimensional hyperspace. The complete and rigorous calculation of such a surface is virtually impossible, and it is necessary to employ approximate methods in order to make the calculations tractable.[1] The experimental approach to the study of the reactions of the intermediate is apparently limited by the fact that the potential energy differences E_r and E_p and the corresponding free energy differences are so large that the intermediate is impossible to detect. Nevertheless, in some reactions the value of E_a, the potential energy of activation for the breakdown of the intermediate, and the corresponding free energy of activation may not be so small that this reaction could not be studied. Therefore, it is a general principle that if one wants to study directly the reactions of such an intermediate, it is useless to approach it directly along the reaction coordinate shown in Figure 1. Instead it must be approached from some other direction on the potential energy surface from a higher energy state. The work described in this Account and also our work on vinyl alcohol[2] are based on this principle.

One of the most widely studied class of reactions for which a potential energy–reaction coordinate diagram of the type shown in Figure 1 may be written is acyl-transfer reactions which are generally thought to proceed through tetrahedral intermediates.[3] Unlike the reactions of aldehydes, ketones, and their derivatives in which the tetrahedral intermediate is frequently detectable,[4] in the reactions of derivatives of carboxylic acids it usually is not. At this oxidation level, the evidence for the incursion of a tetrahedral intermediate is therefore normally indirect, based on, for example, experiments which demonstrate the exchange of the oxygen of the carbonyl group with that of water when this is the solvent[5] and on experiments which demonstrate a change in the rate-determining step, and hence the incursion of an intermediate.[6]

The tetrahedral intermediate which results from the attack of the nucleophile Y⁻ on the carboxylic acid derivative 1 is, after protonation, 2. The intermediate from the corresponding thione derivative would have an SH group instead of an OH group. The groups X

Brian Capon obtained his Ph.D. in physical organic chemistry at the University of Southampton. He subsequently worked in the Semiconductor Materials Group at the GEC Research Laboratories, Wembley, England, at Birkbeck College, University of London, as a Lecturer in physical chemistry, and at the University of Leicester as a Lecturer in organic chemistry. In 1968 he moved to the University of Glasgow where he is now Titular Professor in organic chemistry.

Ashim Kumar Ghosh obtained his B.Sc., M.Sc., and Ph.D. at the University of Calcutta. He subsequently worked as a postdoctoral research fellow at the University of Glasgow and now holds a similar position at the University of Western Ontario.

Duncan McL. A. Grieve obtained his B.A. at the University of Stirling and Ph.D. at the University of Glasgow. He subsequently worked as a postdoctoral research fellow at ETH, Zürich, and again at the University of Glasgow. He is now a Senior Research Scientist at Minnesota 3M Research Ltd., Harlow, Essex, England.

(1) Cf. K. Müller, *Angew. Chem., Int. Ed. Engl.*, **19**, 1 (1980).
(2) B. Capon, D. S. Rycroft, and T. W. Watson, *J. Chem. Soc., Chem. Commun.*, 724 (1979); B. Capon, D. S. Rycroft, T. W. Watson, and C. Zucco, *J. Am. Chem. Soc.*, **103**, 1761 (1981).
(3) Cf. M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley-Interscience, New York, 1971, p 108; W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, 1968, pp 465, 526; T. C. Bruice and S. J. Benkovic, "Bio-Organic Mechanisms", Benjamin, New York, 1966, Vol. 1; S. L. Johnson, *Adv. Phys. Org. Chem.*, **5**, 237 (1967); A. J. Kirby, *Compr. Chem. Kinet.*, **10**, 104 (1972).
(4) Cf. W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959); *Prog. Phys. Org. Chem.*, **2**, 63 (1964); M. Cocivera, C. A. Fyfe, A. Effio, S. P. Vaish, and H. E. Chen, *J. Am. Chem. Soc.*, **98**, 1573 (1976); M. Cocivera and A. Effio, *J. Chem. Soc., Chem. Commun.*, 393 (1976); M. Cocivera, A. Effio, H. E. Chen, and S. Vaish, *J. Am. Chem. Soc.*, **98**, 7362 (1976).
(5) M. L. Bender, *J. Am. Chem. Soc.*, **73**, 1626 (1951).
(6) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **86**, 5616 (1964).
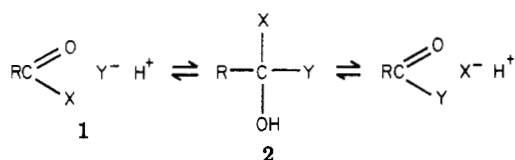
and Y are usually groups such as OR, OAr, NR_2, or Cl which are conjugated with the carbonyl group in **1**. This means that addition to the carbonyl group of **1** is thermodynamically less favored than addition to the corresponding aldehyde or ketone.[7,8]

Although the tetrahedral intermediates **2** are usually transient intermediates, many compounds of this general structure are known. These stable species usually possess at least one of the following four structural features: (i) a bicyclic or polycyclic structure; (ii) a strong electron-withdrawing group, e.g., CF_3, attached to the pro-acyl carbon; (iii) a group, X, for which conjugation with the carbonyl group of the precursor **1** is reduced; (iv) groups X and Y attached to the central carbon by sulfur atoms.

