Substituent Effects on Rates and Equilibria for Benzaldehyde–Benzaldehyde Dimethyl Acetal Interconversion[1]

T. S. Davis,[2] P. D. Feil,[2] D. G. Kubler,*[3] and D. J. Wells, Jr.[2]

Department of Chemistry, Furman University, Greenville, South Carolina 29613

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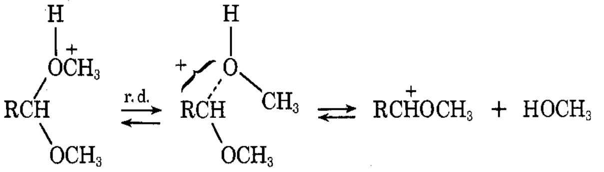
The rates of formation and the rates of hydrolysis of para-substituted benzaldehyde dimethyl acetals have been determined in 95% methanol–5% water at 15, 25, and 35°. Equilibrium constants, thermodynamic constants (ΔG, ΔH, and ΔS) and activation parameters (E_a, $\Delta G^\ddagger$, $\Delta H^\ddagger$, and $\Delta S^\ddagger$) have been calculated from the rate data. The mechanistic implications of these results are discussed.

The evidence supporting the accepted mechanism for the hydrolysis of acetals is substantial and has been reviewed critically by Cordes.[4] To the extent that this accepted mechanism is correct, one can have considerable confidence, via microscopic reversibility, that the mechanism for the formation of acetals is just the reverse of the hydrolytic mechanism. The rate-determining step for the hydrolysis of acetals in water is considered to be the formation of the alkoxycarbonium ion from the protonated acetal. Mechanism studies of the formation reaction are sparse and the studies of the hydrolytic reaction have revealed little about the nature of the steps beyond the formation of the alkoxycarbonium ion. However, it is just these steps in which we must be most interested for understanding the mechanism for the formation of acetals.



$$\mathrm{RCH}(\overset{+}{\mathrm{O}}\mathrm{HCH_3})(\mathrm{OCH_3}) \underset{\longleftarrow}{\xrightarrow{\text{r.d.}}} \mathrm{RCH}\cdots\overset{+}{\mathrm{O}}\mathrm{HCH_3}(\mathrm{OCH_3}) \rightleftharpoons \mathrm{R\overset{+}{C}HOCH_3} + \mathrm{HOCH_3} \quad (1)$$

Most studies of the hydrolysis of acetals have been performed in water or in dioxane–water. There are a number of comments in the literature which suggest, but do not substantiate, that alcohol–water mixtures are undesirable for the study of the hydrolysis of acetals.[4,5,6] There are good reasons for avoiding the use of primary alcohols in a mixture with water if one is interested only in the hydrolysis of acetals and if one wishes to completely repress the formation reaction.

If one wishes to study the formation of acetals from aldehydes and alcohols, then alcohols are the solvent(s) of choice, but if one wishes to study both acetal formation and acetal hydrolysis under identical conditions, then alcohol–water mixtures are necessary.

In previous studies from this laboratory, we reported the equilibrium constants for the formation of dimethyl acetals of aromatic aldehydes, cyclic ketones, and acyclic ketones in methanol–water mixtures.[7] Based upon these data we estimated that a solvent mixture of 95% methanol–5% water would give sufficient reaction in both directions to permit us to study the rates of acetal formation and of acetal hydrolysis without changing the solvent composition. We have verified this estimate and have completed a study of substituent effects and of temperature effects on the hydrolysis of and on the formation of dimethyl acetals of benzaldehydes in 95% methanol–5% water. The results and conclusions are reported herein.

Experimental Section

Preparation and Purification of Reagents. Methanol (Union Carbide Chemicals Co.) was purified in 3-l. batches by the method of Lund and Bjerrum.[8] Each batch was distilled on a 1.5 × 45 cm protruded metal-packed column until the transmittance was 97% or better against a specially purified sample of water at 256 mm (Beckman DU spectrophotometer). In all cases the water content (Karl Fischer) was less than 0.01% (usually 0.005% or less).

