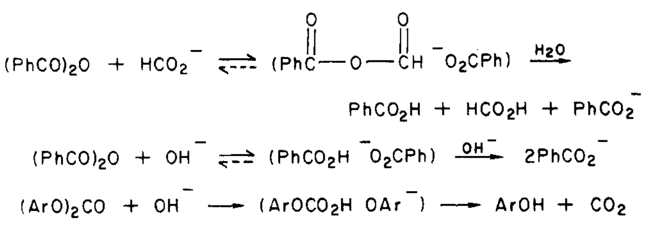
Scheme III



what different geometries of the reaction centers of anhydrides and carbonates may influence the rate constants for nucleophilic attack in the micelles as compared with those in water.

But the differences between the two substrates could also be due to mechanism. Reaction of benzoic anhydride and formate ion goes via a mixed anhydride,[11] which in a micelle may readily recombine with benzoate ion (Scheme III) but should react rapidly with water in the absence of micelle. In reaction with OH^- in a micelle, benzoate ion may react with the adjacent benzoic acid, whereas in water, benzoic acid would be deprotonated before recombination could occur. On the other hand, the carbonate ester formed by nucleophilic attack upon bis(4-nitrophenyl) carbonate could rapidly and spontaneously lose CO_2 both in micellar and aqueous pseudophases so that intermediates would not recombine.[34]

Acknowledgment. Support of this work by the Chemical Dynamics Program of the National Science Foundation is gratefully acknowledged. We thank John R. Moffatt for help with the kinetic simulations.

Registry No. Benzoic anhydride, 93-97-0; bis(4-nitrophenyl) carbonate, 5070-13-3; cetyltrimethylammonium trimethylacetate, 80737-51-5; CTABr, 57-09-0; CTAFor, 80721-50-2; CTAOH, 505-86-2; CTAOAc, 51374-75-5.

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Hydrolysis of Aldal Acetals

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Eleven aldal acetals were synthesized, and the kinetics of their hydrolyses in water and in water–acetonitrile were studied as model systems for the hydrolysis of sucrose. α,α'-Diethoxypropyl ether (an aldal acetal) hydrolyzes in water without hemiacetal buildup. The reaction is not subject to general acid catalysis and the value of $k_{D_3^+O}/k_{H_3^+O} = 2.44$, both results being characteristic of an A1 mechanism. The energy of activation for the hydrolysis of α,α'-diethoxydipropyl ether was 84.98 kJ mol^{-1} in water and showed no temperature dependency over the range of 15–35 °C. The structural effects for the hydrolysis of aldal acetals parallel those for acetal hydrolysis.

The hydrolysis of acetals has occupied a central position in chemical kinetics and in physical organic chemistry.[1,2] Historically, the most important acetal in kinetic studies has been sucrose, and the continued general interest in acetals is because of the functional relationship to the glycosidic link of carbohydrates. Particular emphasis was given to the overall problem during the past decade because of the assignment of the structure of lysozyme and interest in the catalytic mode of lysozyme for the hydrolysis of polysaccharides.[3] Further interest in the problem has intensified due to the worldwide shortages of petroleum hydrocarbons and the need to be able to produce fuels and other materials from biomass.[4]

The hydrolysis of sucrose was the first chemical reaction to be studied as a function of time[5] and was one of the first reactions for which the influence of temperature on reaction rates was studied.[6] From the pioneering work of Wilhelmy in 1850 on the hydrolysis of sucrose up to 1947 there were over 1000 papers published on this subject, and the interest continues.[1,7] In spite of the continued and intense interest in the hydrolysis of sucrose there remain a number of specific and general problems to be solved for the process. Prominent among these problems are the following. (1) There is a marked change in the energy of activation with temperature.[1,8,9] The dramatic change in the energy of activation with temperature has not been explained. This well-documented fact is incredible when one realizes that the prominent reaction used by Arrhenius to establish the equation bearing his name is the hydrolysis of sucrose.[10] (2) Not only does the energy of activation for sucrose hydrolysis change with temperature but it also changes with the kind and amount of acid catalyst and with the supporting electrolyte.[8,11] (3) The specific rate constant (first order) for sucrose hydrolysis changes as the concentration of sucrose is changed.[8] The concentration effects have required that comparative studies be standardized as regards molarities of reactants and catalysts. (4) The site of protonation for bond cleavage and the bonds which cleave to yield the reaction products have not been established. The details of this complex process which includes protonation, bond cleavage, hydration, depro-

