

99-09-2; 4-NO₂C₆H₄NH₂, 100-01-6; HC₆H₄NH₃⁺, 17032-11-0; 3-CH₃C₆H₄NH₃⁺, 18971-81-8; 4-CH₃C₆H₄NH₃⁺, 17112-11-7; 3-NH₂C₆H₄NH₃⁺, 76137-34-3; 4-NH₂C₆H₄NH₃⁺, 19513-42-9; 3-OCH₃C₆H₄NH₃⁺, 20505-55-9; 4-OCH₃C₆H₄NH₃⁺, 28965-97-1; 3-FC₆H₄NH₃⁺, 28966-00-9; 4-FC₆H₄NH₃⁺, 29131-39-3; 3-CF₃C₆H₄NH₃⁺, 76137-35-4; 4-CF₃C₆H₄NH₃⁺, 76137-36-5; 3-CHOC₆H₄NH₃⁺, 76137-37-6; 4-CHOC₆H₄NH₃⁺, 76137-38-7; 3-CNC₆H₄NH₃⁺, 41265-95-6; 4-CNC₆H₄NH₃⁺, 41265-90-1; 3-NO₂C₆H₄NH₃⁺, 18616-84-7; 4-NO₂C₆H₄NH₃⁺, 17126-43-1; 4-N(CH₃)₂C₆H₄NH₃⁺, 55277-36-6; 4-SCH₃C₆H₄NH₃⁺, 33825-42-2; 4-ClC₆H₄NH₃⁺, 37449-65-3; 4-BrC₆H₄NH₃⁺, 40569-40-2; 4-CO₂CH₃C₆H₄NH₃⁺, 76137-39-8; 4-CH₃COC₆H₄NH₃⁺, 17548-88-8; 4-C₆H₅COC₆H₄NH₃⁺, 17548-94-6; 3-N(CH₃)₂C₆H₄NH₃⁺, 71082-06-9; 3-SCH₃C₆H₄NH₃⁺, 33825-41-1; 3-ClC₆H₄NH₃⁺, 53760-42-2; 3-BrC₆H₄NH₃⁺, 19497-30-4; 3-IC₆H₄NH₃⁺, 76137-40-1; 3-

CO₂CH₃C₆H₄NH₃⁺, 76137-41-2; 3-CH₃COC₆H₄NH₃⁺, 17548-86-6; 3-C₆H₅COC₆H₄NH₃⁺, 17548-92-4; *p*-SCH₃C₆H₄NH₃⁺, 76137-42-3; *p*-ClC₆H₄NH₃⁺, 18497-96-6; *p*-BrC₆H₄NH₃⁺, 17374-71-9; *p*-IC₆H₄NH₃⁺, 20505-54-8; *p*-CO₂CH₃C₆H₄NH₃⁺, 76137-43-4; *p*-CH₃COC₆H₄NH₃⁺, 35586-21-1; *m*-SCH₃C₆H₄NH₃⁺, 76137-44-5; *m*-ClC₆H₄NH₃⁺, 18534-21-9; *m*-BrC₆H₄NH₃⁺, 20505-56-0; *m*-IC₆H₄NH₃⁺, 20539-93-9; *m*-CO₂CH₃C₆H₄NH₃⁺, 76137-45-6; *m*-CH₃COC₆H₄NH₃⁺, 76137-46-7; *p*-NH₂C₆H₄NH₃⁺, 72611-47-3; *p*-OCH₃C₆H₄NH₃⁺, 72611-49-5; *p*-CH₃C₆H₄NH₃⁺, 37062-13-8; *p*-FC₆H₄NH₃⁺, 72611-50-8; HC₆H₄NH₃⁺, 27547-14-4; *p*-CF₃C₆H₄NH₃⁺, 72611-52-0; *p*-CNC₆H₄NH₃⁺, 66365-37-5; *p*-NO₂C₆H₄NH₃⁺, 934-70-3; *p*-CHOC₆H₄NH₃⁺, 72611-51-9; *m*-NH₂C₆H₄NH₃⁺, 72611-39-3; *m*-OCH₃C₆H₄NH₃⁺, 72611-41-7; *m*-CH₃C₆H₄NH₃⁺, 37062-12-7; *m*-FC₆H₄NH₃⁺, 72611-42-8; *m*-CF₃C₆H₄NH₃⁺, 72611-46-2; *m*-CNC₆H₄NH₃⁺, 72611-44-0; NO₂C₆H₄NH₃⁺, 72611-43-9; *m*-CHOC₆H₄NH₃⁺, 72611-45-1.

Kinetic Study of the Reversible Formation of Cyclic Hemiacetals from 2-(Hydroxymethyl)benzaldehyde and 2-(β-Hydroxyethyl)benzaldehyde

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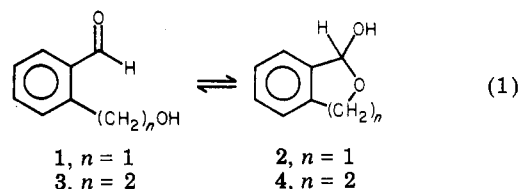
Received July 2, 1980

The title aldehydes **1** and **3** exist in equilibrium with cyclic hemiacetal forms **2** and **4**, respectively, with equilibrium constants in water of 6.7 (**1** ⇌ **2**) and 20 (**3** ⇌ **4**). These equilibria are displaced toward the hemiacetals in strongly basic solutions because of their ionization. Acidity constants have been determined to be 12.29 (**2**) and 12.38 (**4**). The kinetics of the equilibration have been studied in the pH range 1-8 in carboxylic acid and alkylphosphonic acid buffers. The base forms (RCOO⁻ and RPO₃²⁻) produce a common Brønsted line, while the acid forms produce two distinct Brønsted relations, with that for RHPO₃⁻ being displaced about one logarithmic unit above that for RCOOH. It is concluded that the former are not acting as bifunctional catalysts but owe their enhanced reactivity to an electrostatic effect. It is, moreover, suggested that the acid-catalyzed equilibrations are proceeding by way of two competing mechanisms, one involving as an intermediate the protonated hemiacetal and the other the protonated benzaldehyde. Several acetals related to **2** and **4** have also been prepared, and the kinetics and mechanism of their hydrolyses are discussed.

The reversible addition of water and alcohol molecules to aldehydes has been a subject of considerable interest.¹ The reaction represents the simplest example of the important class of reactions in which a nucleophile undergoes reversible addition to a carbonyl group. It requires the making or breaking of only one bond between heavy atoms and the net transfer of one proton. Catalysis by both acids and bases is invariably observed, although the exact nature of the catalysis has been the topic of much speculation, particularly with regards to the timing of the various processes.^{1,2} Detailed investigations have in general been limited to aliphatic systems, since it is only with these that the addition reaction occurs to a significant extent. Acetaldehyde, for example, is approximately 50% hydrated in water, and, consequently, detailed kinetic study presents little problem.³ Benzaldehydes on the other hand are much less hydrated, unless they contain strongly electron-withdrawing substituents.⁴⁻⁸ The parent benzaldehyde, for example, is estimated to be only about 1% hydrated in aqueous solution.^{5,8} Hydroxide ion^{5,7,9} and

methoxide ion¹⁰ do readily undergo addition to benzaldehyde, but studies of this are limited to strongly basic solutions. Kinetic data have recently been reported for the breakdown of benzaldehyde hemiacetals formed as intermediates in the hydrolysis of precursor acylals¹¹ or acetals.^{12,13} These studies are somewhat limited in that the breakdown of the hemiacetal can only be studied when this reaction proceeds more slowly than the hemiacetal is formed. Moreover, information relating to the reverse addition reaction requires certain assumptions to be made. A detailed kinetic study of the hydration of phthalaldehyde has also been recently reported.¹⁴ However, the overall reaction here is not a simple hydration, since the ultimate product is a cyclic species.

