°C). Dioxane was distilled over $LiAlH_4$ immediately prior to use.

The following three paragraphs describe the synthesis of *p*-octylbenzhydryl chloride. A 250-mL three-necked flask containing 14.7 g (0.11 mol) of $AlCl_3$ and 38 mL of carbon disulfide was fitted with a reflux condenser and dropping funnel. A mixture of 19.0 g (0.10 mol) of *p*-octylbenzene and 15.5 g (0.11 mol) of benzoyl chloride in 38 mL of carbon disulfide was added dropwise to the $AlCl_3$ over 90 min with magnetic stirring followed by boiling under reflux for 12 h. The solvent was removed, the residue poured into 250 mL of ice water with stirring, and the organic layer taken up in two 100-mL portions of benzene. After drying the benzene with $MgSO_4$, we removed the solvent and distilled the residue under reduced pressure to give 26.2 g (89% yield) of *p*-octylbenzophenone with the expected spectral properties.

p-Octylbenzophenone (2.62 g, 0.0089 mol), 1.75 g of NaOH, 1.75 g of zinc dust, and 70 mL of 95% ethanol were placed in a 250-mL round-bottomed flask and refluxed for 3 h with stirring. The reaction mixture was cooled and filtered; the filtrate (combined with an ethanol wash) was poured into 500 mL of ice water containing 25 mL of HCl. A benzene extraction (2 × 100 mL) followed by drying of the benzene layer over $MgSO_4$, removal of the solvent, and distillation of the residue at 0.6 mm gave 2.30 g (87% yield) of *p*-octylbenzhydrol (bp 185–186 °C).

p-Octylbenzhydrol (2.30 g, 0.0078 mol) in 70 mL of benzene was subjected to a slow stream of HCl gas while the solution was magnetically stirred over 3.0 g of $MgSO_4$. The mixture was filtered and the benzene removed from the filtrate with the aid of a rotary evaporator. The residue was then chromatographed on a silica column (2 × 35 cm), using pure benzene as the eluant, to give 2.4 g (98% yield) of *p*-octylbenzhydryl chloride. No hydroxyl or carbonyl was evident in the IR spectrum.

Anal. Calcd for $C_{21}H_{27}Cl$: C, 80.0; H, 8.64. Found. C, 80.40; H, 8.89.

Kinetics. Hydrolysis rates of bis(4-nitrophenyl) carbonate were determined by following the appearance of *p*-nitrophenol at 320 nm, using an Acta II spectrophotometer thermostated at 50.0 ± 0.1 °C and set at the 0–0.1 absorbance range. A 3.00-mL aqueous HTAB solution containing 0.01 N HBr (assayed titrimetically) was equilibrated in the cell chamber for greater than 15 min. Reaction was then initiated by adding 20 μL of a concentrated solution of the carbonate in acetonitrile with the aid of a small stirring rod. Concentrations of substrate in the cuvette were approximately 3×10^{-5} M. We followed the reaction to greater than 80% completion and took infinity values at 10 half-lives. First-order rate constants, calculated in the usual manner, were reproducible to within 3% in most cases. Since the rate changes in Table I are small, each run was carried out 3–5 times and the rate constants averaged.

Solvolysis of *p*-chlorobenzhydryl chloride was carried out in much the same manner by following the decrease in absorbance at 245 nm at 25.0 °C.

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Registry No. Bis(4-nitrophenyl) carbonate, 5070-13-3; *p*-chlorobenzhydryl chloride, 134-83-8; octylbenzene, 2189-60-8; benzoyl chloride, 98-88-4; *p*-octylbenzophenone, 64357-43-3; *p*-octylbenzhydrol, 75812-79-2; *p*-chlorobenzhydryl chloride, 75812-80-5.