95% methanol–5% water 0.100 *m* sodium perchlorate was prepared in kilogram lots in the following manner. A 2-l. flask was tared on a solution balance (±0.2 g) and 950 g of spectral grade methanol was added followed by 50.00 ml (pipet) of spectral grade water (distilled and deionized) and 12.245 g of sodium perchlorate (G. Frederick Smith Co. reagent grade). The sodium perchlorate was used as received except for drying in a 110° oven. The pH of each batch of sodium perchlorate was measured as a function of concentration in water and did not change from that of the water.

Perchloric acid solution was prepared by adding 2–3 ml of concentrated perchloric acid (J. T. Baker) to about 500 ml of 95% methanol–5% water that was 0.1 *m* in sodium perchlorate. The acid solution was standardized by titration with aqueous KOH solution (phenolphthalein end point.) The acid and base solutions were standardized biweekly.

Aldehydes. Benzaldehyde (J. T. Baker), *p*-tolualdehyde, furfural, and *p*-anisaldehyde (all from Columbia Organic Chemicals Co.) were each washed three times with 5% sodium bicarbonate and once with water, dried over sodium bicarbonate, and distilled under vacuum. The aldehydes were collected in melting point capillary tubes and sealed under vacuum. This procedure was necessary because even the minimal exposure of the aldehydes to air by the rapid sample transfer with a nitrogen flush caused sufficient oxidation of the aldehydes to prevent attainment of reproducible extinction coefficients and reproducible rate constants.

The distillation system (Ace micro Vigreux assembly) had a four-armed "cow" attached and two of these arms supported small flasks to receive the forerun and afterrun. The other two arms each supported a receiver constructed from a 24/40 female joint sealed at the end and having a small side arm at an angle near the bottom. The side arm was sealed with a silicone rubber septum cap. The melting point capillary tube was sealed on one end, washed with spectral grade methanol, and weighed on an analytical balance. The open end was inserted through the septum cap. When sufficient middle-cut aldehyde had distilled into the receiver, the capillary tube was dipped below the surface of the liquid and a slight increase in pressure was applied to the system by nitrogen. When sufficient liquid (0.05–0.08 g) was in the tube, the end was removed from the surface of the liquid and slight nitrogen pressure was used to push the liquid to the closed end. With the system still under vacuum the tube was sealed off and the tube was pulled off at the seal point. The two parts of the tube were weighed to obtain the weight of the contained aldehyde. Repeated weighings of blank tubes demonstrated a high reproducibility of the weighing procedure.

The weighed, sealed tubes were crushed under the surface of the solvent in a volumetric flask. The flask was filled to the mark with solvent. The aldehyde solution was used for dilution for the kinetic runs and for dilutions to check the extinction coefficients. Repeated preparations of the solutions by the sealed-tube method throughout this work gave extinction coefficients which varied by less than ±1%.

p-Bromobenzaldehyde and *p*-chlorobenzaldehyde were purified by recrystallization from hexane and then vacuum sublimed. These solid aldehydes gave the same extinction coefficients by this handling procedure as we obtained using the sealed-tube method. Apparently these solid aldehydes are much less susceptible to air oxidation than are the liquid aldehydes. The observed properties of the aldehydes are summarized in Table I.

Table I
Physical Properties of Aromatic Aldehydes

Aldehyde	Bp (mmHg)[a] or mp, °C	nD (temp, °C)	ε, M^{-1} cm^{-1}	λ_{max}, nm	Registry no.
p-Anisaldehyde	92 (4)	1.5693 (25)	16,700	283.5	123-11-5
Benzaldehyde	39 (5)	1.5450 (15)	1,250	281	100-52-7
p-Bromobenzaldehyde	57–59		15,200	258	1122-91-4
p-Chlorobenzaldehyde	47–48		1,100	289[b]	104-88-1
Furfural	29 (4)	1.5241 (20)	14,900	271	98-01-1
p-Tolualdehyde	55 (4)	1.5430 (20)	14,600	262	104-87-0

[a] The boiling points (melting points) and *n*D values of these well-known compounds all compare closely with those found in handbooks. [b] This wavelength is not λ_{max} but a shoulder and was used because the corresponding dimethyl acetal absorbed sufficiently at λ_{max} to interfere in the analysis.