We report here a study of the reactions described in eq 1, involving the intramolecular addition of an alcohol group



to a benzaldehyde to form a cyclic hemiacetal.¹⁵ In ad-

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Table I. Second-Order Rate Constants^a for the Hydrolysis of Acetals 5-9

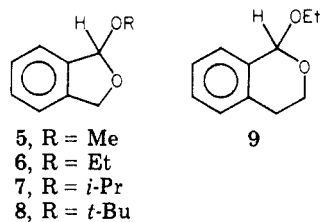
acetal	$k_{H^+}, s^{-1} M^{-1}$	acetal	$k_{H^+}, s^{-1} M^{-1}$
5	49	8	150
6	56	9	57
7	60		

^a At 25 °C; $\mu = 0.6$.

dition to its obvious analogy to intermolecular versions such as benzaldehyde hydration, the systems described in eq 1 are closely related to another reaction of fundamental importance, the mutarotation of glucose and related aldoses.¹⁶ This latter process is generally assumed to proceed with rate-limiting ring opening of the hemiacetal form of the sugar. Although there have been a number of studies in this general area,¹⁶ there appears to have been little attempt to study in detail simple models such as 2 and 4. As we will describe, a basic feature of 2 and 4 which differentiates them from an aldose is the presence at equilibrium of a significant quantity of the ring-opened species. This feature makes possible the direct measurement of ring-opening and ring-closing rates. These rates have not been directly observed for simple sugars because the concentration of the ring-opened form is very small,¹⁷ although the general assumption has been made¹⁶ that ring opening and mutarotation are equivalent.¹⁸

Results

Preparation and Hydrolysis of Acetals. Acetals 5-9 which are related to 2 and 4 were prepared by the reduction of phthalide or homophthalide with diisobutylaluminum hydride,¹⁹ followed by treatment of the crude product of this reduction with excess alcohol and boron trifluoride etherate. The hemiacetals 2 and 4 are the products of the initial reduction, and 2 has in fact been reported in the literature from such a synthesis¹⁹ by this procedure. We, however, found it difficult to obtain pure samples in this way.



Aqueous acid solutions of the acetals exhibit an overall increase in absorbance with time (Figure 1). Kinetic experiments were conducted by following this increase at 255 nm in a series of acetate buffers of pH 4-5.5. The spectral change is first-order in these solutions, and the

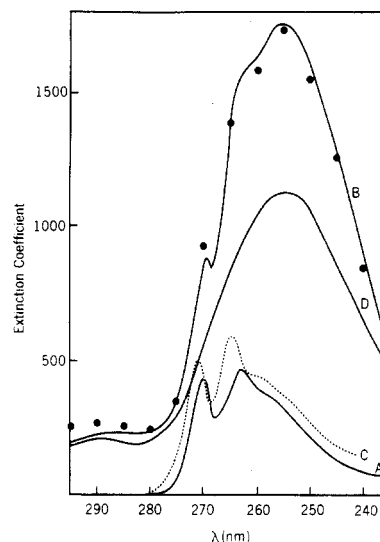


Figure 1. Ultraviolet spectra: curve A, 5 in 0.001 M NaOH; curve B, 5 in 0.001 M HCl, spectrum after 30 min; curve C, solution corresponding to curve B mixed with aqueous sodium hydroxide (NaOH concentration after mixing is 0.8 M); curve D, 2-methylbenzaldehyde in water. Solid circles indicate points calculated by using 0.87ϵ (curve A) + 0.13ϵ (curve D). The ordinate scale for curve D is 10 times that shown.

observed first-order rate constants obey the rate law $k_{\text{obsd}} = k_{H^+}[H^+]$. There is no observable buffer catalysis. Values of k_{H^+} are listed in Table I. In more acidic solutions, for example, 0.01 M HCl, the absorbance increase is no longer first-order but exhibits an induction period of a similar nature to that described by Jensen and Lenz¹² for the hydrolysis of acyclic benzaldehyde acetals.

Hemiacetal-Hydroxy Aldehyde Equilibrium. The UV spectrum of the hydrolysis product is that expected of a mixture of the hemiacetal and hydroxy aldehyde (Figure 1). The aldehyde is represented by a broad peak with λ_{max} at 255 nm, with a second less intense peak at longer wavelength. The hemiacetal is represented by the fairly sharp peaks at 270 and 262 nm which appear as shoulders in the spectrum of the hydrolysis product.

To make a numerical estimate of the value of the equilibrium constant for the interconversion of the two forms, we have assumed that the UV spectrum of the hemiacetal is identical with that of the acetal, while the spectrum of the hydroxy aldehyde is identical with that of 2-methylbenzaldehyde. The equilibrium constant can then be evaluated according to eq 2. The terms ϵ_D , ϵ_A , and

$$K_{\text{cyc}} = \frac{[\text{hemiacetal}]}{[\text{hydroxy aldehyde}]} = \frac{\epsilon_D - \epsilon_B}{\epsilon_B - \epsilon_A} \quad (2)$$

ϵ_B are the extinction coefficients at a given wavelength for the 2-methylbenzaldehyde, acetal, and the hydrolysis product, respectively. This calculation was performed for a number of wavelengths, and the results were averaged. For the equilibrium of 1 and 2 the value of K_{cyc} so produced is 6.7 ± 0.5 , while for $3 \rightleftharpoons 4$ $K_{\text{cyc}} = 20 \pm 2$. The internal consistency of the analysis can be seen in the agreement between curve B of Figure 1 and the solid circles. The latter are extinction coefficients calculated on the basis of the equilibrium constant.

Qualitative confirmation for the presence of a mixture of hydroxy aldehyde and hemiacetal can be seen in Figure 2, which shows the NMR spectrum of a CDCl_3 extract of a fully hydrolyzed solution of the acetal 6. The relative intensities of the aldehyde proton and the C_1 proton of the hemiacetal give a value of K_{cyc} of 3. This number is significantly different from the value of K_{cyc} obtained in the

(15) The Chemical Abstracts name of 1 is 1,3-dihydro-1-hydroxyiso-benzofuran and of 2 is 3,4-dihydro-1-hydroxy-1H-2-benzopyran.

(16) (a) Pigman, W.; Isbell, H. S. *Adv. Carbohydr. Chem.* 1968, 23, 11; (b) Isbell, H. S.; *Rev. W. Ibid.* 1969, 24, 13; (c) Capon, B. *Chem. Rev.* 1969, 69, 407. (d) Capon, B.; Walker, R. B. *J. Chem. Soc., Perkin Trans.* 2 1974, 1600.

(17) (a) A polarographic method has been used to directly measure individual ring-opening and ring-closing rates for D-glucose, but the kinetic derivation still requires the assumption that the rate of mutarotation is equal to the rate of ring opening.^{7b} (b) Los, J. M.; Simpson, L. B.; Weisner, K. *J. Am. Chem. Soc.* 1956, 78, 1564.

(18) (a) This is not true for the hydroxide ion catalyzed reactions of thio sugars, for which the rate of mutarotation is significantly greater than the rate of ring-opening, the latter being measured by a thiol-trapping technique.^{7b} (b) Grimshaw, C. E.; Whistler, R. L.; Cleland, W. W. *J. Am. Chem. Soc.* 1979, 101, 1521.