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Acetal Hydrolysis: The A1 Mechanism[1]

Steven R. Wann and Maurice M. Kreevoy*

Chemical Dynamics Laboratory, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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The hydrolysis of 5-methyl-7-*exo*-methyl-6,8-dioxabicyclo[3.2.1]octane (1) shows no general acid catalysis, with the caveat that general acid catalysis with a Brønsted $\alpha > 0.7$ would probably have escaped detection; k_H/k_D is 0.43; it is not catalyzed by I^-. The rate constant and isotope effect for the H^+-catalyzed hydrolysis of 1 are similar to those for 2-methyl-2-(2-methypropyl)-1,3-dioxolane (2) even though, in 1, steric inhibition to carbon–oxygen cleavage concerted with proton transfer should lead that step to be rate determining if a concerted mechanism were to be used. In fact, both 1 and 2 appear to hydrolyze by a nonconcerted mechanism. Since they are unexceptional acetals, it appears that the concerted mechanism is limited to cases where the A1 mechanism encounters special difficulties and/or the concerted mechanism is especially favorable.

Prior to the late 1960's, general acid catalysis has not been conclusively demonstrated for the hydrolysis of acetals. Ortho esters, on the other hand, were known to be subject to buffer catalysis for quite some time.[2] Due to the structural similarity of these compounds, a considerable amount of effort went into putting their hydrolyses into the same mechanistic scheme. Interest in the mechanism of catalysis by the enzyme lysozyme[3] also led to a search for structural features that would give rise to general acid catalysis in acetal hydrolysis. Considering the accepted A1 mechanism for acetal hydrolysis (eq 1–3), the likeliest modification leading to buffer catalysis would involve coupling of proton transfer and carbon–oxygen cleavage into a single concerted process.[4,5] In this paper the terms "concerted process" and "concerted mechanism" refer to the mechanism ascribed to ortho ester hydrolysis by Eliason and Kreevoy,[4] possibly modified by the admixture of a little hydrogenic motion to the reaction co-

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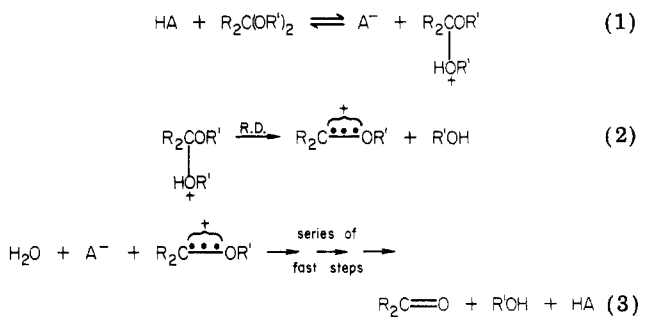
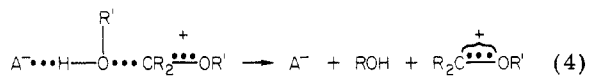


ordinate.[5] The structural features which might encourage such a coupling, and which have been shown to lead to general acid catalysis, are those which facilitate the breaking of the C–O bond and/or low basicity of the oxygen being protonated.[6] Formation of an extraordinarily stable cationic intermediate[7] (A) and relief of strain in

A

forming the cationic intermediate are factors that could facilitate this departure.[8] These same factors would tend to make step 1 rate determining in a nonconcerted process, but the known rapidity of spontaneous proton transfer between oxygens,[9] the magnitude of the solvent hydrogen isotope effect,[4,10] and the linearity of the Brønsted plots[9a] all argue against simple rate-determining proton transfer.

Having accepted a concerted mechanism for the buffer-catalyzed reactions,[4,5,11] it has been tempting to think that it might also apply to acetal hydrolysis for which no buffer catalysis is observable. In this case, the step represented by eq 4, which is the breakdown of the ion pair