Table II
Properties of Dimethyl Acetals of Aromatic Aldehydes[a,b]

Dimethyl acetal of	Bp, °C (mmHg)	n^{25}D	Registry no.
p-Anisaldehyde	86 (1.6)	1.5029	2186-92-7
Benzaldehyde	73 (10)	1.4898	1125-88-8
p-Bromobenzaldehyde	94 (3.3)	1.5296	24856-58-4
p-Chlorobenzaldehyde	90 (6)	1.5076	3395-81-1
Furfural	56 (12)	1.4488	1453-62-9
p-Tolualdehyde	54 (1.1)	1.4916	3395-83-3

[a] All of these acetals had molar extinction coefficients of less than 200 at λ_{max} for the corresponding aldehyde except for *p*-chlorobenzaldehyde. Because of this fact, the molar absorption of the acetal solution never exceeded 0.05 at the start of a hydrolysis run for the concentrations used. [b] Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and satisfactory values (±0.4% for C and H) were found for all compounds.

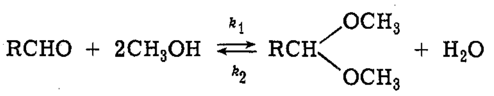
Dimethyl acetals of the aromatic aldehydes were prepared by mixing 0.1 mol of aldehyde, 0.15 mol of trimethyl orthoformate, 15 ml of methanol, and 2 drops of concentrated hydrochloric acid. The solutions were maintained at room temperature for 1 or 2 days and made basic to test paper by the addition of potassium hydroxide in methanol. The low-boiling materials were removed at a water aspirator at room temperature and the residue was fractionated on a Nester-Faust platinum spinning band column having about 25 theoretical plates. An infrared spectrum and a refractive index were obtained for each fraction. Those fractions having the same refractive index (±0.0003) and showing no carbonyl absorption in the infrared were combined. The acetals were stored in the dark in brown bottles and redistilled (micro Vigreux column) just before use in the kinetic experiments. Freshly prepared solutions (methanol–water) for the acetals were used to show the absence or near absence of absorption at the wavelength used for the kinetic studies. The properties measured for these acetals are recorded in Table II.

Rate Measurements. The rate at which aldehyde disappeared (acetal formation) or at which aldehyde appeared (acetal hydrolysis) was followed by monitoring the carbonyl absorption (at the wavelength specified in Table I) with a Beckman DU spectrophotometer as a function of time. The special cell holder and temperature regulation system has been described elsewhere.[9] With this system the temperature can be controlled to at least ±0.025° (widest variation between any two places in the three quartz cells over a period of several hours) over the range of at least 10–45°. Temperatures were monitored in the cell holder throughout the kinetic runs by means of a Hewlett-Packard Model 2801A quartz thermometer (relative readings to ±0.001° and absolute readings to ±0.02°). The readings in the cells were calibrated relative to the readings in the cell holder and the quartz thermometer was calibrated with ice (made from distilled water). All temperature readings reported are those in the light path in the cell and are corrected.

A volume of standard perchloric acid solution (0.06–0.08 *M*) sufficient to give a final [H_3O^+] of about 10^{-4} *M* (but of known value) was pipetted into a 100-ml volumetric flask and diluted to the mark with the solvent. Various amounts of acid were used depending upon the rate of reaction of the particular aldehyde or acetal being studied. The aldehydes (or acetal) were added to the reaction system as diluted solutions in the solvent. These solutions were prepared by weighing the aldehyde (or acetal) just prior to beginning the kinetic experiments and the concentration ranges were 10^{-2}–10^{-3} *M*.

Exactly 1 ml of the diluted perchloric acid solutions was added to each of three 10-ml volumetric flasks by means of a 5-ml buret (±0.001 ml readings). Eight milliliters (buret) of the solvent was added to each of two flasks. The third flask was diluted to the mark (temperature bath) with solvent and served as the reference solution. The two flasks reserved for reaction mixtures were equilibrated in the temperature bath and the reaction was initiated by the addition (pipet) of 1 ml of the aldehyde or acetal solution (timer started). The solutions were transferred to the spectrophotometer cells and readings were usually started within about 2 min of mixing. Absorbance readings were taken at 1–1.5-min intervals over the 15–35-min reaction period. Generally about 20 absorbance readings were recorded. As the system began to approach equilibrium (taken to be an absorbance change of less than 0.002 over 2–3 min), the second run was started. The solutions were maintained in stoppered volumetric flasks in the constant-temperature bath and after about 10–12 half-lives the equilibrium absorbances were read and then checked 1 hr later. Most often these readings were made after the solutions remained in the constant-temperature bath overnight.