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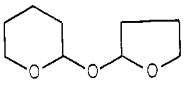
tonation, mutarotation of α-D-glucopyranose, mutarotation of β-D-fructofuranose, and rearrangement of β-D-fructofuranose to mutarotated β-D-fructopyranose are only broadly sketched out. Even the gross details were slow in evolving, and significant errors about and omissions of known facts in modern textbooks often confuse the story.[12]

The complexity of the sucrose structure, particularly as a solvated system in water, reveals a system capable of a melody of interactions. In order to simplify these possible interactions, we have chosen to simplify the chemical structures to begin an attack of the problems related to the reaction pathway. We have synthesized a group of compounds to model the basic sucrose disaccharide link. In contrast to most disaccharides and polysaccharides, sucrose is not a typical acetal. The two monosaccharide units of sucrose are connected through their glycosidic carbons[13] so that sucrose is an aldal acetal having the bonding array of $RC(OR^1)HOC(OR^1)HR$ or is an α,α′-dialkoxy ether.[14] A simple open-chain analogue for sucrose would be α,α′-dimethoxydimethyl ether (or acetaldal dimethyl acetal as an aldal acetal) $CH_3C(OCH_3)HOC(OCH_3)HCH_3$, and a simple cyclic model would be 2-[(tetrahydrofuran-2-yl)oxy]tetrahydropyran (I). We report here



I

our initial work on the syntheses of a series of aldal acetals and of the kinetic studies of their hydrolysis as model compounds for the hydrolysis of sucrose.

Results and Discussion

Kinetics and Catalysis. Recent studies have demonstrated the presence of hemiacetal buildup during the early stages of the hydrolysis of certain acetals.[15,16] For this reason we studied the hydrolysis of α,α′-diethoxydipropyl ether in water by conventional spectroscopy and by stopped-flow spectroscopy. At 25 °C, the values of $k_{H_3^+O}$ otained by both methods were the same within experimental error (for conventional spectroscopy, $k_{H_3^+O} = 4.1$ for 1.2×10^{-3} M perchloric acid with $\mu = 0.4$ and for stopped-flow spectroscopy, $k_{H_3^+O} = 3.2\ 1$ mol L^{-1} s^{-1} for 0.5 M perchloric acid). The kinetic plots were first order over the entire extents of reaction studied (50–80%). The results effectively rule out the possibility for hemiacetal buildup during the hydrolysis of these acetals and most likely for the other aldal acetals as well.[15]

The hydrolysis of most acetals do not show general-acid catalysis.[17] We chose α,α′-diethoxydipropyl ether to search for general-acid catalysis for aldal acetals. The results of this study are summarized in Table II. α,α′-Diethoxydipropyl ether was hydrolyzed in water with phosphoric acid–sodium dihydrogen phosphate. The acid–salt catalyst was used at three different ratios, with the ionic strength being maintained constant at 0.2 with the necessary amount of sodium perchlorate. As may be seen from the last column of the table, the value of $k_{H_3^+O}$ is independent of the amount of general acid present. The average value of $k_{H_3^+O}$ from these 27 experiments is 4.15 ± 0.05 L mol^{-1} s^{-1}. A plot of k_{obsd} vs. $[H_3^+O]$ is linear with a slope of 4.13 ± 0.05 L mol^{-1} s^{-1} obtained by least squares methods and with an intercept term of zero. This value is slightly different from the values reported for this same compound in Table III ($k_{H_3^+O} = 4.58$) for the energy of activation study and that reported in Table IV ($k_{H_3^+O} = 4.24$) as part of the general structure–reactivity study. These discrepancies occurred because of slight differences in the temperature, because of significant differences in ionic strengths, and because of differences in acidities (pH measurements were used in the general-acid catalysis study and in the structural study whereas the known concentration of perchloric acid was used in the energy of activation study). The results for this study clearly rule out general-acid catalysis for the hydrolysis of α,α′-diethoxydipropyl ether, and this result is most likely to hold true for the hydrolysis of the other aldal acetals studied.

Table I. Yields and Properties of Aldal Acetals

RC(OR′)HOC-(OR′)HR R	R¹	% yield[a]	bp, °C (torr)	n^{25}_D
H	CH_3	12	96 (740)[b]	1.3772
H	C_2H_5	38	130 (740)[c]	1.3868
CH_3	CH_3	21	123 (740)[d]	1.3873
CH_3	C_2H_5	23	58 (25)[e]	1.3949
CH_3	n-C_3H_7	22	73 (9)[f]	1.4058
CH_3	n-C_4H_9	27	72 (1)	1.4134
C_2H_5	CH_3	12	59 (12)	1.4035
C_2H_5	C_2H_5	32	58 (15)	1.4058
C_2H_5	n-C_3H_7	34	72 (1)	1.4153
C_2H_5	n-C_4H_9	31	79 (0.5)	1.4203
n-C_3H_7	C_2H_5	36	63 (1)	1.4130