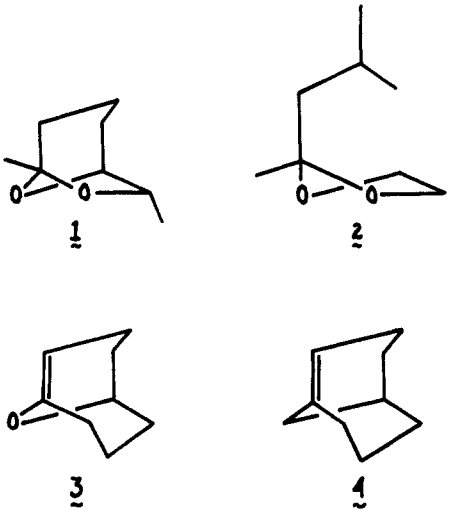


first produced by the C–O cleavage concerted with proton transfer, could be rate determining. That is, it might be slower than the reversion to starting materials or the attack of water on the carbocation. This hypothesis would explain the observation of carbocation-like electronic properties for the transition states of these reactions over a very wide range of reactivity.[12] The conjugate base of the donor acid would still be present, but in a "spectator" role,[13] so that a value close to unity would be expected for α and buffer catalysis might be very hard to observe.

5-Methyl-7-*exo*-methyl-6,8-dioxabicyclo[3.2.1]octane (1) was prepared and its hydrolysis mechanism was examined to test the hypothesis that the concerted mechanism is general. Compound 1 is designed so as to provide some steric inhibition to the resonance stabilization of the carbocation *during its formation.* Neither 1 itself, nor its conjugate acid, nor the fully formed carbocation are badly strained, but the geometry of 1 is seriously imperfect for the transition state of the concerted cleavage. Thus, if the mechanism consists of concerted cleavage and proton transfer, followed by the separation of the ion pair (eq 4), the former should be rate determining in this case, since the latter has, at most, a small free energy of activation. Hence, buffer catalysis with an α well below 1.0 should be observed, even though 1 is an otherwise ordinary acetal.

We believe that the transition state for concerted cleavage would be more vulnerable to steric problems than the transition state for the A1 (stepwise) mechanism, because the latter very closely resembles the carbocation,[12,14] in which the empty p orbital is no longer required to point directly at the leaving oxygen. However the rest of this paper does not rest on this supposition. Even if the transition state for the A1 mechanism *were* also sterically strained, that would not lead to a mechanistic change or the appearance of general acid catalysis.

The cationic intermediate in acetal hydrolysis and the transition state leading to it are both stabilized by delocalization of unshared electrons from the neighboring oxygen to the empty p orbital of the carbon from which R'OH is leaving. Assuming that the seven-membered ring is cleaved first in 1, the unshared pair of electrons makes a dihedral angle of ~30° with the incipient empty orbital, which is replacing the leaving group. A similar situation exists in the seven-membered ring if the six-membered ring should be cleaved first. This sort of stereoelectronic inhibition of acetal hydrolysis has been demonstrated by Deslongchamps,[15] and by Kirby and Martin.[16] Its importance is further illustrated by the observation that 3 is hydrated more slowly than 4, by a factor of 10^2, even



though vinyl ether hydration is faster than that of analogous simple olefins by 5 and 8 powers of 10 in other examples.[17] The heat of hydrogenation of cyclohexene is lower by 1–2 kcal/mol than that of open-chain analogues and cyclopentene.[18] This effect would certainly be exaggerated in 1 because of the bicyclic structure, which would be maintained in the concerted transition state, and would tend to freeze the nonplanar, chair conformation of the six-membered ring. Similar steric inhibition of resonance appears to occur in the hydrolysis of triethyl

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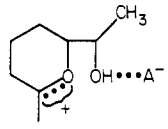
orthobenzoate, but it is relieved when the alkyl groups are tied back in 2-phenyl-2-ethoxy-1,3-dioxolane.[19] Even the introduction of a single trigonal center is inhibited in a six-membered ring. The equilibrium constant for the addition of HCN to the carbonyl group is larger by a factor of 50–120 than that for addition to cyclopentanone or unbranched open-chain carbonyl compounds.[20] This effect again would be much exaggerated because the chair structure is prevented from flattening in 1 and in its concerted cleavage transition state. The reaction shown in eq 4 cannot have an activation energy of more than a few kilocalories mol^{-1} because it involves no covalent changes. The foregoing discussion suggests that the structure of 1 adds at least 3 and probably 4–5 kcal mol^{-1} to the barrier for concerted cleavage or concerted reformation of 1 from **5**. This addition would, surely, make



5

the concerted cleavage rate determining, in competition with the facile reaction shown in eq 4, if the concerted cleavage were part of the required mechanism at all.