Calculations. The first-order reaction rate constants were calculated for the equilibration



$$\mathrm{RCHO} + 2\mathrm{CH_3OH} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{RCH}(\mathrm{OCH_3})_2 + \mathrm{H_2O} \qquad (2)$$

by means of standard expressions[10] modified for our analytical system. These expressions for reversible first-order processes follow.

(a) For acetal formation corrected for the hydronium ion concentration

$$k_1 = \frac{-(\text{slope})(A_0 - A_\infty)}{60\,A_0[\mathrm{H_3O^+}]}\,M^{-1}\ \text{sec}^{-1} \qquad (3)$$

$$k_1 + k_2 = \frac{-(\text{slope})}{60[\mathrm{H_3O^+}]}\,M^{-1}\ \text{sec}^{-1} \qquad (4)$$

with slope = ln ($A - A_\infty$) vs. time (minutes).

(b) For acetal hydrolysis corrected for hydronium ion concentration

$$k_2 = \frac{-(\text{slope})[\text{aldehyde}]_\infty}{60[\text{acetal}]_0[\mathrm{H_3O^+}]}\,M^{-1}\ \text{sec}^{-1} \qquad (5)$$

with slope = ln ($A_\infty - A$) vs. time (minutes), and the ($k_1 + k_2$) expression is the same as for acetal formation. A, A_0, and A_∞ are the measured absorptions at time *t*, at zero time, and at infinite time, respectively. All data were plotted to eliminate gross errors and calculations of the rate constants were made by the method of least squares on an IBM 1130 computer.

The activation parameters E_a, $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $\Delta G^\ddagger$ were calculated by least-squares treatment of the rate constant-temperature data in the usual manner.[11] The error analyses for the values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated by the procedure recommended by

Table III
Rate and Equilibrium Data for the Formation and Hydrolysis of Dimethyl Acetals of Aromatic Aldehydes[a]

		Acetal formation[b]		Acetal hydrolysis[d]				
Aldehyde	Temp, °C	k_1	k_2[c]	k_2	k_1[c]	Average of all ($k_1 + k_2$) values[e]	k_1[f]/k_2	$K_e \times 10^3$
p-Anisaldehyde	15.02	3.92	7.56	7.13	3.99	11.4 ± 0.2 (8)	0.550	2.01
	25.39	9.06	21.7	21.3	9.50	30.7 ± 0.6 (4)	0.426	1.56 (1.5)[g]
	35.04	15.7	46.6	46.2	17.5	63.0 ± 0.7 (4)	0.340	1.26
p-Tolualdehyde	15.02	2.09	1.11	1.07	2.18	3.21 ± 0.04 (9)	1.95	7.12
	25.39	4.82	3.26	3.30	4.92	8.16 ± 0.08 (4)	1.46	5.37 (6.6)
	35.04	9.60	7.31	7.96	9.36	17.1 ± 0.2 (5)	1.21	4.47
Benzaldehyde	15.02	0.782	0.150	0.152	0.765	0.924 ± 0.007 (4)	5.14	18.8
	20.00	1.13	0.247	0.257	1.10	1.37 ± 0.013 (6)	4.40	16.1
	25.39	1.74	0.495	0.510	1.80	2.26 ± 0.04 (6)	3.41	12.5 (14.2)
	30.04	2.64	0.858	0.897	2.70	3.55 ± 0.05 (4)	2.94	10.8
	35.04	3.68	1.42	1.36	3.60	5.02 ± 0.08 (4)	2.71	10.0
Furfural	15.02	0.363	0.164	0.158	0.370	0.527 ± 0.003 (4)	2.30	8.38
	25.39	0.841	0.504	0.513	0.814	1.34 ± 0.01 (4)	1.64	6.02 (7.4)
	35.04	1.64	1.22	1.38	1.69	2.94 ± 0.1 (5)	1.19	4.41
p-Chlorobenzaldehyde	15.02	0.303	0.033	0.032	0.314	0.340 ± 0.005 (5)	9.47	34.5
	25.39	0.761	0.106	0.116	0.762	0.872 ± 0.005 (4)	6.53	24.1
	35.04	1.74	0.285	0.360	1.70	2.04 ± 0.02 (6)	4.83	17.9
p-Bromobenzaldehyde	15.02	0.269	0.027	0.028	0.276	0.302 ± 0.006 (6)	9.61	35.0
	35.39	0.693	0.105	0.103	0.694	0.796 ± 0.002 (9)	6.73	24.7 (28.7)
	35.04	1.56	0.283	0.315	1.55	1.85 ± 0.01 (4)	4.95	18.4