(19) Kraiss, G.; Povarny, M.; Nador, K. *Acta Chim. Acad. Sci. Hung.* 1976, 88, 93.

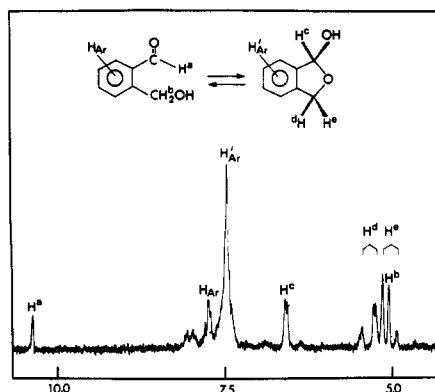


Figure 2. NMR spectrum of a CDCl_3 extract of a fully hydrolyzed solution of 6.

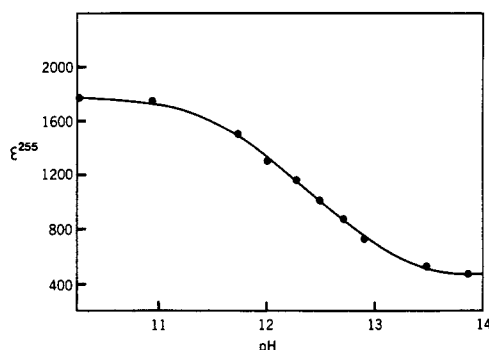
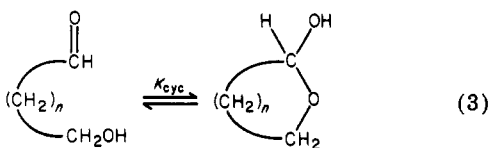


Figure 3. Apparent extinction coefficients at 255 nm for $1 \rightleftharpoons 2$.

UV analysis, but the solvents in the two cases are different.²⁰ We were able to obtain an NMR spectrum of the hydrolyzed acetal in 50:50 D_2O - $\text{Me}_2\text{SO}-d_6$ although a very dilute solution was involved because of solubility problems. In this case the relative intensities of the same two peaks provided $K_{\text{cyc}} = 5$, which is closer to the number obtained in H_2O by UV analysis.

The values of K_{cyc} can be compared with values previously estimated for the aliphatic systems of eq 3.²¹ A UV



analysis similar to that carried out here has provided $K_{\text{cyc}} = 8.1$ for $n = 2$ and $K_{\text{cyc}} = 16$ for $n = 3$, these numbers referring to 75:25 dioxane-water as solvent. Considering that the solvent is different, the remarkable similarity of these numbers to those of the present study is certainly fortuitous. Both systems do, however, show the same effect of ring size. The values for the systems of eq 3 are probably somewhat in error,²² since hydration of the aldehyde should occur to a significant extent, and this factor was ignored in the original treatment.²¹ Hydration is probably not significant in the present case, since benzaldehydes are less likely to add water to an appreciable extent.^{5,8}

Ionization of Hemiacetals. When the aqueous solution containing the hydroxy aldehyde-hemiacetal mixture

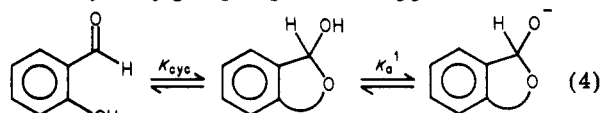
Table II. Observed Rate Constants^a for Hemiacetal-Hydroxy Aldehyde Equilibration. Comparison of the T-Jump and pH-Jump Methods

solution	$1 \rightleftharpoons 2$		$3 \rightleftharpoons 4$	
	T-jump	pH-jump	T-jump	pH-jump
0.09 M HCl	27.6	29.7	103	110
0.02 M HCl	7.4	6.6	24.1	23.1
phosphate, pH 7.26	18.3	21.2		
TRIS, pH 8.21	140	ca. 150	26.5	24.3

^a Temperature, 25 °C; ionic strength 0.6; units, s^{-1} .

is made strongly basic, the UV spectrum resembles much more closely the spectrum of the acetal, (curve C, Figure 1). The change is fully reversible, reacidification quantitatively regenerating the UV spectrum of the neutral or the acidic solution. If the change is monitored as a function of pH, a typical acid-base titration curve (Figure 3) is produced with $\text{p}K_a$ (apparent) = 12.35 ± 0.05 for $1 \rightleftharpoons 2$ and 12.40 ± 0.05 for $3 \rightleftharpoons 4$.

The spectral change can be attributed to a shift in equilibrium toward the hemiacetal, caused by the ionization of its hydroxy group (eq 4). The apparent ionization



constant is given by eq 5. Substitution of the values of

$$K_a(\text{apparent}) = K_a^1 K_{\text{cyc}} / (1 + K_{\text{cyc}}) \quad (5)$$

K_{cyc} obtained in the UV analysis provides values of $\text{p}K_a = 12.29$ for the hemiacetal 2 and $\text{p}K_a = 12.38$ for the hemiacetal 4. The difference between $\text{p}K_a$ (apparent) and $\text{p}K_a^1$ caused by the presence of the hydroxy aldehyde can be seen to be quite small and is relatively insensitive to the exact value of K_{cyc} . One assumption is needed to produce eq 5, namely, that the ionization of the hydroxy group of the hydroxy aldehyde can be ignored. This is a reasonably valid assumption since the $\text{p}K_a$ values of simple alcohols are generally greater than 14.²³

The hemiacetal acidity constants can be compared to those for similar compounds: benzaldehyde hydrate ($\text{p}K_a \approx 12.8$),⁵ 4-nitrobenzaldehyde hydrate (12.1 ± 0.2),⁶ and α - and β -D-glucose (12.47 and 12.17, respectively).²⁴

Kinetics of Equilibration. The rates of equilibration of the hemiacetal and hydroxy aldehyde were measured in two ways. The method most commonly employed involved the mixing in a stopped-flow spectrophotometer of an NaOH solution of hemiacetal and hydroxy aldehyde and a buffer containing the exact amount of HCl necessary to neutralize the base. This procedure, "a pH jump", has its basis in the shifting of the hemiacetal-hydroxy aldehyde equilibrium in base because of the ionization of the hemiacetal. The immediately neutralized solution contains an excess quantity of hemiacetal, and the return to equilibrium is monitored spectroscopically in the stopped-flow instrument. A second approach involved the T-jump method.²⁵ An equilibrated solution of hemiacetal and

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(25) Eigen, M.; DeMaeyer, L. "Techniques of Organic Chemistry"; Weissberger, A., Ed.; Interscience: New York, 1963; Vol. 8.

(26) (a) The formation constant of benzaldehyde methyl hemiacetal in methanol solvent is 0.09.^{26b} Conversion to unit molarity in methanol gives 0.004. (b) Crampton, M. R. *J. Chem. Soc., Perkin Trans. 2* 1975, 185.

(20) It might have been expected that K_{cyc} would be greater in the less polar solvent which would favor the (presumably) less polar hemiacetal form. Possibly the hydroxy aldehyde derives additional stabilization in CDCl_3 from some form of internal hydrogen bonding.