Compound **2**, 2-methyl-2-(2-methylpropyl)-1,3-dioxolane, which is drawn so as to show its structural similarity to **1**, was examined for comparison, and solvent hydrogen isotope effects were obtained for both.

Experimental Section

Materials. Bis(cyanoethyl)ethylammonium chloride was prepared by Oh[21] and used without further purification. Solutions of this acid and glycine hydrochloride were standardized by the method of Volhard.[22] Silver nitrate used in this method was generously provided by American Chemical Enterprises, Inc. Buffered solutions were prepared by half-neutralization of solutions of the acids. For buffered solutions in D_2O, concentrated protio acids were dissolved in D_2O and half-neutralized with standardized sodium hydroxide in D_2O. Dilute solutions of DCl were made from 38% DCl in D_2O.

5-Methyl-7-*exo*-methyl-6,8-dioxabicyclo[3.2.1]octane (**1**) was prepared by the method of Kossanyi et al.[23] in an overall yield of 12%, bp 54–56 °C (22 mm) [lit.[24] bp 48 °C (15 mm)]. The compound had spectroscopic properties identical with those described.[24]

2-Methyl-2-(2-methylpropyl)-1,3-dioxolane (**2**) was prepared by modification of a procedure by Roelofson and Wils.[25] Molecular sieves were used to remove the water in place of azeotropic distillation with benzene. Fractional distillation afforded a 65% yield of **2**, bp 65 °C (23 mm) [lit.[26] bp 48 °C (10 mm)]. No attempt was made to maximize the yield of either **1** or **2**.

All other materials were commercial products of the highest available purity and were used as received.

Kinetic Methods. The hydrolysis reaction was monitored by following the growth of absorbance at 270 nm. A hybrid spectrophotometer was employed, with the optics of a Beckman DU and Gilford source and electronics. The temperature in the cells was maintained at 25.0 ± 0.1 °C with a jacketed-cell compartment, through which water was passed from a constant-temperature bath. The temperature was measured in a dummy cell from time to time. Sufficient $NaNO_3$, $NaClO_4$, or $(CH_3)_4NCl$ was added to each reaction mixture to give an ionic strength of about 0.11 M. With mineral acid or carboxylic acid buffers, $NaNO_3$ or $NaClO_4$ was used as the unreactive salt. When the trialkylammonium ion was the acid the salt was $(CH_3)_4NCl$. The reaction was generally followed until the absorbance, A, reached a constant value (on the order of 10 half-lives). For reactions that were slow enough to make this difficult, a computer program[27] was available that would determine both A_∞ and the rate constant from the data covering at least four half-lives. This program works by minimizing the sum of the squares of the differences between observed absorbances and those calculated from eq 5, using trial

$$A_t = A_\infty(1 - e^{-kt}) + A_0e^{-kt} \tag{5}$$

values of k and A_∞, where k is a pseudo-first-order rate constant and the A's are absorbances. When a reliable measured value of A_∞ was available, k was obtained graphically.[28] Plots of log $(A_\infty - A_t)$ as a function of time were subjectively linear. For five separate reactions both methods were used, giving an average 2% discrepancy between k values obtained by the two methods. Solvent hydrogen isotope effects were always determined from reactions carried out side by side in solutions of comparable acidity. The adventitious H content of the D_2O solutions was determined spectrophotometrically by the method of Kreevoy and Straub.[29] Rate constants for D_2O were obtained by a short extrapolation, using eq 6.[30] The mole fractionation of deuterium

$$\frac{k_{H_2O}}{k_x} = \frac{(1 - x) + xl^3(k_{H_2O}/k_{D_2O})}{(1 - x + xl^3)^3} \tag{6}$$

is x and l is the fractionation factor for hydronium ion, taken as 0.69.[31]