[a] Yield calculated on the amount of starting aldehyde. All 11 compounds gave C and H combustion results in agreement with theory. [b] Descude[26] reported a boiling point of 106–108 °C (atmospheric pressure). [c] Litterscheid and Thimme[26] reported a boiling point of 140 °C (atmospheric pressure) and n_D 1.3873. [d] Geuter and Laatsch[26] reported a boiling point of 126 °C (atmospheric pressure). [e] Geuter and Laatsch[26] reported a boiling point of 153 °C (atmospheric pressure). [f] Geuter and Laatsch[26] reported a boiling point of 184 °C (atmospheric pressure).

The rate constants for the hydrolysis of α,α′-diethoxydipropyl ether in H_2O and in D_2O were studied by stopped-flow spectroscopy at 25 °C with perchloric acid as a catalyst. For 0.0811 g of 70% perchloric acid diluted to 10.0 mL with water, the value of $k_{obsd} = 0.133$ s^{-1}. For 0.0811 g of 70% perchloric acid diluted to 10.0 mL with deuterium oxide, the value of $k_{obsd} = 0.324$ s^{-1}, giving an approximate $k_{D_3^+O}/k_{H_3^+O} = 2.44$. This value is in the range for reactions involving a preequilibrium protonation of the substrate followed by the rate-determining step as is normally observed for A1 mechanisms.[18]

Energy of Activation. Rates of hydrolysis of α,α′-diethoxydipropyl ether were measured in water at 15, 20, 25, 30, and 35 °C by using perchloric acid as a catalyst and sodium perchlorate to regulate the ionic strength. These data are summarized in Table III along with the calculated values of E_a, ΔG^*, ΔH^*, and ΔS^*, which were calculated by standard procedures.[19] The least-squares value of the energy of activation was 84.93 kJ mol^{-1} (20.3 kcal mol^{-1})

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Table II. General Acid Catalysis Study of the Hydrolysis of α,α'-Diethoxypropyl Ether in Water at 25 °C[a]

$[H_3PO_4]$	$[NaH_2PO_4]$	acid/salt ratio	$[NaClO_4]$	pH	$10^2 k_{obsd}$, s^{-1}	$k_{H_3^+O}$, L mol^{-1} s^{-1} [b]
0.07	0.35	0.20	0.05	2.740	0.759	4.17
0.04	0.20	0.20	0.20	2.713	0.808	4.17
0.02	0.10	0.20	0.30	2.752	0.728	4.11
0.043	0.30	0.14	0.10	2.881	0.560	4.24
0.028	0.20	0.14	0.20	2.874	0.545	4.07
0.014	0.10	0.14	0.30	2.895	0.520	4.08
0.03	0.30	0.10	0.10	3.049	0.380	4.26
0.02	0.20	0.10	0.20	3.021	0.395	4.15
0.01	0.10	0.10	0.30	3.040	0.377	4.15

[a] All concentrations are in moles per liter. [b] The rate constants are the average of triplicate runs.

Table III. Temperature and Rate Constants for the Hydrolysis of α,α'-Diethoxypropyl Ether in Water[a]

temp, °C	$k_{H_3^+O}$, L mol^{-1} s^{-1} [b]	E_a [c]	$\Delta G^{\ddagger}$ [c]	$\Delta H^{\ddagger}$ [c]	$\Delta S^{\ddagger}$ [c]
15	1.41		67.2	82.5	53.1
20	2.56		67.0	82.5	52.9
25	4.58	84.93	66.7	82.4	52.7
30	8.06		66.5	82.4	52.6
35	14.10		66.2	82.4	52.6

[a] The catalyst was 1.240×10^{-3} M perchloric acid. The acid solution was prepared by diluting 10.00 mL (pipet) of standard 0.1240 M $HClO_4$ in 0.100 M $NaClO_4$ to 1 L in 0.100 M $NaClO_4$. [b] The values of $k_{H_3^+O}$ were calculated from k_{obsd} values at the known concentration of perchloric acid. [c] All activation parameters are in kilojoule per mole.