Tetrodotoxin (**3**) is an example of a tetrahedral intermediate with a polycyclic structure.[9] It has an
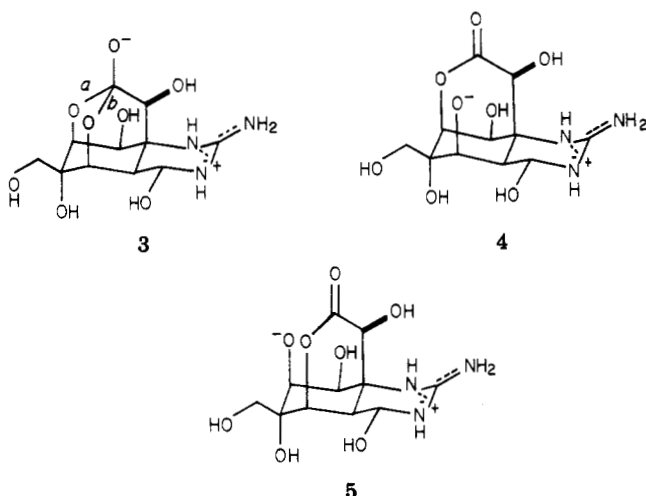
ionized hemi ortho ester group built into an adamantane-like structure. It is also interesting that this structure is, according to Deslongchamps' stereoelectronic theory,[10] favorable for breakdown since both the bonds labeled a and b are antiperiplanar to lone-pair orbitals on the two oxygen atoms not involved in the bond. Presumably the rigid structure makes the hemi ortho ester structure **3** thermodynamically more stable than the alternative structures **4** and **5** that would be formed on its breakdown, since recyclization of the latter would be entropically very favorable.

Stable tetrahedral intermediates with an electron-withdrawing group attached to the pro-acyl carbon are **6**,[11-13] **7**,[14] **8**,[15] and **9**.[16] Guthrie has estimated[17] that the
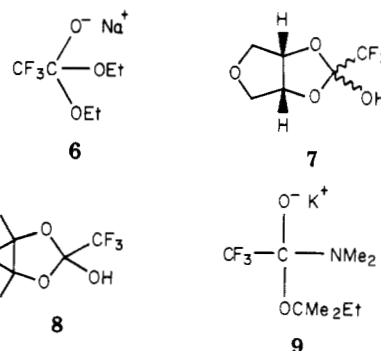
free energy of formation of tetrahedral intermediate **2** from a precursor **1** is 4 to 8 kcal mol^{-1} more favorable when R = CF_3 than when R = H.

Examples of a compound of the type **2** in which the conjugation between X and the carbonyl group of the precursor is reduced are **10**[18] and **11**.[19] In ergotamine (**10**), N_4 is conjugated to a carbonyl group and hence the new carbonyl group that would be formed on breaking the C_{12}–O_1 bond would be less strongly conjugated with N_4 than in a normal amide. This type of ring–chain tautomerism has been investigated by Shemyakin[20] and by Frey[21] and their co-workers (eq 1),
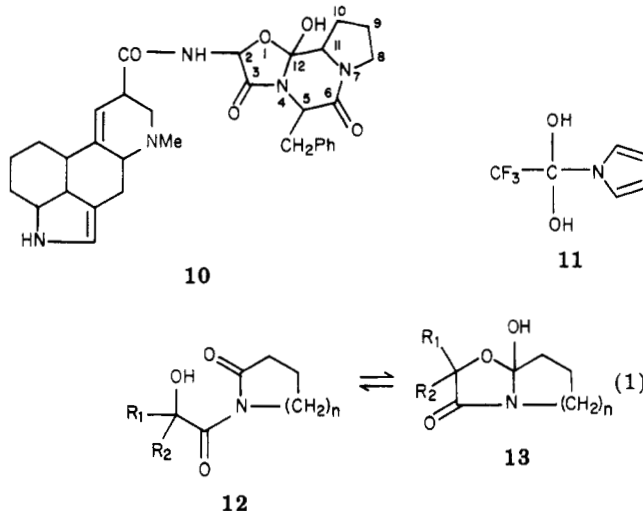
and the corresponding thio compounds have been studied by Rothe and Steinberger.[22] Appreciable amounts of the ring tautomer **13** (i.e., the tetrahedral intermediate) are present at equilibrium, and the exact proportion depends on R_1, R_2, and n. When, however, the exocyclic carbonyl group of **12** was replaced by a methylene group, the ring form was never detected.[20] In **12** the conjugation of the nitrogen with the carbonyl group in the ring is reduced, and this group becomes more like an aldehyde or ketone carbonyl. Hence, addition to it is easy. When the exocyclic carbonyl is

(7) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, 1968, p 465.

(8) J. Fastrez, *J. Am. Chem. Soc.*, **99**, 7004 (1977).

(9) R. B. Woodward, *Pure Appl. Chem.*, **9**, 49 (1964); R. B. Woodward and J. Z. Gougoutas, *J. Am. Chem. Soc.*, **86**, 5030 (1964); T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron*, **21**, 2059 (1965).

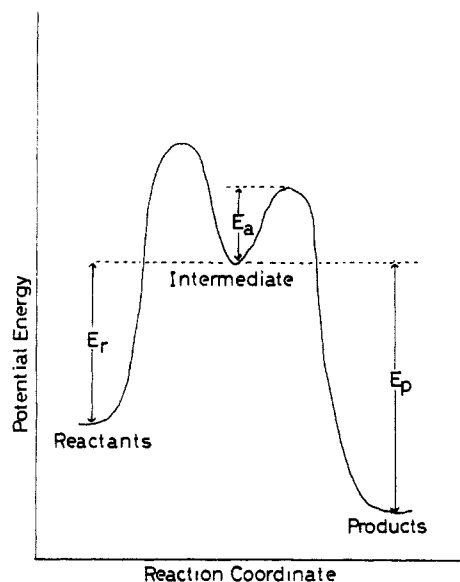(10) P. Deslongchamps, *Tetrahedron*, **31**, 2463 (1975).