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Table III. Catalytic Coefficients^a for Reversible Formation of Hemiacetals^c

buffer acid form	pK _a	1 ⇌ 2 ^b		3 ⇌ 4 ^b	
		k _{acid}	k _{base}	k _{acid}	k _{base}
H ₃ O ⁺ (1)	-1.74	330	0.12 ^a	1.16 × 10 ³	0.07 ^a
cyanoacetic acid (2)	2.34	5.21	0.19	4.27	
chloroacetic acid (3)	2.65	3.97	0.39	3.23	
methoxyacetic acid (4)	3.35	2.26	1.09	1.19	0.10
formic acid (5)	3.60	1.81	1.84	1.11	0.11
3-chloropropionic acid (6)	3.88	1.11	2.39	0.56	0.19
acetic acid (7)	4.60	0.67	4.95	0.27	0.33
cacodylic acid (8)	5.89		32	0.12	2.07
CCl ₃ PO ₃ H ⁻ (9)	4.30	4.34	3.67	5.14	0.20
CHCl ₂ PO ₃ H ⁻ (10)	4.95	2.69	9.81	2.64	0.71
CH ₂ ClPO ₃ H ⁻	5.97	1.5	48	1.35	3.03
CH ₂ OHPO ₃ H ⁻ (12)	6.58		125	0.93	7.86
CH ₃ PO ₃ H ⁻ (13)	7.30		350	0.5	20
H ₂ PO ₄ ⁻ (14)	6.68		210	1.18	16.9
TRIS·H ⁺ (15)	8.30				100
H ₂ O (16)	15.74	0.12 ^a	1.1 × 10 ⁸	0.07 ^a	1.7 × 10 ⁷

^a Units of M⁻¹ s⁻¹, with the exception of k_{H₂O}, which has units of s⁻¹. ^b Coefficients in each direction can be calculated as k(2 → 1) = 0.13k(1 ⇌ 2), k(1 → 2) = 0.87k(1 ⇌ 2), k(4 → 3) = 0.048k(3 ⇌ 4) and k(3 → 4) = 0.952k(3 ⇌ 4). ^c At 25 °C, ionic strength 0.6.

Table IV. Rate Constants for the Formation and Breakdown of Hemiacetals and the Hydrolysis of Acetals

	formation				breakdown			acetal hydrolysis k _{H⁺} ^d
	k _{form} ^a	k _{H⁺} ^b	k _{H₂O} ^c	k _{OH⁻} ^b	k _{H⁺} ^d	k _{H₂O} ^e	k _{OH⁻} ^d	
3	6.7	2.9 × 10 ²	1.1 × 10 ⁻¹	9.4 × 10 ⁷	43.0	1.6 × 10 ⁻²	1.4 × 10 ⁷	49.0 (Me)
4	20.0	1.1 × 10 ³	6.8 × 10 ⁻²	1.6 × 10 ⁷	56.0	3.4 × 10 ⁻³	8.2 × 10 ⁵	57.0 (Me)
PhCH(OH)OR R = Me					2.6 × 10 ² ^g	5.2 × 10 ⁻³ ^g	6.9 × 10 ⁵ ^g	30.0 (Me ₂) ^j
R = Et	0.004 ^f	1	2 × 10 ⁻⁵	3 × 10 ³	3.5 × 10 ² ^h		7.8 × 10 ⁵ ⁱ	1.6 × 10 ² (Et ₂) ^k
β-D-glucopyranose ^l	2.5 × 10 ⁴	30	1	5 × 10 ⁷	1.3 × 10 ⁻³	4.8 × 10 ⁻⁵	2.1 × 10 ³	3.6 × 10 ⁻⁹ (Me) ^m
CH ₃ CH(OH) ₂ ⁿ	0.02	9	7 × 10 ⁻⁵	8 × 10 ²	4.4 × 10 ²	3.9 × 10 ⁻³	3.9 × 10 ⁴	2.5 × 10 ⁻¹ (Et ₂) ^o
CH ₂ (OH)(OEt) ^p	9.1 × 10 ²	6.7 × 10 ²	2.6 × 10 ⁻²	1.2 × 10 ⁶	7.4 × 10 ⁻¹	2.9 × 10 ⁻⁵	1.3 × 10 ³	2.2 × 10 ⁻⁴ (Et ₂) ^q

^a Unitless if intramolecular, units of M⁻¹ if intermolecular. ^b Units of s⁻¹ M⁻¹ if intramolecular and of s⁻¹ M⁻² if intermolecular. ^c Units of s⁻¹ if intramolecular and of s⁻¹ M⁻² if intermolecular. ^d Units of s⁻¹ M⁻¹. ^e Units of s⁻¹. ^f Reference 26. ^g Reference 11; temperature 15 °C. ^h Reference 12. ⁱ Reference 13. ^j Reference 27. ^k Reference 28. ^l Reference 29. ^m Reference 30. ⁿ Reference 31. ^o Reference 32. ^p Reference 2. ^q Reference 33.

hydroxy aldehyde was subjected to a very rapid temperature increase of 3 °C and the relaxation to the slightly different equilibrium position at the new temperature monitored spectroscopically. For our systems the T-jump approach is the less accurate of the two, since it involves a considerably smaller optical density change. Moreover, in the pH region 3–6, the equilibration is too slow for this technique, since the temperature in the T-jump cell after the rapid increase does not remain constant over the period of time required for equilibration. The T-jump method does, however, provide a check on the pH-jump procedure, and, indeed, where rates have been measured in the same solution, both techniques give the same result (Table II).

First-order rate constants were measured by using the pH-jump approach in a series of buffers over a range of

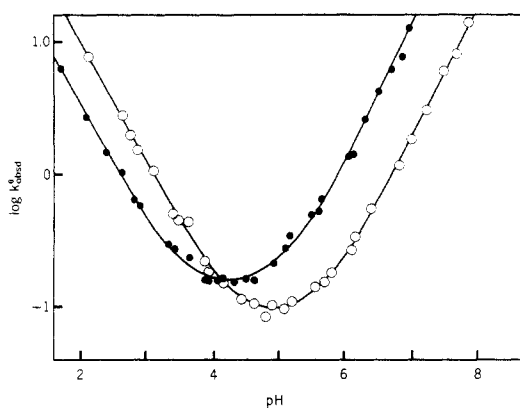


Figure 4. First-order rate constants (25 °C, ionic strength 0.6) extrapolated to zero buffer concentration for hemiacetyl-hydroxy aldehyde equilibration: ●, 1 ⇌ 2; ○, 3 ⇌ 4.

pH from 1.5 to 8 and exhibit the expected behavior^{1,2,16} (eq 6). Figure 4 depicts values of k_{obsd} extrapolated to zero

$$k_{\text{obsd}} = k_{\text{H}^+}[\text{H}^+] + k_{\text{H}_2\text{O}} + k_{\text{OH}^-}[\text{OH}^-] + k_{\text{HA}}[\text{HA}] + k_{\text{A}^-}[\text{A}^-] \quad (6)$$

buffer concentration. Table III lists the various catalytic coefficients. These constants refer to the approach to equilibrium and are therefore equal to the sum of the rate constants for the ring-opening and ring-closing reactions catalyzed by the same species. The rate constants in each

(27) Capon, B.; Nimmo, K. *J. Chem. Soc., Perkin Trans 2* 1975, 1113.

(28) Jensen, J. L.; Herold, L. R.; Lenz, P. A.; Trusty, S.; Sergei, V.; Bell, K.; Rogers, P. *J. Am. Chem. Soc.* 1979, 101, 4672.

(29) (a) Rate constants for the individual steps of the equilibrium α -glucose ⇌ free aldehyde ⇌ β -glucose have been estimated and provide the formation constant.^{17b} These also provide the partitioning ratio of the free aldehyde^{16d} which can be applied to the mutarotation rate constant to give a direct ring-opening rate.^{16d} The rates of ring-opening in Table IV are 0.55 times the mutarotation rate constants.^{29b,c} (b) Bronsted, J. N.; Guggenheim, E. A. *J. Am. Chem. Soc.* 1927, 49, 2554. (c) Los, J. L.; Simpson, L. B. *Recl. Trav. Chem. Pays-Bas* 1954, 73, 941.