Table IV. Structural Variation and Rates of Hydrolysis of Aldal Acetals in Water at 25 °C[a]

no[b]	RC(OR')HOC(OR')HR R	 R^1	$k_{H_3^+O}$, L mol^{-1} s^{-1}
1	H	CH_3	0.25 (± 0.04)
2	H	C_2H_5	0.77 (± 0.02)
3	CH_3	CH_3	1.03
4	CH_3	C_2H_5	3.56
5	CH_3	n-C_3H_7	3.60
6	C_2H_5	CH_3	1.31
7	C_2H_5	C_2H_5	4.24

[a] Perchloric acid was the catalyst used at a concentration of about 1.5×10^{-3} M, and the supporting electrolyte was 0.1 M sodium perchlorate. The values of $k_{H_3^+O}$ were calculated from k_{obsd} values and $[H_3^+O]$ was determined with a pH meter. Compounds 1 and 2 were followed by dilatometry. The rate constants are the average of duplicate results. For compounds 3-7, the results were obtained by UV spectrophotometric studies, and the rate constants are the averages of quadruplicate results.

with a preexponential term of $A = 3.53 \times 10^{15}$ mol L^{-1} s^{-1}. The plot of ln $k_{H_3^+O}$ vs. $1/T$ was linear for this aldal acetal over the indicated temperature range.

For sucrose hydrolysis, the value of the energy of activation is 106.4 kJ mol^{-1} (25.4 kcal mol^{-1}) at 25 °C but decreases with increasing temperature to a value of 95.72 kJ mol^{-1} (22.88 kcal mol^{-1}) at 50 °C. Over the temperature range of 0–50 °C, the value of E_a decreases 17%. Given the fact that for the temperature change of 15–35 °C the energy of activation for the hydrolysis of α,α'-diethoxydipropyl ether is temperature invariant, we probably can rule out the aldal acetal structure as being responsible for the nonzero values of dE/dT for sucrose. Further confirmation of this conclusion should be made by studying the hydrolysis of 2-[(tetrahydropyran-2-yl)oxy]tetrahydrofuran and 2-[(tetrahydropyran-2-yl)oxy]-2-methyltetrahydrofuran as model structures for sucrose hydrolysis.

Table V. Structural Variation and Rates of Hydrolysis If Aldal Acetals in Water–Acetonitrile at 25 °C by Stopped-Flow Methods[a,b]

no.	RC(OR')HOC(OR')HR R	 R^1	$k_{H_3^+O}$,[c] L mol^{-1} s^{-1}
1	Me	Me	1.0
2	Me	Et	5.4
3	Me	n-Pr	5.8
4	Me	n-Bu	6.5
5	Et	Me	3.1
6	Et	Et	8.1
7	Et	n-Pr	(15.4)
8	Et	n-Bu	(8.0)
9	n-Pr	Et	(22.2)

[a] All reactions were performed in 50/50 (v/v) water–acetonitrile at 25 °C and were followed by stopped-flow spectroscopy. The catalyst was 0.99 M perchloric acid. [b] The rate constants are the average of duplicate runs and were calculated from k_{obsd} values and the known concentration of perchloric acid. [c] The values in parentheses are considered questionable because of some solvent m mixing effects observed for these systems.

Structural Studies. Eleven aldal acetals were studied to evaluate structural effects on the rates of hydrolysis. For the general aldal acetal structure, $RC(OR^1)HOC(OR^1)HR$ (α,α'-dialkoxy ethers), we evaluated changes in rates due to changes in both R and R^1. The results at 25 °C for the seven aldal acetals which were water soluble and which were followed by dilatometry or spectrophotometry are summarized in Table IV. The results for the hydrolysis of nine of the aldal acetals which were studied by the stopped-flow spectrophotometric method in 50/50 (v/v) water–acetonitrile at 25 °C are summarized in Table V. For both systems perchloric acid was used as a catalyst. Sodium perchlorate was used to provide a constant ionic strength for the regular spectrophotometric and dilatometric studies, but no electrolyte other than the perchloric acid was used for the stopped-flow studies.

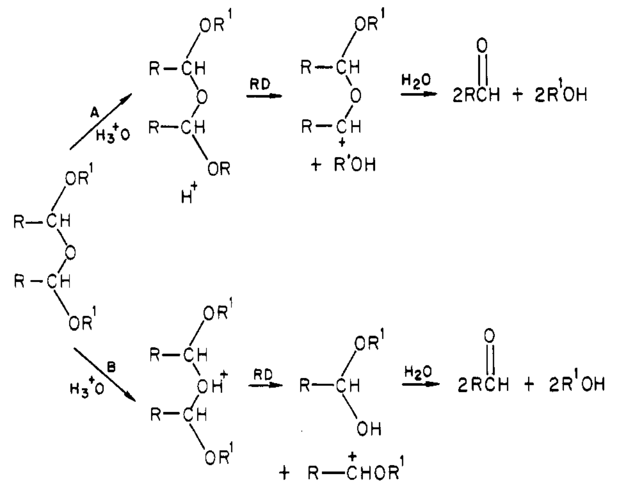
The results show the following relationships.