(11) F. Swarts, *Bull. Soc. Chim. Belg.*, **35**, 414 (1929).

(12) M. L. Bender, *J. Am. Chem. Soc.*, **75**, 5986 (1953).

(13) A. Moffat and H. Hunt, *J. Am. Chem. Soc.*, **81**, 2082 (1959).

(14) P. Bladon and G. C. Forrest, *Chem. Commun.*, 481 (1966).

(15) J. Hine, D. Ricard, and R. Perz, *J. Org. Chem.*, **38**, 110 (1973).

(16) G. Fraenkel and D. Watson, *J. Am. Chem. Soc.*, **97**, 231 (1975).

(17) J. P. Guthrie, *Can. J. Chem.*, **54**, 202 (1976).

(18) A. Stoll, A. Hofmann, and T. Petrzilka, *Helv. Chim. Acta*, **34**, 1544 (1951).

(19) A. Cipiciani, P. Linda, and G. Savelli, *J. Chem. Soc., Chem. Commun.*, 857 (1977).

(20) M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, Y. N. Sheinker, and L. B. Senyavina, *Tetrahedron Lett.*, 701 (1962); V. K. Antonov, A. M. Shkrob, and M. M. Shemyakin, *ibid.*, 439 (1963); M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, V. I. Shchelokov, and Z. E. Agadzhanyan, *Tetrahedron*, **21**, 3537 (1965); V. K. Antonov, A. M. Shkrob, and M. M. Shemyakin, *Zh. Obshch. Khim.*, **35**, 1380 (1965); *J. Gen. Chem. USSR*, **35**, 1385 (1965).

(21) R. G. Griot and A. J. Frey, *Tetrahedron*, **19**, 1661 (1963).

(22) M. Rothe and R. Steinberger, *Angew. Chem., Int. Ed. Engl.*, **7**, 884 (1968); *Tetrahedron Lett.*, 649, 2467 (1970).

Figure 1. Plot of potential energy vs. reaction coordinate for a reaction which passes through an unstable intermediate.

changed to a methylene group, the endocyclic carbonyl becomes a true amide carbonyl again, and addition becomes difficult. It has been estimated that the "free energy associated with the interruption of conjugation between the carbonyl function . . . and the lone pair of the NR_2 group" is 18–19 kcal mole^{-1}.[8] In addition, compound 13 has a polycyclic structure which is also favorable for its formation. In compound 11[19] the nitrogen forms part of the conjugated pyrrole ring and hence is less available for conjugation with the carbonyl group of its precursor.[23]

The more favorable equilibrium constants for the addition of thiols to the carbonyl group of aldehydes and ketones compared to those for the addition of alcohols are well documented,[24] if not fully understood. There appears to be a similar tendency for thiols to add to the carbonyl (or thiocarbonyl) group of esters (or thioesters), and several tetrahedral intermediates with two or more sulfur atoms attached to the central carbon atom are known, e.g., 14,[25] 15,[26] and 16.[27]
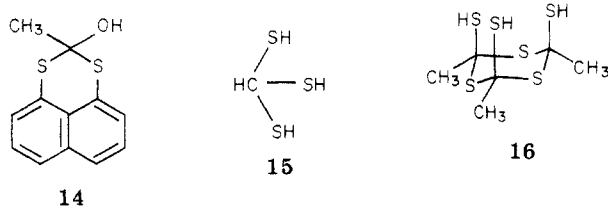
Before our investigations started, two kinetic investigations had been reported on the decomposition of tetrahedral intermediates, 17[28] and 20.[29] Both these

(23) Cf. F. M. Menger and J. A. Donohue, *J. Am. Chem. Soc.*, **95**, 432 (1973).

(24) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 104 (1964); G. E. Lienhard and W. P. Jencks, *J. Am. Chem. Soc.*, **88**, 3982 (1966); M. S. Kanchuger and L. D. Byers, *ibid.*, **101**, 3005 (1979).

(25) M. Takagi, R. Ishihara, and T. Matsudu, *Bull. Chem. Soc. Jpn.*, **50**, 2193 (1977).

(26) K. Olsson, L. Adolfsson, and R. Andersson, *Chem. Scripta*, **10**, 122 (1976).

(27) G. Levesque, A. Mahjoub, and A. Thuillier, *Tetrahedron Lett.*, 3847 (1978); see also F. Khouri and M. K. Kaloustian, *J. Am. Chem. Soc.*, **101**, 2249 (1979).

(28) G. A. Rogers and T. C. Bruice, *J. Am. Chem. Soc.*, **95**, 4452 (1973); **96**, 2473, 2481 (1974).

compounds have bicyclic structures, and the acyl compounds from which they are derived have a group attached to the carbonyl group with a reduced conjugating ability. Compound 17 undergoes decomposition to 19,
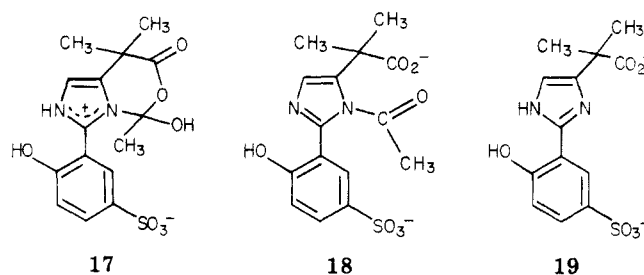
and the kinetics were interpreted in terms of a scheme in which the tetrahedral intermediate 17 and its conjugate bases are in equilibrium with the acylimidazole 18 and its conjugate bases. The measured rate constants are therefore complex constants which depend on the equilibrium constants for these equilibria, which are unknown, as well as the rate constants for the decomposition of 18 and its conjugate base. Hence the rate constant for the breakdown of 17 could not be evaluated.[28] The decomposition of 20 proceeds directly to 21, and at 25 °C the rate constant for this process
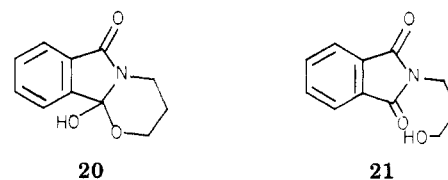

follows the rate law shown in eq 2.