(30) Timell, T. E. *Can. J. Chem.* 1964, 42, 1456.

(31) The data were taken from ref 3, with the formation constant and formation rate constant divided by 55 to convert to unit molarity in water.

(32) Kreevoy, M. M.; Taft, R. W. *J. Am. Chem. Soc.* 1955, 77, 5590.

(33) Skrabal, A.; Eger, H. H. *Z. Phys. Chem.* 1926, 122, 349.

direction can be calculated from eq 7 and 8. These

$$k_i(\text{ring closing}) = k_i(\text{equilibration})K_{\text{cyc}}/(1 + K_{\text{cyc}}) \quad (7)$$

$$k_i(\text{ring opening}) = k_i(\text{equilibration})/(1 + K_{\text{cyc}}) \quad (8)$$

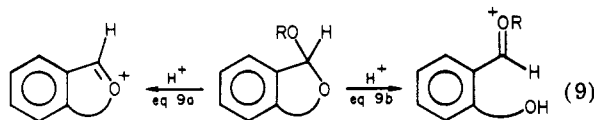
equations are valid since $K_{\text{cyc}} [=k_i(\text{ring closing})/k_i(\text{ring opening})]$ is independent of pH and buffer in the solutions where the kinetic data were obtained. A further consequence of this fact is that the Brønsted plot using the equilibration rate constants takes an identical form with both the Brønsted plots for ring opening and ring closing, the only difference being a vertical displacement corresponding to the constants involving K_{cyc} which appear in eq 7 and 8.

In Table IV we compare rates of formation and breakdown of a series of hemiacetals. The rates of breakdown of the cyclic benzaldehyde hemiacetals are remarkably similar to the rates of breakdown of their acyclic analogues. There is a considerable difference in the formation direction, due to the fact that one reaction is intramolecular and the other is intermolecular. The rate differences amount to factors of about 10^3 and are not unusual for a comparison involving intramolecular vs. intermolecular carbonyl addition.³⁴ There is no marked effect of ring size on the rates of the two systems of this study, although there is an interesting change in relative reactivity. The formation of 2 is 5.9 times faster than the formation of 4 with hydroxide ion as catalyst but 3.7 times slower with the hydronium ion.

Discussion

Acetal Hydrolysis. The H^+ -catalyzed hydrolysis of acetals is now well established^{35,36} to occur in three stages: (i) formation of an oxocarbenium ion, (ii) hydration of this ion to form a hemiacetal, (iii) decomposition of the hemiacetal. Stage i is normally rate-limiting, although there have recently been found several exceptions^{11-13,37} including some simple acyclic acetals of benzaldehyde for which stage iii becomes partially rate limiting in acid solutions.^{12,13} This complication was avoided in studying the kinetics of hydrolysis of 5-9 by using solutions of sufficiently high pH that hemiacetal decomposition is rapid. Interference from the hemiacetal breakdown is probably the cause of the nonlinear kinetics observed in more acidic solutions, as has been discussed by Jensen and Lenz¹² for simple benzaldehyde acetals.

There is some mechanistic uncertainty since the first stage can proceed in two different ways, with loss of an exocyclic alkoxy group or with ring opening (eq 9). A



choice between these can be made on the basis of the rate changes observed on variation of the exocyclic alkoxy group. Structural variation in an alkoxy or aryloxy group which remains on the oxocarbenium ion center is usually

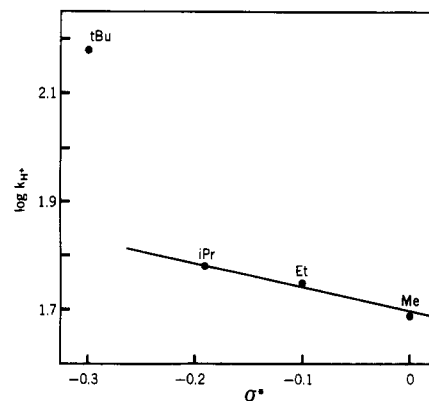


Figure 5. Rate constants for the hydrolysis of 5-8 as a function of σ^* (alkyl). The line has a slope of -0.5.

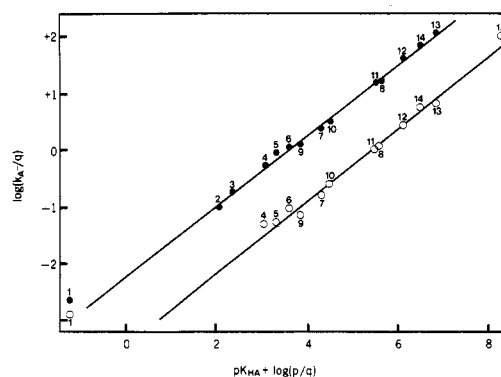


Figure 6. Brønsted plots for general base catalysis of 1 \rightleftharpoons 2 (●) and 3 \rightleftharpoons 4 (○). For the catalyst number see Table III. The point for water is based on $k_{\text{H}_2\text{O}}/55.5$.

associated with a substantial negative ρ or ρ^* value of the order of -3 to -4.³⁶ Variation in a departing alkoxy or aryloxy group generally produces ρ or ρ^* values in the range -1 to +1, and in some instances a parabolic plot is observed.³⁶ As seen in Figure 5, the behavior in the series 5-8 points to the second possibility, initial loss of the exocyclic alkoxy group (eq 9a).³⁸ This same behavior is proposed to occur in the hydrolysis of related sugar acetals such as methyl α -D-glucopyranoside.^{16,39} A related ortho ester, 1,1-diethoxy-1,3-dihydroisobenzofuran, can also be shown to hydrolyze in this way.⁴⁰

Hemiacetals. Base Catalysis. The general-base catalysis of the formation or breakdown of a hemiacetal can occur through either of two kinetically equivalent mechanisms.¹ The reaction of eq 10 involves true general-base catalysis in the formation direction and specific-base-general-acid catalysis in the breakdown direction, while the opposite assignments can be made for the reaction of eq 11. There has in the past been little general agreement as to which of these mechanisms is the correct one.¹ Recently Funderburk, Aldwin, and Jencks presented a series of arguments favoring the reaction of eq 10 for form-

(34) (a) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* 1972, 94, 9155, 9156; 1973, 95, 8308, 8313, 8319. (b) Milstein, S.; Cohen, L. A. *Ibid.* 1972, 94, 9158. (c) Kirby, A. J.; Lancaster, P. W. *J. Chem. Soc., Perkin Trans. 2* 1975, 1206.

(35) Fife, T. H. *Acc. Chem. Res.* 1972, 5, 264.

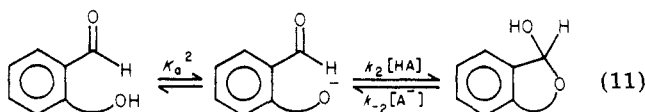
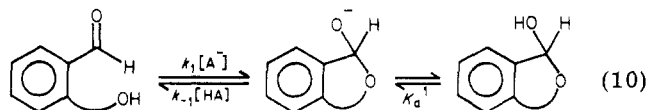
(36) Cordes, E. H.; Bull, H. G. *Chem. Rev.* 1974, 74, 581.