(1) The same structural effects were observed in water and in water–acetonitrile.

(2) For the alkyl group R^1 of the aldehyde held constant while R' of the alcohol was varied, the rate increased significantly from methyl to ethyl, but there was little change beyond ethyl. For the three different cases where the aldehyde R group was CH_3 and C_2H_5, the rate increased consistently by a factor of 3 as R^1 goes from methyl to ethyl (cf. 1 to 2, 3 to 4, and 6 to 7 of Table IV). The results were not quite as consistent for the stopped-flow results of Table V but show the same trends.

The most difficult problem we encountered in the stopped-flow studies, and which contributed to uncertainties in the results, was that due to mixing effects of the substrate in water–acetonitrile. With the higher homologues, a slight cloudiness could be observed on mixing

Scheme I

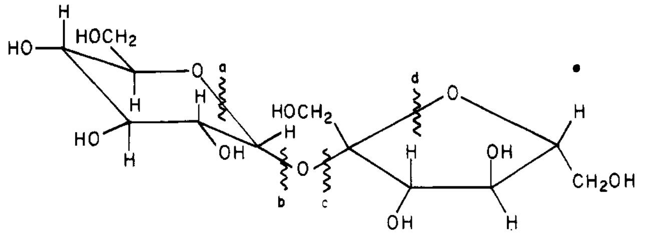


the reactants which took a few seconds to clarify. This effect causes an uncertainty in the results for the last three compounds of Table V. The results are of the right order of magnitude and do confirm, in general, the results of Table IV.

(3) For the alkyl portion, R^1, of the alcohol held constant and for the R group of the aldehyde being changed, a relatively large change in the rate was observed as R went from H to CH_3 (rate change of over 4 in comparing **1** to **3** and **2** to **4**). As R increases from CH_3 to C_2H_5, the rate change was much smaller (ca. 1.25) and likely will change little with longer R. We were unable to confirm this saturation effect because of the limited solubility in water of α,α'-dipropoxydipropyl ether, of α,α'-dibutoxydipropyl ether, and of α,α'-diethoxydibutyl ether and because of the lack of consistency of the stopped-flow results for these compounds.

Mechanism. The results of our kinetic studies for the first-order hydrolysis of α,α'-diethoxydipropyl ether demonstrate specific hydronium catalysis and a solvent isotope effect of 2.44. These results are consistent with an A1 mechanism for the hydrolysis of these aldal acetals.[18] In that sense they are not different in mechanism from the hydrolysis of the simple acetals of aldehydes and ketones.[2] The results for the structural effects due to changes in R and R^1 of the aldal acetals are also consistent with an A1 mechanism. They also are consistent with the results observed by Skrabal and Eger for the hydrolysis of acetals of formaldehyde,[20] results which were first used to rationalize the mechanism for the hydrolysis of acetals.[2] Whether the rate-determining (RD) step involves path A or path B or both cannot be answered at this time. Protonation of the alkoxy oxygens (pathway A, Scheme I) should be favored because these oxygens should be more basic than the aldal oxygen by 2–2.5 pK_a units, and there are two of these.[2b,21] On the other hand, pathway B should be favored over pathway A because the ion $R{-}C^+HOR^1$ is substantially more stable than the ion $RC^+HOCHROR^1$. We do not know of an experiment to distinguish the two paths.

The answers to these questions are important to understanding the pathways for the hydrolysis of sucrose and other nonreducing saccharides of similar structure. The hydrolysis of sucrose involves cleavage of an aldal acetal to form mutarotated α-D-glucopyranose, and β-D-fructofuranose, and the other mutarotated products.[12] The position of the carbon–oxygen cleavage for sucrose has not been determined.[7] In contrast to the open-chain compounds we have studied for which there are three possible bond cleavages (two of which are identical), sucrose has four bonds which could be cleaved and these are marked as a–d. Barnett and O'Conner state that cleavages b and c would be preferred over cleavages a and d because the latter require ring opening.[7] They also prefer the fructosyl–oxygen cleavage (bond c) over the glucosyl–oxygen cleavage (bond b) because of the added stability of a tertiary carboxonium ion over a secondary carboxonium ion. We also favor this cleavage because of the added stability of a cyclic five-membered carboxonium ion over a cyclic six-membered carboxonium ion.[20]