$$k_0 \ (\text{s}^{-1}) = 1.8 + 10.6 a_{H^+} + (6.2 \times 10^9) a_{HO^-} \quad (2)$$

The reaction was general base but not general acid catalyzed, and the general–base catalysis was interpreted as a general acid catalyzed breakdown of the monoanion of 20.[29]

Simple Tetrahedral Intermediates

From this short review it can be seen that a large number of compounds with the general structure 2 are known but that these generally have some special feature which increases their stability relative to that of the acyl precursor. We define simple tetrahedral intermediates by analogy to Hart's definition of a simple enol[30] to be a tetrahedral intermediate at the oxidation level of a carboxylic acid which has none of the above listed special types of functionality. We became interested some years ago to find if we could generate simple tetrahedral intermediates with structures closer to those usually postulated in the reactions of simple esters and amides than the more complex structures previously studied. For example, could acyclic compounds such as 22–25 be generated and observed
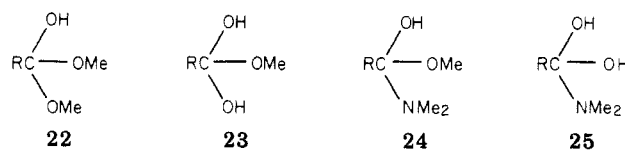

spectroscopically? As explained in the opening para-

(29) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 489 (1974).

(30) H. Hart, *Chem. Rev.*, **79**, 515 (1979).

graph of this Account, in order to do so it would be necessary to approach them from a direction on the potential energy surface other than the reaction coordinate for the corresponding acyl transfer reaction. The precursor to use was suggested to us by some experiments that we had carried out previously on the detection of hemiacetals[31] and by some calculations carried out by Guthrie.[32] We had observed that the hydrolysis of benzaldehyde methyl phenyl acetal (27) was
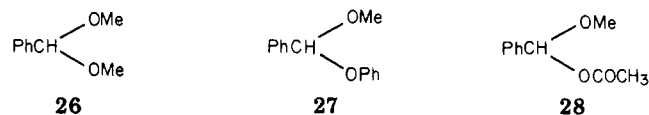
general acid catalyzed, in contrast to that of benzaldehyde dimethyl acetal (26), which is specific acid catalyzed, and wondered what would be the effect of replacing the phenoxy group by a better leaving group still, acetoxy, as in 28. We studied the hydrolysis of 28 by following the formation of benzaldehyde spectrophotometrically and concluded that the rate-determining step was the decomposition of the hemiacetal (see eq 3). The basis for this was that the rate of

PhCHO (3)

$$R = CH_3, CH_2Cl$$
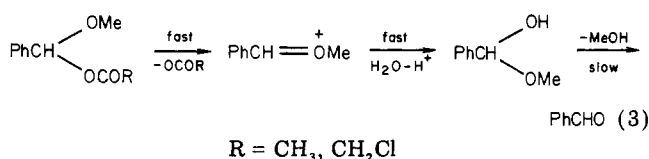
formation of benzaldehyde was the same within experimental error whether the leaving group was acetate or chloroacetate and that the reaction was general base as well as general acid catalyzed. This was confirmed by following the reaction by proton NMR spectroscopy when the buildup and decomposition of the hemiacetal could be seen. We therefore wondered if it would be possible to extend this experiment to the next highest oxidation level, i.e., that of a carboxylic acid as in eq 4. Compound 29 would, of course, be the tetrahedral
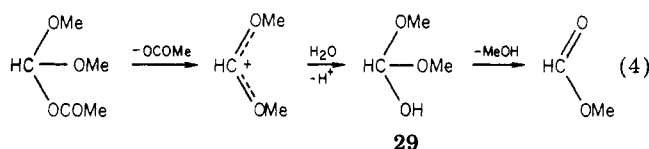
intermediate that would be expected in the methanolysis of methyl formate. That it might be possible to detect 29 was indicated by the calculations of Guthrie on the free energies of the species involved in the hydrolysis of methyl formate.[32] Using these calculations, we constructed the pH–rate profile for the decomposition of methyl hemiorthoformate (30) at 25 °C, and
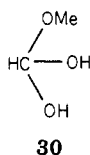
at pH 4 the estimated rate constant is only 10^{-1} s^{-1}. Clearly there would never be any possibility of detecting methyl hemiorthoformate as an intermediate in the hydrolysis of methyl formate, but if it could be gener-

(31) B. Capon, K. Nimmo, and G. P. Reid, *J. Chem. Soc., Chem. Commun.*, 871 (1976).
(32) J. P. Guthrie, *J. Am. Chem. Soc.*, 95, 6999 (1973).