For evaluation of the H^+ concentration for buffered solutions, activity coefficients were estimated by means of eq 7.[32] A and

$$\log \gamma_\pm = \frac{-A(Z)^2\mu^{1/2}}{1 + Bd\mu^{1/2}} \tag{7}$$

B are constants with the values 0.5115 $mol^{-1/2}\ l^{1/2}\ K^{3/2}$ and 0.3291 $\times 10^8$ $mol^{-1/2}\ l^{1/2}\ K^{1/2}$, respectively. The ionic strength is μ, and d is the mean diameter of the hydrated ions, taken as 4.00 Å.[33] The H^+ concentration was then determined by using 8–10.

$$\frac{K}{\gamma_\pm^2} = \frac{(H^+)(A^-)}{(HA)} \tag{8}$$

$$(A^-) = (A^-)_0 + (H^+) \tag{9}$$

$$(HA) = (HA)_0 - (H^+) \tag{10}$$

Results

Rate constants determined in a variety of buffered and unbuffered solutions are shown in Tables I–III. They give no indication of general acid catalysis for **1** or **2**. The hydronium ion catalytic coefficient, k_H, for **1**, obtained by dividing k by (H^+), is the same for buffered and unbuffered solutions. It shows no systematic variation with molecular

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Table I. Hydrolysis of 1 by Acetic Acid Buffers

10^2(HAc), M	10^3k, s^{-1}	$k/(H^+)$, M^{-1} s^{-1} [a]
11.4	1.61 [b]	5.15 [b]
5.7	1.71	5.48
1.14	1.83	5.88
0.57	1.55	4.97

[a] The acetic acid–sodium acetate ratio was constant in these experiments. Using 4.76 for the pK of acetic acid,[34] (H^+) is 3.12×10^{-5} in all these experiments. [b] Average of five determinations.

Table II. Hydrolysis of 1 in Various Buffered and Unbuffered Solutions [a]

acid	10^3(HA), M	$k/(H^+)$, M^{-1} s^{-1} [b]	$k/(D^+)$, M^{-1} s^{-1} [b]
HCOOH	1.50–172	5.42 ± 0.13	14.7 ± 0.8 [c]
CH_3COOH	5.7–114.0	5.26 ± 0.10 [d]	11.2 ± 0.5 [e]
$(R)_2R'NH^+$ [f]	10.1–109.3	5.38 ± 0.08 [g]	12.2 ± 0.7 [h]
H_3O^+ [i]	0.07–1.05	5.37 ± 0.28	
H_3O^+	0.07–0.37	5.26 ± 0.04	
H_3O^+ [j]	0.03–2.44	5.28 ± 0.17	11.02 ± 0.10 [k]

[a] The ionic strength was 0.11 M except as noted. [b] The uncertainty cited is the probable error. [c] Using 4.21 for the pK_{DA} of HCOOD.[35] [d] Using 4.76 for the pK_{HA} of CH_3COOH.[34] [e] Using 5.27 for the pK_{DA} of CH_3COOD.[36] [f] R = CH_2CH_2CN; R′ = CH_3CH_2. [g] Using 4.24 for the pK_{HA} of the tertiary ammonium ion.[21] [h] Using 4.80 for the pK_{DA} of the deuterated tertiary ammonium ion.[21] [i] The reaction mixture contained 0.11 M NaI. [j] No added salt. [k] DCl, no added salt.

Table III. Hydrolysis of 2 in Various Buffered and Unbuffered Solutions [a]

acid	10^3(HA), M	$k/(H^+)$, M^{-1} s^{-1} [b]	$k/(D^+)$, M^{-1} s^{-1} [b]
$ClCH_2COOH$	10.9–118.0	0.632 ± 0.020 [c]	1.77 ± 0.04 [d]
HCOOH	1.36–13.57	0.673 ± 0.006	1.76 ± 0.13
$GlyH^+$ [e]	0.7–128.4	0.614 ± 0.016	
H_3O^+	0.187–1.87	0.635 ± 0.023	
H_3O^+ [f]	0.35–1.05	0.605 ± 0.006	
H_3O^+ [g]	0.560–8.25	0.629 ± 0.016	1.29 ± 0.04 [h]