(37) (a) Mori, A. L.; Parzio, M. A.; Schaleger, L. L. *J. Am. Chem. Soc.* 1972, 94, 5034. (b) Mori, A. L.; Schaleger, L. L. *Ibid.* 1972, 94, 5034. (c) Atkinson, R. F.; Bruce, T. C. *Ibid.* 1974, 96, 819. (d) Capon, B. *Pure Appl. Chem.* 1977, 94, 1001.

(38) Initial ring opening may not be completely unimportant. This reaction is modeled by the H^+ -catalyzed ring-opening of the hemiacetal, and the rate of this latter reaction is remarkably similar to the observed rates of the hydrolysis of the acetals (Table IV). It has been argued that the mechanisms of the H^+ -catalyzed decomposition of acetals and hemiacetals are different,² and in the formaldehyde system this is seen by a 10^3 - 10^4 greater reactivity for the hemiacetal. However, with benzaldehyde derivatives there is a much smaller difference in the rates, H^+ -catalyzed hemiacetal breakdown being only 2-10 times faster than acetal decomposition (Table IV).

(39) Banks, B. E. C.; Meinwald, Y.; Rhind-Tutt, A. J.; Sheft, I.; Vernon, C. A. *J. Am. Chem. Soc.* 1961, 3240.

(40) McClelland, R. A.; Alabhai, M. *Can. J. Chem.*, in press.



aldehyde hydrates and hemiacetals.² These authors also dismissed the possibility of a fully concerted cyclic mechanism, possibly involving solvent water molecules in addition to the base.^{1e}

The Brønsted plots for general base catalysis of the equilibration reactions of this study are shown in Figure 6. The points for all of the base catalysts lie on a common line. This feature was noted previously with phthalaldehyde hydration,¹⁴ although other studies have shown that sterically hindered bases deviate from the normal Brønsted line.³ The β value for $1 \rightleftharpoons 2$ is 0.62 and for $3 \rightleftharpoons 4$ is 0.63. There is some difference in the rates in the two systems, but this rate difference is independent of base strength.

Comparison of these β values with literature data⁴¹ reveals a rough trend of increasing β values with increasing rates of hemiacetal breakdown and increasing aldehyde stability ($\text{H}_2\text{CO} < \text{RCHO} < \text{ArCHO}$). This variation is consistent with the mechanism of eq 10 and not with that of eq 11. In terms of the former there is a decrease in the α value of the rate-limiting step (k_{-1}) with the increased rate of breakdown. This seems quite reasonable since, for a more reactive hemiacetal, a smaller amount of proton transfer should be required to reach the transition state. For the mechanism of eq 11 on the other hand, the observed β value corresponds to the β value of the rate-limiting step (k_{-2}). This requires a greater amount of proton transfer for the more reactive hemiacetals, and this seems less likely.⁴²

Additional support for the mechanism of eq 10 comes from a calculation of the values of k_{-1} and k_2 ⁴³ which are required to produce the observed rate constants. For the cyanoacetate-catalyzed equilibration of 1 and 2, the rate constant k_{-1} in the mechanism of eq 10 is required to be $2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, while the rate constant k_2 of eq 11 is required to be $2 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$. Very similar numbers are obtained for $3 \rightleftharpoons 4$; for other base catalysts somewhat smaller rate constants are required. The first number above is below the diffusion limit,⁴⁴ so that the reaction of eq 10 is permissible. The second number, however, is somewhat greater than the diffusion limit, and the reaction of eq 11 therefore seems less likely.

The points for catalysis by the hydroxide ion lie reasonably close to the Brønsted lines of Figure 6, falling just 0.3 and 0.5 logarithmic units above the plots. This observation suggests that this catalysis is mechanistically

(41) The β values are as follows: for phthalaldehyde hydration, 0.51;¹⁴ for acetaldehyde hydration, 0.45³; for the mutarotation of glucose, 0.34;^{16b} for the breakdown of the hydrate, ethyl hemiacetal, and methyl hemiacetal of formaldehyde, 0.24, 0.26, and 0.26,² respectively.

(42) Our arguments here are based only on considerations of the effect along the reaction coordinate. The same conclusion is reached if the effect perpendicular to the reaction coordinate² is also considered.

(43) (a) These values can be calculated by using values of $\text{p}K_a^1$ and $\text{p}K_a^2$. The former have been measured in this work. The latter refer to the ionization of a benzyl alcohol and a phenethyl alcohol. Values of $\text{p}K_a$ for the parent alcohols can be estimated to be 15.0 and 15.6, respectively, by using the relationship²³ $\text{p}K_a(\text{RCH}_2\text{OH}) = 15.9 - 1.42\sigma^*$. The alcohols 1 and 3 should be somewhat stronger acids because of the *o*-CHO group. On the basis of substituent effects on trifluoroacetophenone hydrates,^{43b} we estimate $\text{p}K_a$ values of 14.2 for 1 and 15.0 for 3. (b) Stewart, R.; Van der Linden, R. *Can. J. Chem.* 1960, 38, 400.

(44) Eigen, M. *Angew. Chem., Int. Ed. Engl.* 1964, 3, 1.

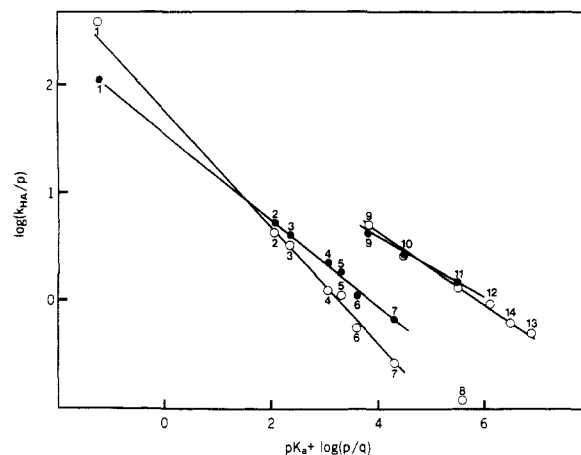
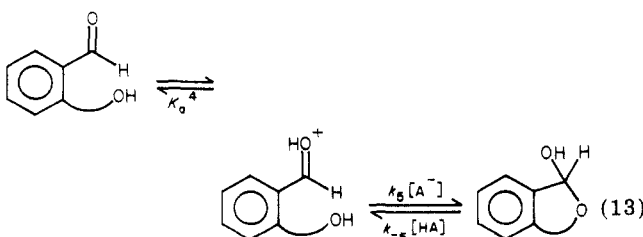
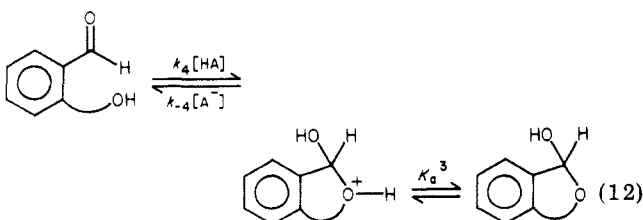


Figure 7. Brønsted plots for general-acid catalysis of $1 \rightleftharpoons 2$ (●) and $3 \rightleftharpoons 4$ (○). For the catalyst number see Table III.

similar to that of the general bases, although this is not always suggested to be the case.^{2,7,10}

Considerable uncertainty also exists over the mechanism of the pH-independent or water reaction. For formaldehyde systems, Funderburk, Aldwin, and Jencks² proposed that this reaction represents general-base catalysis by water, the principal piece of evidence being that the water rate constant falls reasonably close to the Brønsted line for base catalysis. This is true to a certain extent with our systems. For $1 \rightleftharpoons 2$ the water point is 0.3 logarithmic units above the base Brønsted plot although for $3 \rightleftharpoons 4$ this difference increases to 1.3 logarithmic units (Figure 6). In neither case is the point near the line for acid catalysis. There are, however, two features which suggest that the simple general-base interpretation cannot be totally correct. (a) For the base catalysts, including hydroxide ion, the rate constants for $1 \rightleftharpoons 2$ and $3 \rightleftharpoons 4$ differ by a factor of about 10. For water, however, this difference is only 1.7. (b) In order to account for the observed $k_{\text{H}_2\text{O}}$ (ring opening) in terms of eq 10, one sees that the values of k_{-1} which are required are $3 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ (2) and $8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (4). These values are not greater than the diffusion limit, but they are close enough that some other mechanism may be more plausible.