Scheme I^a
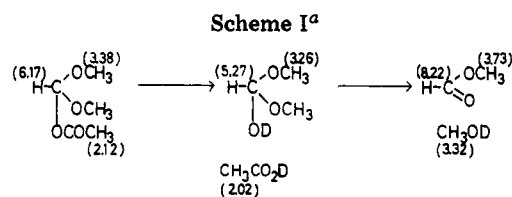
^{a} The figures in parentheses are δ values.

ated from a high energy precursor, it should be sufficiently stable to be detected by use of a flow method at 25 °C or without the use of this at low temperatures. The intermediate that we were hoping to detect was dimethyl hemiorthoformate (29), which has two methoxyl groups and one hydroxyl group bonded to the central carbon, whereas 30 has two hydroxyls and one methoxyl. However, it was not thought that this difference would have a large effect on their relative rates of breakdown in neutral or acidic solutions. It is clearly important to have one hydroxyl group which, through proton loss, can form the carbonyl group (cf. ref 29), but at low pHs it seems unlikely that removal of the proton from the second hydroxyl group of 30 would provide much additional driving force for its decomposition.

After trying a large number of conditions unsuccessfully, we found that in a mixture of [^{2}H$_6$]acetone (95–85 volumes) and deuterium oxide (5–15 volumes) it was possible to detect hemiorthoformate in the hydrolysis of acetoxydimethoxymethane by proton NMR spectroscopy, as indicated in Scheme I.[33] The decomposition of acetoxydimethoxymethane generates acetic acid; hence the rate constant of the decomposition of the dimethyl hemiorthoformate measured after the disappearance of the acetoxydimethoxymethane is for a solution which contains a concentration of acetic acid equivalent to that of the starting material (i.e., 0.15 M). It is therefore probably a composite constant and contains terms for spontaneous and acid catalyzed hydrolyses which we have not separated. Its value in 9:1 (v/v) [^{2}H$_6$]acetone–deuterium oxide at –35 °C, 3.5 × 10^{-4} s^{-1}, should be compared with the value (10^{-1} s^{-1}) for the rate constant at the minimum of the pH–rate profile based on Guthrie's calculations for the decomposition of methyl hemiorthoformate at 25 °C in water. Although it is impossible to make an exact extrapolation, the two figures do not appear to be inconsistent with one another.[33]

We then set up a program of work to make compounds 31–36 where R = CH$_3$ or ClCH$_2$. The purpose
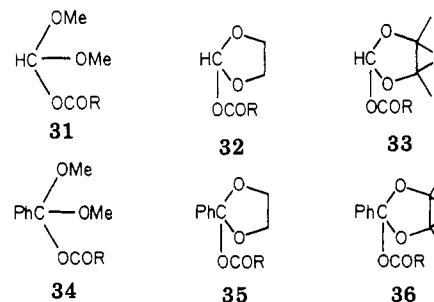
of making the chloroacetates was to give a greater ratio for the rate constants for formation to decomposition of the tetrahedral intermediate and hence make it de-

(33) B. Capon, J. H. Gall, and D. McL. A. Grieve, *J. Chem. Soc., Chem. Commun.*, 1034 (1976); B. Capon and D. McL. Grieve, *J. Chem. Soc., Perkin Trans. 2*, 300 (1980).

Scheme II
Changes in (a) the ^{1}H and (b) the ^{13}C NMR Spectrum of
2-Acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan on hydrolysis
in CD_3COCD_3-D_2O (9:1 v/v)^a

(a)

(b)
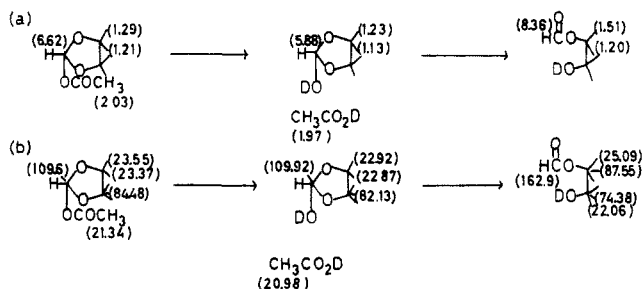
^{a} *The figures in parentheses are δ values.*

tectable over a wider range of conditions. The relative rates of hydrolysis of **31, 32,** and **33** (R = CH_3) are ca. 3:1:6 and of the decomposition of the resulting tetrahedral intermediates **37, 38,** and **39** are ca. 1:0.3:0.03.

37　　　　**38**　　　　**39**
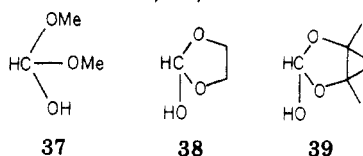
This means that **39** is more easy to detect than **37** or **38**. The changes in the ^{1}H and ^{13}C NMR spectra on decomposition of **33** are given in Scheme II.

The purpose of making compounds **34–36** was to make it easier to study the decomposition of the tetrahedral intermediate by UV spectroscopy. So far, however, we have been unable to prepare them. However, McClelland and Kresge and their co-workers have succeeded in generating the intermediates that would be formed from **34–36** from other precursors.[34]

One of the problems of the precursors that we have described up to now is that they generate 1 molar equiv of acid with the tetrahedral intermediate, and this can make control of the pH of the reaction solutions difficult. We therefore sought a precursor without this disadvantage and tried ketene acetals. These should yield tetrahedral intermediates on addition of water, and the reported rate constants for the H_3O^+-catalyzed reaction $(10^6–10^7 \text{ M}^{-1} \text{ s}^{-1})$[35] suggested that this reaction should be fast enough for the intermediate to be detected in favorable cases. This proved to be so, and 2-hydroxy- (or deuterioxy-) 2,4,4,5,5-pentamethyl-1,3-dioxolane and 2-hydroxy- (or deuterioxy-) 2-methyl-1,3-dioxolane were detected by ^{1}H and ^{13}C NMR spectroscopy[36] in the hydration of 2-methylene-4,4,5,5-tetramethyl-1,3-dioxolane and 2-methylene-1,3-dioxolane. The kinetics of the first of these reactions and the breakdown of the resulting hemi ortho ester (eq 5) were studied by UV spectroscopy. At pHs above 6 only the disappearance of the ketene acetal could be observed, but at pHs below 6 the second step, the breakdown of the hemi ortho ester (**40**), could be fol-