[a] The ionic strength was 0.11 M except as noted. [b] The uncertainty cited is the probable error. [c] Using 2.86 as the pK_{HA} of $ClCH_2COOH$; ref 34, p 292. [d] Using 3.33 as the pK_{DA} of $ClCH_2COOD$.[35] [e] Glycine hydrochloride, the pK_H is 2.35; ref 32, p 315. [f] The reaction mixture contained 0.11 M NaI. [g] No added salt. [h] DCl, no added salt.

acid type or concentration. It has an average value of 5.32 M^{-1} s^{-1}, averaging over all acids. The average deviation from the mean is ±0.36 and the probable error of the mean is ±0.06. For compound 2, for which an A1 hydrolysis mechanism may be anticipated,[2] k_H has an average value of 0.63 M^{-1} s^{-1}. The average deviation from the mean is ±0.03 and the probable error of the mean is ±0.01.

High values of α can make general acid catalysis hard to detect. Jensen and Jencks have shown that eq 11 gives

$$\alpha_{min} = \frac{-\log \Delta + pH + \log (HA)}{1.74 + pK} \qquad (11)$$

the value of α above which general acid catalysis becomes undetectable,[37] α_{min}. The minimum detectable fractional contribution to k_{obsd} by general acid catalysis is Δ. When applied to the data for acetic acid catalysis of the hydrolysis of 1, eq 11 gives 0.7 for α_{min} if a 10% contribution is assumed to be detectable and 0.65 if it is assumed that a 20% contribution would have been required. Actually, it may be noted, the average k_H obtained from five experiments at the highest acid concentration is 3% *below* the global average for k_H. Thus, a general acid catalysis with α below 0.65 seems definitely excluded, but general acid catalysis with α above 0.7 would probably have gone undetected. General acid catalysis was not seriously sought for 2, as it is structurally similar to many aliphatic acetals for which only hydronium ion catalysis is observable.[2]

The solvent hydrogen isotope effect (k_H/k_D) for the hydrolysis of 1 is 0.43 with an average deviation from the mean of ±0.03. It is very similar to that for 2: 0.40 with an average deviation from the mean of ±0.06. A combination of random and systematic errors probably make these values uncertain by 0.02–0.04. Both of these solvent isotope effects fall within the accepted limits for an A1 mechanism.[2,31] The results were not altered by varying the charge type and donor atom of the molecular acid, although it has been suggested that they might do so.[38] For neither 1 nor 2 was there any systematic change in k_D over a 20-fold range of D^+ concentrations, although in both cases there are distinct variations from one buffer system to another. In part, these may arise from errors in the published pK's of the deuterio acids.

Finally, if eq 4 were to depict the rate-determining step, one would expect strong, nonbasic nucleophiles to accelerate the reaction, since they would attack the aggregate.[39] In fact addition of up to 0.11 M NaI, in place of inert supporting electrolyte gave no acceleration at all (Table II).

Discussion

As indicated above, the special structural features of 1 would make concerted proton transfer and C–O cleavage particularly difficult and would make that step rate determining if it were a generally required feature of acetal hydrolysis. This would make the hydrolysis of 1 general acid catalyzed, probably with a value of α below 0.7.[4] It would probably lead to a value of k_H/k_D above 0.5 and certainly yield a substantially higher value of k_H/k_D for 1 than for 2. It would probably lead to a smaller value of k_H for 1 than for 2. None of this actually occurs, so we conclude that 1 does not use the concerted mechanism for its hydrolysis. There is a strong presumptive case for the conventional A1 mechanism (eq 1–3) with the protonated acetal as a discrete intermediate. Further, the similarity in rate and isotope effect between 1 and 2 argues that this result has not been imposed by the bicyclic structure but demonstrates the ordinary mechanism for the hydrolysis of aliphatic acetals. This conclusion has been anticipated by others,[5,13] but we believe the present results are particularly unambiguous.