Hemiacetals. Acid Catalysis. Two kinetically equivalent reactions can also be written for the general-acid-catalyzed reactions¹ (eq 12 and 13). For formaldehyde hydrate and hemiacetals, Funderburk, Aldwin, and Jencks again favored one of these possibilities, that of eq 12.²



The Brønsted plots for acid catalysis of $1 \rightleftharpoons 2$ and $3 \rightleftharpoons 4$ are shown in Figure 7 and show two features different

from the plots for base catalysis. (a) The acid catalysts do not all lie on a common line. There are, in fact, two quite distinct lines, one defined by carboxylic acids and a second defined by alkyl hydrogen phosphonate anions. The H_2PO_4^- ion is included with the latter. The point for H_3O^+ lies reasonably near the extrapolated line for the former. Cacodylic acid does not fit with either line. (b) There are significantly different α values associated with $1 \rightleftharpoons 2$ and $3 \rightleftharpoons 4$; $\alpha(\text{RCOOH}) = 0.40$ and 0.54 , respectively, and $\alpha(\text{RHPO}_3^-) = 0.32$ and 0.27 , respectively.

Observation a is implied in a number of examples in the literature,^{14,45} in which a considerably enhanced reactivity is reported for H_2PO_4^- . This is usually explained in terms of bifunctional acid-base catalysis, with the H_2PO_4^- ion simultaneously donating a proton and receiving a proton in the transition state. The present study represents the first time that the structurally homogeneous set of alkyl hydrogen phosphonate anions⁴⁶ has been included with H_2PO_4^- . It appears as if the members of this set are functioning as acid catalysts but that they conform to a different Brønsted relation compared to the carboxylic acids. Behavior of this type is not uncommon^{47,48} and is normally ascribed to the different charges on the catalysts. An explanation at the molecular level has been advanced by Kresge and Chiang⁴⁸ for vinyl ether hydrolysis, and their arguments can be extended to the hemiacetal systems. The basic feature is that there is an electrostatic interaction between the catalyst and the reagent in the transition state of the reaction which is not present in the starting state or the final state. Such an interaction is present, in fact, for both transition states of eq 12 and 13. In each case the substrate molecule at the transition state bears a partial positive charge. In the case of a carboxylic acid catalyst this is offset by a partial negative charge on the catalyst. This stabilizing interaction is also present for RHPO_3^- but is augmented by the full negative charge already present for these catalysts. For a comparison involving an RHPO_3^- catalyst and a carboxylic acid catalyst of the same acid strength, the electrostatic interaction results in a transition state of lower energy for the former, and it is a more effective catalyst. It can be seen that the interaction is present in the transition states for either acid-catalyzed mechanism, and, in fact, in each case the interacting charges are separated by the same number of bonds. It is also interesting that no electrostatic effect is seen for the general-base-catalyzed equilibration. In this case the effect would operate to make RPO_3^{2-} a less effective catalyst than RCOO^- .

Funderburk, Aldwin, and Jencks² argued that a hemiacetal decomposition by the mechanism of eq 13 is closely related to the oxocarbenium ion forming stage in the hydrolysis of a corresponding acetal. The observation with formaldehyde derivatives of much greater rates of acid breakdown of the hemiacetals suggests, therefore, that its mechanism must be different. This same argument cannot, however, be applied to the benzaldehyde system, where the hemiacetal and acetal rates are much closer (Table IV). One argument² which does apply against eq 13 concerns the Brønsted α values. For the hydrolysis of simple acetals of benzaldehydes these are generally large,²⁸ while this is not true for the hemiacetals.

What can be proposed, however, is that the benzaldehyde hemiacetals undergo acid decomposition by both

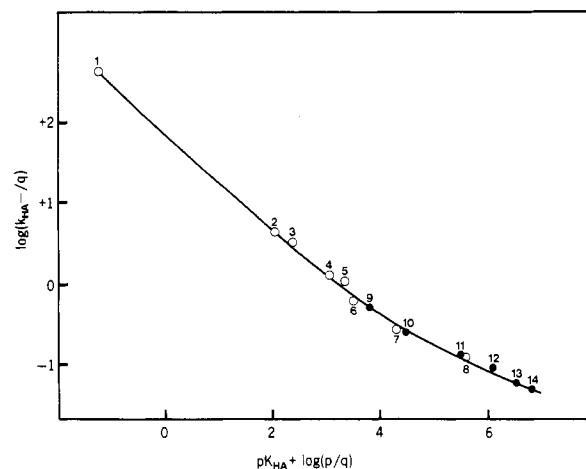


Figure 8. Brønsted plot for general-acid catalysis of $3 \rightleftharpoons 4$, with points for RHPO_3^- (●) lowered by 1.02 logarithmic units.

mechanisms. This interpretation provides an explanation for the different α values associated with the two sets of acid catalysts. As in the vinyl ether systems,⁴⁹ this observation can be accounted for by regarding the apparently linear Brønsted plots for each catalyst as segments of a more extensive curved correlation. This curved correlation is pictured for $3 \rightleftharpoons 4$ in Figure 8; the points for RHPO_3^- catalysts have been lowered by a constant factor which places the point for $\text{CCl}_3\text{PO}_3\text{H}^-$ on the carboxylic acid line.⁴⁹ Support for such an operation can be seen from the cacodylic acid point, which fits nicely on the curve so produced.⁵⁰

Curved Brønsted relations for the vinyl ether hydrolysis were analyzed according to Marcus rate theory.⁴⁹ In the present case, however, the curvature is in the wrong direction, since the Marcus theory predicts a decrease in α with increased catalyst acidity. The explanation proposed here is that the reaction is occurring by both eq 12 and 13, so that the curved Brønsted plot represents a change in the relative importance of the two reactions with changing acidity. The reaction of eq 12 is associated with a low α value as in the case of the hydrates and hemiacetals of formaldehyde,² while the reaction of eq 13 is associated with a relatively large α value.²⁸ If the energies of the two reactions are fairly close, their quite different sensitivity to changing catalyst acidity will give rise to the situation where their relative importance will vary. Weak acids such as RHPO_3^- will tend to catalyze by the mechanism of eq 12 and give a low α value, while with stronger acids some of the reaction proceeds by way of eq 13, and the apparent α value shows an increase.

The different Brønsted slopes for $1 \rightleftharpoons 2$ and $3 \rightleftharpoons 4$ also can be accounted for simply as being due to a small difference in the relative contributions of the two acid-catalyzed reactions. It is more difficult to explain these different α values in terms of a single mechanism, particularly since there is little difference in the two systems in the energy change between the hydroxy aldehyde and the hemiacetal.