(34) M. Ahmad, R. G. Bergstrom, M. J. Cashen, A. J. Kresge, R. A. McClelland, and M. F. Powell, *J. Am. Chem. Soc.*, **99**, 4827 (1977); M. Ahmad, R. G. Bergstrom, M. J. Cashen, Y. Chiang, A. J. Kresge, R. A. McClelland, and M. F. Powell, *ibid.*, **101**, 2669 (1979); R. A. McClelland and R. Somani, *J. Chem. Soc., Chem. Commun.*, **407** (1979); R. A. McClelland and M. Ahmad, *J. Org. Chem.*, **44**, 1855 (1979).
(35) A. Kankaanperä and H. Tuominen, *Suom. Kemistil. B*, **40**, 271 (1967); A. Kankaanperä and R. Aaltonen, *Acta Chem. Scand.*, **26**, 1698 (1972).
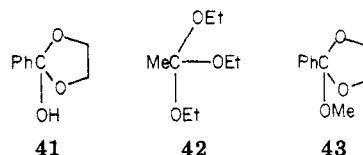(36) B. Capon and A. K. Ghosh, *J. Am. Chem. Soc.*, **103**, 1765 (1981).

$$(5)$$

40
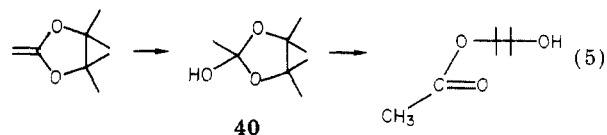
lowed.[36] This reaction was studied in the absence of buffers, and the variation of k_0 with pH follows eq 6.

$$k_0 \text{ (s}^{-1}) = 3.01 \times 10^{-2} + 77.8a_{H^+} + (1.6 \times 10^7)a_{HO^-} \tag{6}$$

It is interesting to compare these results with those for the breakdown of **20**, eq 2, reported by Gravitz and Jencks[29] and those for the breakdown of **41** reported by

41　　　　**42**　　　　**43**

Kresge, McClelland, and their co-workers, eq 7.[34] The

$$k_0 \text{ (s}^{-1}) = 1.5 + 300a_{H^+} + (6.0 \times 10^{10})a_{HO^-} \tag{7}$$

hydronium ion catalyzed reactions of these species appear to be similar to the hydrolysis of an ortho ester, and an OH group does not appear to have a large rate-enhancing effect above that of an O-alkyl group. Thus $k_{D_3O^+}/k_{H_3O^+}$ for the breakdown of **40** is 1.54, which is similar to that for the hydrolysis of triethyl orthoacetate (**42**), 1.84.[37] Also, the rate constant for the hydronium ion catalyzed hydrolysis of **43** when fission of the exocyclic C–O bond is rate limiting is 16 times greater than that for breakdown of **41** with fission of the endocyclic C–O bond,[34] and the hydrolysis of triethyl orthoacetate is 340 times faster than breakdown of **40**. Unfortunately, a more exact comparison is not possible at present. The relatively low rate for the hydronium ion catalyzed breakdown (**20**) is another indication of the weak electron-releasing ability of a nitrogen which is already conjugated to a carbonyl group.

The spontaneous or water-catalyzed breakdown of **20** was considered to involve a reversible ionization followed by hydronium ion catalyzed breakdown of the monoanion (eq 8).[29] When a reasonable estimate for

$$TH + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} T^- + H_3O^+ \xrightarrow{k_2} \text{product} \tag{8}$$
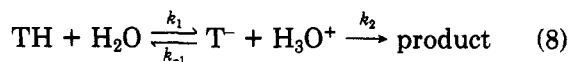
the pK_a of **20** of 7.5 was used, a value of $5.9 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ was calculated for k_2, i.e., well within the diffusion-controlled limit. It was, however, suggested that for "a more ordinary tetrahedral intermediate" the value of k_2 would be larger and that "the breakdown would become diffusion controlled".[29] This appears to be what is happening with **40** and **41**, as a similar analysis yields values for k_2 of $3.01 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ and $2.3 \times 10^{11} \text{ M}^{-1}$ s^{-1}.[36] The rate-limiting step in these reactions may therefore be k_1 (eq 8), and the H_3O^+-catalyzed breakdown of T^- occurs in the encounter complex before diffusion apart. Interestingly, estimates of k_1 for **40** and **41** using the estimated pK_as and the assumption that the reverse reaction occurs with a rate constant of $5 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ yields values which are of the same order of magnitude as the experimental values of k_{H_2O} whereas

(37) C. A. Bunton and J. D. Reinheimer, *J. Phys. Chem.*, **74**, 4457 (1970).

a similar analysis for **20** yields a value almost 10^3 times greater than k_{H_2O}.[36] If this mechanism is correct, the solvent isotope effect on k_{H_2O} should be almost the same as on the K_a because the recombination of T⁻ with H_3O^+ should have almost the same rate constant as for recombination with D_3O^+. For **40**, this is approximately correct since $k_{D_2O}/k_{H_2O} = 0.28$ and the estimated value of $K_a(D_2O)/K_a(H_2O) = 0.22$.[36]

The kinetic results for the hydroxide ion catalyzed breakdown of **20** were interpreted in terms of a unimolecular breakdown of the reversibly formed anion (eq 9 and 10). This leads to an estimate for k_2 (eq 10) of

$$TH + HO^- \rightleftharpoons T^- + H_2O \qquad (9)$$

$$T^- \xrightarrow{k_2} product \qquad (10)$$
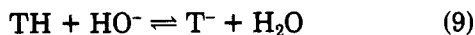
1.6×10^3 M^{-1} s^{-1}.[29] A similar analysis for **40** and **41** yields values of 1.6×10^5 s^{-1} and 9.52×10^7 s^{-1}. These are considerably less than the frequencies of molecular vibrations and are, hence, reasonable values. Therefore, these results can also be accommodated by this mechanism. Again, the relatively slow breakdown of the monoanion of **20** indicates the weakened electron-releasing ability of a nitrogen which is conjugated with a carbonyl group.