For both 1 and 2 the values of k_H/k_D are a little higher than might have been anticipated for a transition state resembling A.[12] In that case all three of the hydrogens of the original L_3O^+ [40] would be converted to L_2O or R′OL. The fractionation factor of L_3O^+, l, is 0.69,[31] that of L_2O is 1.00 by definition, and that of R′OL is thought to be close to 1.0. Thus a value close to $(0.69)^3$, 0.33, might have been anticipated for k_H/k_D.[31] The higher values actually observed may be due to a failure of transfer isotope effects[41] for the substrate and the transition state to cancel.

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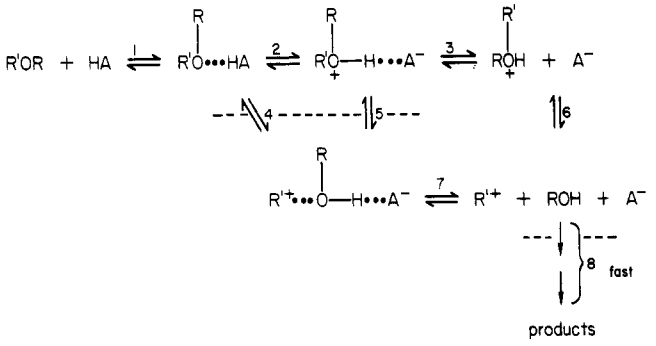
(40) L is used as a symbol for an atom that may be either H or D.

Scheme I



Another conceivable explanation would be that process 8 of Scheme I, the hemiacetal hydrolysis, has become rate determining. This seems unlikely, because, even for cyclic acetals, the first stage is generally considered rate determining.[2] Hemiacetal hydrolyses are general acid catalyzed. Glucose mutarotation, a well-studied example of hemiacetal hydrolysis, has a Brønsted α of 0.3,[42] and its k_H/k_D is 1.4;[43] it also has a measurable "uncatalyzed" reaction, apparently involving only water.[42] Tetramethylglucose has a 1.3 as k_H/k_D.[44] All of these characteristics are quite different from those of the present reactions. Our results do not exclude a minor contribution from step 8 to the overall free energy of activation, and such a contribution would not alter our conclusion that the concerted path, step 4 in Scheme I, is neither required nor used. "Spectator" catalysis is not excluded for either **1** or **2** and may also make a minor perturbation in k_H/k_D.

Scheme I summarizes the mechanisms apparently available for the acid-catalyzed hydrolysis of ortho esters and acetals, allowing for both A1 and concerted mechanisms. Steps 1, 4, 7, and 8 represent the concerted mechanism. Steps 1, 2, 3, 6, and 8 represent the conventional A1 mechanism. Steps 1, 2, 5, 7, and 8 represent the "spectator catalysis" mechanism.[13] This results if carbon–oxygen cleavage is rapid, but nevertheless rate determining, so that there is insufficient time for the conjugate base to diffuse away from the rest of the transition state. Steps 1, 2, and 3 are not considered reasonable rate-determining steps because of the rapidity of spontaneous, bimolecular proton transfer between oxygens.

Owing the very low basicity and the relative ease of carbon–oxygen cleavage for ortho esters and some acetals, a concerted mechanism appears to offer the lowest energy pathway to products. However, for most ordinary acetals this is not the case, and the protonated substrate is a real intermediate. For certain acetals, in which the buildup of R'^+ is particularly rapid, step 8 can also become partially rate limiting.[45,46] The dashed lines are drawn to show steps which will lead to the observation of general acid catalysis if they are rate determining.

Scheme I rationalizes the appearance of general acid catalysis in ortho ester hydrolysis, because K_2 and k_2 would be particularly small for ortho esters. The concerted pathway permits step 2 to be bypassed. In hydrolyses of benzaldehyde acetals,[11] the facility of carbocation formation probably leads to spectator catalysis, although, particularly with *p*-methoxybenzaldehyde the concerted path may be involved.

Registry No. **1**, 56057-15-9; **2**, 2035-08-7.

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