[a] The reactions were conducted in 95% methanol–5% water with 0.1 *m* $NaClO_4$ and $HClO_4$ catalyst. [b] These data were determined by following spectrophotometrically the disappearance of the carbonyl absorbance (uv) for the reaction of the aldehyde with methanol to form the dimethyl acetal. k_1 values were calculated by eq 3 and ($k_1 + k_2$) values by eq 4; k's in M^{-1} sec^{-1}. [c] Calculated from ($k_1 + k_2$) data and the opposite rate constant. [d] These data were determined by following spectrophotometrically the appearance of the carbonyl absorbance (uv) for the reactions of the dimethyl acetal with water to form the aldehyde. k_2 values were calculated by eq 5 and ($k_1 + k_2$) values by eq 4; k's in M^{-1} sec^{-1}. [e] This is the average of all ($k_1 + k_2$) from forward and reverse measurements at each temperature. The number in parentheses is the number of values. [f] This ratio of rate constants is not K_e. The ratio is multipled by the factor $[H_2O]/[CH_3OH]^2$ to yield K_e. [g] The values in parentheses are the equilibrium constants measured by a static method which we previously reported.[7]

Wiberg.[12] The thermodynamic values, ΔH, ΔS, and ΔG, were calculated from the equilibrium constant–temperature data in the usual manner using the method of least squares.

Results

Rate and equilibrium constants at 15.02, 25.39, and 35.04° were calculated for the acid-catalyzed hydrolysis of the dimethyl acetals of *p*-anisaldehyde, benzaldehyde (also at 20.00° and 30.04°), *p*-bromobenzaldehyde, *p*-chlorobenzaldehyde, furfural, and *p*-tolualdehyde. The reactions were conducted in 95% methanol–5% water which was 0.100 *m* in sodium perchlorate with perchloric acid as the catalyst. Under identical conditions the rate constants and equilibrium constants were calculated for the acid-catalyzed formation of the dimethyl acetals from the corresponding aldehydes. The hydrolysis reaction (k_2) is first order each in the concentration of acetal and of hydronium ion. The formation reaction (k_1) is first order each in the concentration of aldehyde and of hydronium ion. Because of the solvent composition the system is swamped with the concentrations of methanol and of water and the order for these substances has not been determined. The rate law of constant salt concentration is of the form

$$k_{\mathrm{obsd}} = k_{\mathrm{H_3O^+}}[\mathrm{H_3O^+}]$$

and all rate constants reported are those of $k_{\mathrm{H_3O^+}}$ for unit concentration of hydronium ion. All of the rate constants are average values of at least two experiments and usually of three and four experiments. Values generally agreed to within ±1%. Discordant data were eliminated by the Q test.[13]

The rate constants at the specified temperatures are given in Table III for acetal formation and for acetal hydrolysis with the aldehydes listed in order of decreasing reactivity. Table III also includes the sums and ratios of the formation and hydrolysis rate constants as well as the equilibrium constants for acetal formation.

The acetal formation rate constants, k_1, were calculated from the net forward data by the use of eq 3 and the values of $k_1 + k_2$ were calculated by means of eq 4. The hydrolytic rate constants, k_2, were obtained directly from these forward rate values by the difference. The hydrolytic rate constants, k_2, were calculated from the net hydrolytic data by means of eq 5 and the values of $k_1 + k_2$ were calculated by means of eq 4. Again the opposite rate constants, k_1, were obtained by difference.

The forward and reverse reaction studies give an additional test of reproducibility of the data. One may compare the k_1 and the k_2 values for the formation data to those of the hydrolytic data and can see that these values are quite reproducible. A better evaluation is the average of the k_1 + k_2 values, forward and reverse, for a given aldehyde and its acetal at a given temperature. As may be seen in Table III, this gives at least four experiments for each aldehyde and its acetal and up to as many as nine experiments in some cases. The greatest deviation observed was a 3.4% average deviation for furfural at 35° and the least deviation was 0.3% average deviation for *p*-bromobenzaldehyde at 25°. The average of the average deviations for all of these values was 1.2%.