Unsuccessful Experiments

In addition to the successful experiments already described for the detection of tetrahedral intermediates at the oxidation level of carboxylic acids, we have carried out a large number of unsuccessful experiments using a variety of possible precursors. We were particularly interested to detect the species that would be the intermediate in an acyl transfer to or from nitrogen, as the calculations of Guthrie indicate that these should be less stable than those for acyl transfer between two oxygens.[32,38] Some of the precursors that we have used are **44–50**. With none of these compounds were we able
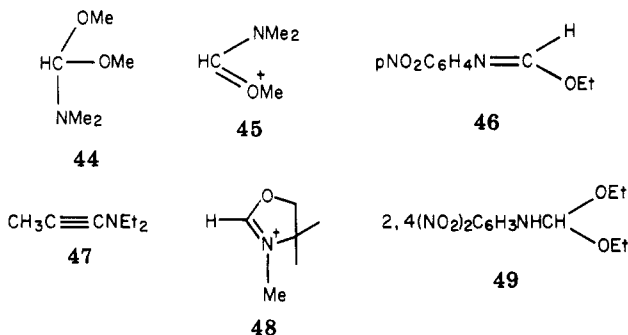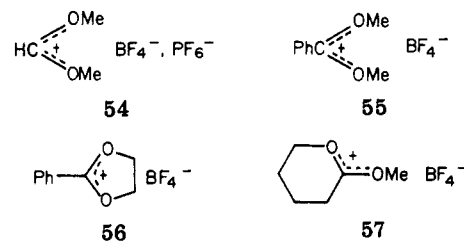

to detect a tetrahedral intermediate (i.e., a hemiorthoamide).[39] Of course this does not mean that the intermediate is not detectable; it may mean that we have not found the right conditions. Compound **47** was of especial interest[40] since the addition of 2 mol of water to the triple bond would generate a tetrahedral intermediate that carries two hydroxyl groups at the pro-acyl carbon. However, it is possible that the enol formed on addition of the first mole of water ketonizes before addition of the second mole can occur, and the failure

to detect the hemi ortho amide may be because of this reaction. The reaction of **50** with hydroxide ion was investigated by Robinson by UV spectroscopy, and an intermediate was detected which was thought to be the tetrahedral intermediate **51**.[41] Working under different
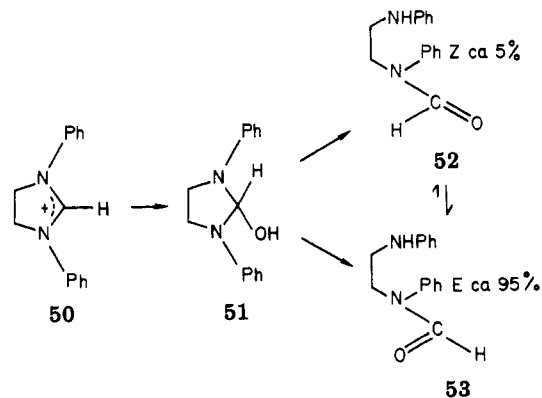
conditions $(CH_3COCH_3-CD_3SOCD_3-H_2O)$, we were unable to detect any **51** in the hydrolysis of **50**. We did, however, detect an intermediate.[42] The product *N*-phenyl-*N*-[(phenylamino)ethyl]formamide exists in *E* and *Z* forms, **53** and **52**. At equilibrium the *E* form predominates to the extent of about 95%. This is similar to that reported for *N*-methyl- and *N*-ethylformamide.[43] Hydrolysis of **48** yields a mixture of **52** and **53** which contains about 30% of **52**. This is subsequently mainly converted into **53**. Thus a part of the **53** in the product is formed via **52**. A similar phenomenon has been reported recently by Halliday and Symons.[44] Our failure to detect **51** does not, of course, invalidate Robinson's conclusions[41] as the two sets of conditions were quite different.

We have also tried to generate tetrahedral intermediates from the carbonium ion salts **54–57**. The cation

54 is the one that we had postulated as an intermediate in the hydrolysis of acetoxydimethoxymethane in which we detected the dimethyl hemiorthoformate as an intermediate. However, we have never detected any tetrahedral intermediates in the hydrolysis of any of these cations (**54–57**). We suspect that there are two reasons for this: (i) the heat of reaction of the ion with water causes local heating and hence the tetrahedral intermediate is generated at a higher temperature than that of the NMR probe; (ii) the tetrahedral intermediate is generated in the presence of a high concentration of a strong acid (e.g., fluoroboronic acid) and this catalyzes its breakdown. We have tried to stop this by carrying out the reaction in the presence of sufficient