(49) (a) Chwang, W. K.; Eliason, R.; Kresge, A. J. *J. Am. Chem. Soc.* 1977, 99, 805. (b) Chiang, Y.; Chwang, W. K.; Kresge, A. J.; Robinson, L. H.; Sagatys, D. S.; Young, C. I. *Can. J. Chem.* 1978, 56, 456.

(50) We can also comment on a possible criticism of the electrostatic effect explanation, namely, the fact that the point for H_3O^+ lies relatively close to the carboxylic acid Brønsted line. The H_3O^+ catalyst has an unfavorable $\delta^+-\delta^+$ interaction in the transition state and would therefore be predicted to react at a slower rate. This may in fact be the case. Extension of the curved plot of Figure 8 to more acidic catalysts gives an intersection of $\text{pK}_a(\text{H}_3\text{O}^+)$ which is above the observed position.

(45) For references see: Lee, Y. N.; Schmir, G. L. *J. Am. Chem. Soc.* 1979, 101, 3026.

(46) Kresge, A. J.; Tang, Y. C. *J. Org. Chem.* 1977, 42, 757.

(47) Bell, R. P. "Acid-Base Catalysis"; Oxford University Press: London, 1941.

(48) Kresge, A. J.; Chiang, Y. *J. Am. Chem. Soc.* 1973, 95, 803.

One can also see why there might be a difference in behavior between formaldehyde and benzaldehyde hemiacetals. The former react by eq 12 since in that way formation of the highly unstable $\text{H}_2\text{C}=\text{O}^+\text{H}$ ion of eq 13 is avoided.² The corresponding ion in the benzaldehyde series is, however, much more stable. For example, the value of $\text{p}K_a^3$ of the protonated hemiacetal of eq 12 can be estimated to be somewhere around -5 ,⁵¹ while the value of $\text{p}K_a^4$ of the protonated benzaldehyde of eq 13 should lie somewhere around -4 .⁵² The similarity in these two numbers suggests that these two cations should be of similar stability.

Finally, if these $\text{p}K_a$ estimates are used to calculate what rates are required in the base-catalyzed steps of eq 12 and 13, very little difference is seen. For acetic acid catalysis of $3 \rightleftharpoons 4$, the value of k_{-4} required in eq 12 is $5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, while the value of k_5 required in eq 13 is $1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$.

Experimental Section

Materials. Alkylphosphonic acids were prepared as described in ref 47. All other buffers were the best commercial grade and were used without further purification. Acetals 5–9 were prepared as previously described for 1,3-dihydro-1-methoxyisobenzofuran 5.⁵³

1,3-Dihydro-1-ethoxyisobenzofuran (6): bp 76 °C (3 mm); NMR (CCl_4) δ 7.1–7.3 (m, 4 H), 6.06 (d, $J = 3 \text{ Hz}$, 1 H), 5.10 (dd, $J = 3 \text{ Hz}$, $J = 13 \text{ Hz}$, 1 H), 4.83 (d, $J = 13 \text{ Hz}$, 1 H), 3.60 (aa' m, 2 H), 1.16 (t, $J = 7 \text{ Hz}$, 3 H).

1,3-Dihydro-1-isopropoxyisobenzofuran (7): bp 77–78 °C (3 mm); NMR (CCl_4) δ 7.2–7.3 (m, 4 H), 6.20 (d, $J = 3 \text{ Hz}$, 1 H), 5.13 (dd, $J = 3 \text{ Hz}$, $J = 13 \text{ Hz}$, 1 H), 4.83 (d, $J = 13 \text{ Hz}$, 1 H), 3.98 (septet, $J = 7 \text{ Hz}$, 1 H), 1.19 (d, $J = 7 \text{ Hz}$, 6 H).

1,3-Dihydro-1-tert-butoxyisobenzofuran (8): bp 100 °C (3 mm); NMR (CCl_4) δ 7.22 (br s, 4 H), 6.32 (d, $J = 3 \text{ Hz}$, 1 H), 6.16 (dd, $J = 3 \text{ Hz}$, $J = 13 \text{ Hz}$, 1 H), 4.83 (d, $J = 13 \text{ Hz}$, 1 H), 1.31 (s, 9 H).

3,4-Dihydro-1-methoxy-1H-2-benzopyran (9): bp 87–90 °C (1.5 mm); NMR (CCl_4) δ 7.2–7.4 (m, 4 H), 5.23 (s, 1 H), 3.8–4.1 (m, 2 H), 3.43 (s, 3 H), 2.4–3.0 (m, 2 H).

Satisfactory analyses were obtained only in the case of 6. For 7–9, the contaminant was shown by NMR to be unreacted lactone. No attempt was made to purify these samples further.

(51) A value of -4.6 was estimated for the protonated form of formaldehyde ethyl hemiacetal,² and the phenyl ring of the benzaldehyde hemiacetals should make this somewhat more negative.

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Kinetics. The hydrolyses of acetals 5–9 were studied on a Unicam sp 1800 spectrophotometer by following the increase in absorbance at 255 nm. The hydroxy aldehyde-hemiacetal equilibrations were studied on a Messanglagen T-jump spectrophotometer or on a Durrum-Gibson stopped-flow spectrophotometer. The photomultiplier output from the T-jump apparatus was linked with a Biomation transient recorder, followed by transfer to a strip-chart recorder. In stopped-flow kinetic runs the photomultiplier output was digitized, and this signal was transferred directly to a Tektronix 4051 minicomputer equipped with graphics display. Excellent first-order kinetic plots were obtained in each case. Rate constants determined on the T-jump apparatus are the average of 3 or 4 different runs; rate constants from the stopped-flow apparatus are the average of 5–8 kinetic runs. The experimental procedure involved the preparation of a solution of acetal 5 or acetal 9 in 0.001 M HCl. The acetal is relatively rapidly hydrolyzed in this acid. After a time sufficient for complete hydrolysis, the solution was mixed with an appropriate buffer (T-jump kinetic study) or excess sodium hydroxide (stopped-flow kinetic study). In the latter case the final solution containing the substrate was arranged to contain 0.05 M NaOH and 0.55 M NaCl. This was mixed in the stopped-flow spectrophotometer with buffers containing 0.05 M HCl and also having an ionic strength of 0.6. Control experiments confirmed that there is no optical density change on mixing the acid and base solutions in the absence of substrate. The optical density change observed in the T-jump experiments involved an increase in absorbance of about 0.005 absorbance units in each case. (This indicates a shift to more hydroxy aldehyde at higher temperature.) The optical density change in the stopped-flow experiments involved an increase in absorbance of 0.1–0.2 absorbance units. This change is not as great as that predicted on the basis of the displacement of the hydroxy aldehyde-hemiacetal equilibrium in 0.005 M NaOH (Figure 3). We attribute the smaller change to the fact that the mixing process in a stopped-flow spectrophotometer is not instantaneous. There is a time in our experiments where the substrate is an environment which is less basic than that in which it started but which is not the final environment obtained on full mixing and neutralization. Because of the very rapid rate of equilibrium in base, the equilibrium will have a chance to shift in the partially mixed less basic solution. The result is that on full mixing, the hydroxy aldehyde-hemiacetal equilibrium is shifted toward its neutral position relative to where it started in the 0.05 M NaOH solution.

Acknowledgment. The financial support of the Natural Sciences and Engineering Research Council of Canada and the Research Corporation is gratefully acknowledged.

Registry No. 1, 55479-94-2; 2, 496-14-0; 3, 75802-18-5; 4, 493-05-0; 5, 67536-29-2; 6, 75802-19-6; 7, 75802-20-9; 8, 75802-21-0; 9, 75802-22-1.