Calculations of the ratios of the rate constants (k_1/k_2) provided values which did not correspond with the equilibrium constants we had previously reported for acetal formation.[7] When these ratios of rate constants were multiplied by the factor $[H_2O]/[CH_3OH]^2$, the equilibrium constants did correspond with those we had previously mea-

Table IV
Activation and Reaction Parameters for the Formation and Hydrolysis of Dimethyl Acetals of Aromatic Aldehydes

	Formation reaction[a]				Hydrolysis reaction[b]				Calcd from activation values[c]			Calcd from equil – T data[d]		
Aldehyde or the dimethyl acetal	E_a, kcal mol^{-1}	$\Delta G^\ddagger_{298}$, kcal mol^{-1}	$\Delta H^\ddagger$, kcal mol^{-1}	$\Delta S^\ddagger$, eu	E_a, kcal mol^{-1}	$\Delta G^\ddagger$ 298, kcal mol^{-1}	$\Delta H^\ddagger$, kcal mol^{-1}	$\Delta S^\ddagger$, eu	ΔG_{298}, kcal mol^{-1}	ΔH, kcal mol^{-1}	ΔS, eu	ΔG_{298}, kcal mol^{-1}	ΔH, kcal mol^{-1}	ΔS, eu
p-Anisaldehyde	12.4	20.0	11.8 ± 0.2	−27.5 ± 0.8	16.4	16.2	15.8 ± 0.2	−1.3 ± 0.6	3.8	−4.0	−26.2	3.8	−4.0 (−3.8)	−26.2 (−26)
p-Tolualdehyde	13.6	20.4	13.0 ± 0.2	−24.8 ± 0.5	17.5	17.3	16.9 ± 0.2	−1.2 ± 0.6	3.1	−3.9	−23.6	3.1	−4.0 (−5.2)	−23.8 (−28)
Benzaldehyde	14.3	20.9	13.7 ± 0.1	−24.3 ± 0.4	20.4	18.4	19.9 ± 0.2	+5.0 ± 0.9	2.5	−6.2	−29.3	2.6	−5.9 (−5.7)	−28.0 (−28)
Furfural	13.2	21.4	12.6 ± 0.1	−29.6 ± 0.2	18.8	18.4	18.2 ± 0.2	−0.44 ± 0.08	3.0	−5.7	−29.2	3.1	−5.6 (−5.6)	−29.0 (−29)
p-Bromobenzaldehyde	15.6	21.5	15.0 ± 0.1	−21.9 ± 0.3	21.2	19.3	20.0 ± 0.2	+4.2 ± 0.8	2.2	−5.6	−26.1	2.2	−5.8 (−4.7)	−26.8 (−23)
p-Chlorobenzaldehyde	15.4	21.5	14.8 ± 0.1	−22.4 ± 0.1	21.2	19.2	20.6 ± 0.1	+4.5 ± 0.5	2.2	−5.8	−26.9	2.2	−6.0	−27.4

[a] Calculated using $k_1 = k_{H_3O^+}/[CH_3OH]^2$. [b] Calculated using $k_2 = k_{H_3O^+}/[H_2O]$. [c] Calculated from formation parameters minus hydrolysis parameters. [d] Calculated from log K_e vs. $1/T$ data.

sured or with those which could be independently calculated for the rate systems from the initial and equilibrium concentrations. These equilibrium constants are of the same degree of reliability as the rate constants (better than ±2% average deviation), since they are derived from the rate constants and the concentrations of both the methanol and water are known to a greater accuracy than are the concentrations of the aldehydes and acetals. The values in Table IV in parentheses in the equilibrium column are those equilibrium constants we previously measured at 25°.[7] The agreement between the two methods is seen to be reasonably good but we consider the values reported for the kinetic study as being more reliable.