There are further complications for the sucrose hydrolysis because of the large number of protonation sites. There are a total of 11 oxygen atoms which can accept protons in addition to the oxygens on the waters of hydration sheath of sucrose in water. It has been suggested that there are eight water molecules per sucrose molecule, but the number apparently is variable from as low as two to as high as eight, depending upon the concentration of sucrose and the interpretation of the various experimental methods.[21,22] The large number of unproductive protonation sites relative to the three possible productive sites provides part of the reason as to why sucrose and other disaccharides hydrolyze relatively slowly in dilute mineral acid compared to simple acetals. For example, $k_{H_3^+O} = 9.03$ L mol^{-1} s^{-1} for dimethyl acetal[25] and 2.56 L mol^{-1} s^{-1} for α,α'-diethoxydipropyl ether at 20 °C, while $k_{H_3^+O} = 0.015$ L mol^{-1} s^{-1} for sucrose and 1.68×10^{-5} L mol^{-1} s^{-1} for maltose[1] at 60 °C. Perhaps the most important reason for the relatively low rate of hydrolysis of glycosides compared to simple acetals is that the α-hydroxy groups of the glycosides destabilize the oxocarbonium ions which form in the rate-determining step.

Experimental Section

All boiling points are uncorrected. Elemental analyses were made by Galbraith Laboratories. All proton NMR were recorded on a Perkin-Elmer R-20 spectrometer, and the infrared spectra were recorded on a Perkin-Elmer 580 spectrometer.

Aldal Acetals. These compounds were made by the conversion of the aldehydes to α,α'-dichlorodialkyl ethers followed by the subsequent reaction with sodium alkoxides[24] (eq 1 and 2). In each case, except for the formaldehyde systems, the dichloro ether synthesis involved the use of dry gaseous hydrogen chloride with the appropriate aldehyde. For the formaldehyde systems, bis(chloromethyl) ether was made by a procedure mentioned in the

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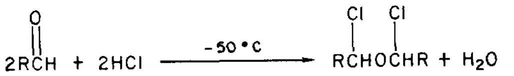
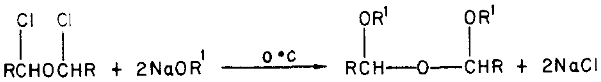
 (1)

$$2RCHO + 2HCl \xrightarrow{-50\ °C} RCHCl{-}O{-}CHClR + H_2O \quad (1)$$

 (2)

$$RCHCl{-}O{-}CHClR + 2NaOR^1 \xrightarrow{0\ °C} RCH(OR^1){-}O{-}CH(OR^1)R + 2NaCl \quad (2)$$

literature.[25] Bis(chloromethyl) ether should be handled with great caution because of its high carcinogenic activity reported for inhalation by and subcutaneous injection in rats.[28]

The details are given here for the preparation of α,α′-diethoxydipropyl ether, and this will serve as a general procedure for other compounds. Freshly distilled propionaldehyde (348 g, 6.0 mol) was transferred (nitrogen purge) to a 1-L, three-necked flask equipped with a mechanical stirrer, a gas inlet tube for hydrogen chloride, a thermometer, and a liquid nitrogen/toluene cooling bath. Dry hydrogen chloride (dried with a concentrated sulfuric acid tower) was added to the aldehyde while the mixture was vigorously stirred at −40 to −60 °C. The addition was continued until 440 g of dry HCl (twice the theoretical amount) had been used. As a visual indicator of the correct amount of hydrogen chloride without weighing we could observe the HCl fumes at the gas outlet when about twice the theoretical amount of HCl had been absorbed. The mixture was allowed to warm to 0 °C with stirring. The crude mixture was transferred to a separatory funnel and the lower aqueous layer removed as rapidly as possible. The organic layer was transferred to a chilled (ice–salt bath) Erlenmyer flask and dried with anhydrous sodium sulfate, and excess hydrogen chloride was removed by means of a nitrogen purge. There was obtained 400 g (78% yield) of residue α,α′-dichlorodipropyl ether which was stored over molecular sieves in a refrigerator. We have found that the dichloro ethers may be stored in a refrigerator for at least 3 months and still be useful for conversion to the aldal acetals.

Sodium metal (6.9 g, 0.3 mol) was dissolved in absolute ethanol (105 mL, 1.8 mol) in a 500-mL round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a pressure-equalizing addition funnel. The sodium ethoxide solution was cooled to 0 °C (ice–salt bath), 24 g (0.14 mol) of α,α′-dichlorodipropyl ether was added dropwise over a period of 1.5 h, and the solution was allowed to warm to room temperature. The salt was removed by filtration, and the filtrate was distilled through a 2-ft spinning-band column. There was obtained 11.0 g (41% yield based on the crude dichloro ether) of α,α′-diethoxydipropyl ether: bp 58–59 °C (1.5 torr); $n^{25}{}_D$ 1.4058. Anal. Calcd for $C_{10}H_{22}O_3$: C, 63.12; H, 11.66. Found: C, 62.64; H, 11.67.