(38) J. P. Guthrie, *J. Am. Chem. Soc.*, **96**, 3608 (1974).
(39) Unpublished observations of D. McL. A. Grieve, M. W. Cuthbert, and C. Labbé.
(40) For an investigation of the kinetics of hydrolysis of ynamines, see W. F. Verhelst and W. Drenth, *J. Am. Chem. Soc.*, **96**, 6692 (1974).
(41) D. R. Robinson, *Tetrahedron Lett.*, 5007 (1968); *J. Am. Chem. Soc.*, **92**, 3138 (1970).
(42) M. W. Cuthbert, unpublished observations.
(43) A. J. R. Bourne, D. R. Gillies, and E. W. Randall, *Tetrahedron*, **22**, 1825 (1966).
(44) J. D. Halliday and E. A. Symons, *Can. J. Chem.*, **56**, 1463 (1978).

sodium acetate to neutralize the acid, but we were still unable to detect the tetrahedral intermediate. It is probable that the mixing in our system was inefficient and that there were still local concentrations of strong acid for short times after adding one reagent to the other. Possibly with the use of a flow system the tetrahedral intermediate could be detected.

In conclusion, this work and the complementary investigations of Kresge, McClelland, and their co-workers[34] show that the tetrahedral intermediates of *O,O*-acyl transfer reactions are sufficiently stable to be detected when generated from suitable precursors and for the kinetics of their breakdown to be measured by standard techniques. As more results accumulate, a much better understanding of acyl transfer reactions should emerge.
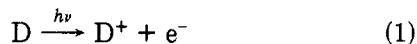
Ionic Photodissociation of Electron Donor–Acceptor Systems in Solution

HIROSHI MASUHARA* and NOBORU MATAGA

*Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan*

Photochemical generation of ionic species in solution has high potential for the investigation and design of various chemical systems, and its importance has increased rapidly over the last 10 years. The primary photoprocesses can be classified in two categories: photoionization and ionic photodissociation. In the former an electron is ejected from the excited state of an absorbing molecule and a cation radical and a solvated electron are produced (eq 1). On the other hand,

$$D \xrightarrow{h\nu} D^+ + e^- \qquad (1)$$

ionic photodissociation is brought about by an interaction between one excited- and one ground-state molecule to produce a free cation from the donor and a free anion from the acceptor (eq 2). Similar disso-

$$D + A \xrightarrow{h\nu} D^* + A \rightarrow D^+ + A^- \qquad (2)$$
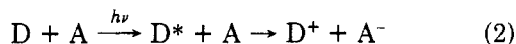
ciation phenomena are also observed by exciting the charge-transfer absorption band of electron donor–acceptor complexes stable in the ground state (eq 3).

$$(DA) \xrightarrow{h\nu} (DA)^* \rightarrow D^+ + A^- \qquad (3)$$
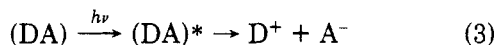
Whereas photoionization requires that the excitation photon have an energy larger than the ionization potential of the molecule in solution, ionic photodissociation can occur by low-energy photons available from sunlight, indicating a wide utility.

Hiroshi Masuhara is Research Associate in Chemistry at Osaka University. He was born in Tokyo and attended Tohoku University, where he received his B.Sc. and M.Sc. degrees. He received the Ph.D. from Osaka University with N. Mataga in 1971, followed by a year as postdoctoral fellow of the Japanese Council for Promotion of Science. Among his research interests are picosecond and nanosecond laser photolysis studies on aromatic hydrocarbons, biological substances, metal ions, and transition-metal complexes as well as laser photophysics and photochemistry of polymer solutions and films.

Noboru Mataga is Professor of Chemistry in the Faculty of Engineering Science at Osaka University. He was born in 1927 in Shimane Prefecture, Japan. He received both his B.Sc. and D.Sc. degrees from the University of Tokyo and was on the faculty at Osaka City University before moving to Osaka University. His research interests include picosecond laser photochemistry, the photochemistry of molecular aggregates, and structures and dynamics of excited EDA systems.

Ionic photodissociation is important in various fields of chemistry. Some bimolecular photochemical reactions, e.g., cycloaddition and hydrogen abstraction, are very sensitive to the surrounding environment and correlated to the formation mechanism of ionic species in polar solvents. Generation of superoxide anion, reduction of metal ions, and polymerization are triggered by photoinduced electron transfer. Artificial photochemical storage of solar energy and water-splitting reactions are important problems in relation to the energy crisis. The design of photosensitive materials, photoconductors, and laser technology are developing rapidly, and some of these processes have ionic photodissociation as an elementary initial step. Furthermore it is well-known that primary photochemical reactions in green plant and bacterial reaction center are photoinduced electron transfer. Many kinds of chemical species of aromatic compounds and their derivatives, dyes, biological substances, polymers, metal ions, and transition-metal complexes are involved in ionic photodissociation under various kinds of conditions.

Although ionic photodissociation is a simple and common process, the following fundamental questions were unanswered when we started our investigation: What is the dissociative state from which ionic species are formed? What are the dissociation mechanisms? Can the dissociation be understood from the redox potentials of component molecules and of environmental effects? These important problems have been clarified by applying physicochemical methods to typical excited electron donor–acceptor systems.

The first indication of electron transfer in the excited state came from fluorescence quenching studies.[1] A direct demonstration in nonpolar solvents was given for the perylene–*N,N*-dimethylaniline system by measuring a broad, structureless emission due to the complex formed in the excited state (eq 4).[2] This complex is

$$D + A \xrightarrow{h\nu} D + A^* \rightarrow (DA)^* \qquad (4)$$
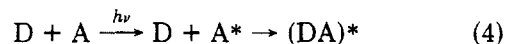
(1) Th. Förster, "Fluoreszenz Organischer Verbindungen", Vandenhoeck und Ruprecht, Göttingen, 1951, p 219.