The yields, physical properties, and elemental analyses for the 11 aldal acetals are summarized in Table I. The infrared spectra for all of the compounds showed all of the expected absorption frequencies and no extraneous absorption frequencies. The proton NMR spectra were as expected for these structures with the correct number of protons of each kind.

Kinetic Studies. Solutions. The water used for all kinetic studies was deionized and distilled. A stock solution of perchloric acid was prepared by dilution of 70% acid (Fisher Scientific Co.) and standardized with standard base. Ionic strengths were maintained by the addition of weighed quantities of sodium perchlorate. The sodium perchlorate (G. F. Smith) was recrystallized from water, air-dried overnight, dried for 48 h at 110 °C, and stored in a desiccator.

The phosphate buffers were prepared from dilute stock solutions of phosphoric acid (standardized with base) and of sodium dihydrogen phosphate. As the ratio of H_3PO_4 to NaH_2PO_4 was changed, the ionic strength was maintained constant at $\mu = 0.2$ with added sodium perchlorate.

pH Measurements. All pH measurements were made with a Corning Model 10 pH meter equipped with an Orion double-junction electrode (90-02-00) and an Orion glass electrode (13-639-3).[29] The electrodes were washed with distilled water and blotted dry with Kimwipes for each measurement. Coleman certified buffer tablets pH 4.00 were used to standardize the meter.

The rate measurements reported were made by three different methods which are described. The tables record which method was used for the systems studied.

Spectrophotometric Measurements. The hydrolyses of the aldal acetals which were sufficiently soluble in water were followed by monitoring the increase in the UV absorbance due to aldehyde formation.[30] The spectrophotometer was a Beckman DU equipped with a special temperature regulated cell.[31] This system permits the regulation of the temperature of reaction solutions in the cells to better than ±0.01 °C over the range of 10–50 °C for several hours. The aldal acetals studied by this method were α,α′-dimethoxy-, α,α′-diethoxy-, and α,α′-dipropoxydiethyl ethers and α,α′-dimethoxy- and α,α′-diethoxydipropyl ethers. The hydrolysis rates were followed at 276 nm.

A solution of the aldal acetal was prepared from a weighed amount of the acetal in water (50-mL volumetric flask) and shaken vigorously for a few minutes. Exactly 5.00 mL (pipet) of the solution was transferred to a 50-mL Erlenmeyer flask followed by 5.00 mL (pipet) of the perchloric acid sodium perchlorate solution. Both solutions were essentially at reaction temperature prior to mixing (main regulated bath). The contents were transferred to the temperature-regulated UV cell and absorption readings taken as often as possible over about 2 half-lives. At least 15 readings were taken, and the infinity absorption readings were taken after 10–15 half-lives. Unused portions of the reaction mixtures (stoppered) were stored in the constant-temperature bath and were used to determine the pH. Values of ln $(A_\infty - A_t)$ were plotted to eliminate spurious data points and values of the slope and the correlation coefficient were calculated by least squares. The values of $k_{H_3^+O}$ were calculated from the slopes and $[H_3^+O]$. Each run was performed in triplicate and the values reported are average values with agreement being ±3% or better.

Dilatometric Measurements. The hydrolysis of α,α′-dimethoxydimethyl ether and of α,α′-diethoxydimethyl ether produces formaldehyde. Insufficient free carbonyl is available in solution to permit the measurement of the extent of reaction by UV spectroscopy. For this reason we followed the hydrolysis of these acetals by dilatometry.[20] The dilatometer was a modified version of that of Brönsted and Guggenheim[32] with a reaction compartment of 125 mL and a capillary diameter of 0.7 mm. The dilatometer was immersed in a large (65 gal) constant-temperature bath (25 ± 0.005 °C), with the temperature being measured by a Hewlett-Packard 2801A quartz thermometer.

To 140 mL of a standardized solution of perchloric acid–sodium perchlorate (at bath temperature) in a 500-mL Erlenmeyer flask there was added 0.5 mL (syringe) of the α,α′-diethoxydimethyl ether. The flask was shaken vigorously (10 s), and the solution was transferred to the dilatometer. The solution was forced into the capillary tube by nitrogen pressure, and the level of the solution was followed with time by means of a cathetometer (±0.1 mm) as the volume contracted. The infinity reading was taken after 10–15 half-lives. After each run, the dilatometer was cleaned by water rinsing, followed by a 4-h soaking in 10% nitric acid and then by a thorough rinsing with distilled water. The dilatometer was oven dried (110 °C) before reuse. Plots of ln $(H_\infty - H_t)$ vs. time were made to eliminate spurious points, and the slopes and the correlation coefficients were calculated by the method of least squares. The values of $k_{H_3^+O}$ were calculated from the slopes and $[H_3^+O]$. The values of $k_{H_3^+O}$ reported in Table IV are the average of duplicate runs.

Stopped-Flow Measurements. The hydrolyses of nine of the aldal acetals were studied spectroscopically in a Durrum stopped-flow reactor.[15] The hydrolyses were run in 50/50 (v/v) of water–acetonitrile solution. This solvent readily dissolved all of the aldal acetals and was convenient for use in the stopped-flow system. The carbonyl absorption at 278 nm was monitored for all of the aldal acetals as hydrolysis proceeded. The entire system was purged with water and the photodetector zeroed with distilled water in the tube. One of the reservoir syringes was filled with

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1.980 N perchloric acid, and the second syringe was filled with an acetonitrile solution of the aldal acetal. The entire system was flushed out several times by firing the accuator to force equal volumes of the two solutions into the reactor. The system was then rezeroed (scope) and the reaction started by firing the accuator. The trace of absorbance vs. time was recorded on the scope and then transferred onto a strip-chart recorder. The values of absorption and time were taken from the chart, and rate constants were calculated by least-squares methods. These k_{obsd} values were converted to $k_{\mathrm{H_3^+O}}$ values by division with the known concentration of perchloric acid (0.99 M).

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Registry No. (R = H, R′ = Me), 628-90-0; (R = H, R′ = Et), 5648-29-3; (R = Me, R′ = Me), 3752-99-6; (R = Me, R′ = Et), 80243-06-7; (R = Me, R′ = *n*-Pr), 80243-07-8; (R = Me, R′ = *n*-Bu), 80243-08-9; (R = Et, R′ = Me), 80243-09-0; (R = Et, R′ = Et), 80243-10-3; (R = Et, R′ = *n*-Pr), 80243-11-4; (R = Et, R′ = *n*-Bu), 80243-12-5; (R = *n*-Pr,R′ = Et), 80243-13-6.

Temperature-Dependent Acid Dissociation Constants (K_a, ΔH_a, ΔS_a) for a Series of Nitrogen-Substituted Hydroxamic Acids in Aqueous Solution

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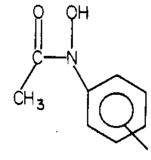
The acid dissociation constants (K_a) of a series of eight substituted *N*-phenylacetohydroxamic acids, $CH_3C(O)N(OH)C_6H_4X$ (X = H, 4-CH_3, 4-Cl, 4-I, 3-I, 3-CN, 4-CN, 4-C(O)CH_3), have been determined in aqueous solution ($I = 2.0$) for a range of temperatures. The pK_a data at 25 °C exhibit a small variation with the substituent X in the direction expected according to their Hammett substituent constants ($\rho \approx 0.1$). These small variations in pK_a values are due to compensating trends in ΔH_a and ΔS_a, which show significant variation with substituent. These results are discussed in terms of the substituent's influence on hydroxamate anion–solvent interactions and the relative influence on pK_a of a substituted phenyl group attached to the C or N end of the hydroxamate moiety.

Hydroxamic acids[1] are remarkably versatile as reagents in organic and inorganic analysis, in pharmaceuticals, in food additives, and in nuclear fuel processing. They form very stable transition-metal complexes,[2] hence their usefulness as analytical reagents.[3]

The application of these compounds often depends upon the acidity of the hydroxamic acid functional group. The factors which influence proton dissociation are therefore of interest. This report[4] describes an investigation of the electronic influence of substituents on the proton dissociation reaction in aqueous solution. Temperature-dependent acid dissociation constants have been determined for a series of substituted *N*-phenylacetohydroxamic acids (I). ΔH_a and ΔS_a values have been calculated and related to values determined for another series of C- and N-substituted hydroxamic acids previously reported from this laboratory.[5] Only very limited temperature-dependent pK_a data for hydroxamic acids are available in the literature.[2a,6-8]



I, X = H, 4-CH_3, 4-Cl, 4-I, 3-I, 3-CN, 4-CN, 4-C(O)CH_3

Our results, along with those obtained previously from our laboratory[5] are compared with pK_a data in the literature for substituted benzohydroxamic acids, $YC_6H_5C(O)N(OH)H$.[7,9] This comparison allows us to comment on the origin and relative effectiveness of the influence of the C and N substituent on hydroxamic acid acidity in aqueous solution.

Experimental Section

Materials. Aqueous solutions were prepared by using water distilled once from acidic $K_2Cr_2O_7$ and then slowly from basic $KMnO_4$ in an all glass apparatus with Teflon sleeves and stop-

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