The activation parameters for acetal formation and for acetal hydrolysis are summarized in Table IV. Calculation of these parameters for forward and reverse reactions by the use of $k_{H_3O^+}$ variations with temperature provided values which did not sum exactly to the thermodynamic parameters calculated from the equilibrium constants variation with temperature. For this reason, we multiplied the forward rate constant, k_1, by the factor $1/[CH_3OH]^2$ and the reverse rate constant, k_2, by the factor $1/[H_2O]$. The values in Table IV in parentheses under the ΔH and ΔS columns for equilibrium are those we reported previously.[7] The earlier values, which agree reasonably with those reported here, are not as reliable because they were obtained from equilibrium constants measured at only two temperatures.

Discussion

Examination of the kinetic results summarized in Table IV reveals a number of interesting effects. The most evident effect of structural changes seen is that both the forward rate constants and the reverse rate constants increase as the electron-donating ability of the para substituent is increased. The effect holds over the temperature range studied. In contrast to this effect on rates, it is seen that the equilibrium constants for acetal formation show just the reverse effect with structure.

For all substituents except the *p*-methoxy, the forward rate constant is greater than the reverse rate constant for the temperatures studied. Both the forward and reverse rate constants increase with an increase in temperature but the reverse rates increase to a greater extent. This result means that the ratio k_1/k_2 decreases as the temperature increases, which is another statement that the equilibrium constants decrease with an increase in temperature. The fact that the acetal formation reaction is exothermic requires that the equilibrium constant decrease with an increase in temperature. However, the complete tautologism requires the statement that the kinetic reason for the change in equilibrium with temperature is that the enthalpy of activation is greater for the hydrolysis reaction for all substrates studied than is the enthalpy of activation for the acetal formation reaction.

The activation parameters for acetal formation were calculated from the rate constants in the form $k_1' = k_1/[CH_3OH]^2$. The activation parameters for acetal hydrolysis were calculated from the rate constants in the form $k_2' = k_2/[H_2O]$. If one wishes to compare energies of activation for the forward reaction with those for the reverse reaction or with the $\Delta H^\ddagger$ values or with the ΔH values, then these corrected rate constants are not necessary (except for slightly different slope values of E_a and $\Delta H^\ddagger$ owing to changes in concentrations of methanol and water as the temperature changes). However, these correction terms make significant differences in the values of $\Delta G^\ddagger$ and these, in turn, affect the values of $\Delta S^\ddagger$. Once the correction terms are made, the ratio $k_1'/k_1' = K_e$, and the activation parameters can be directly compared to the reaction parameters. As may be seen from Table IV, the reaction parameters calculated from the activation parameters agree quite closely (as they must) with those obtained from ln K_e vs. $1/T$ plots.

Entropies of activation have been used as mechanistic criteria to distinguish A-1 from A-2 reactions.[4,14] Reactions which proceed with unimolecular decomposition of a protonated substrate (A-1) are presumed to have entropies of activation near zero or somewhat positive. On the other hand, those reactions which proceed with nucleophilic attack of the solvent on the protonated substrate (A-2) are presumed to have entropies of activation which are large and negative. All evidence obtained to date indicates that acetal hydrolyses in water proceed by an A-1 mechanism in spite of certain ambiguities[4] and details of the mechanism seem to be fairly well understood.[15]

The entropies of activation for the hydrolysis of the six acetals (Table IV) are all near zero or slightly positive in

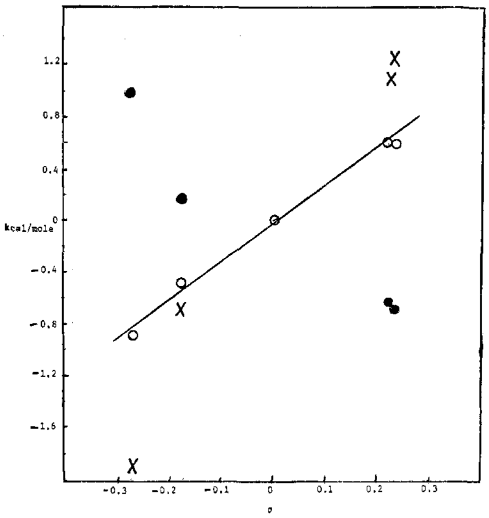


Figure 1. Plot of activation parameters for the acetal formation reaction vs. Hammett's σ: O, values for $\Delta\Delta G^{\ddagger}$; X, values for $\Delta\Delta H^{\ddagger}$; ●, values for $-T\Delta\Delta S^{\ddagger}$; only the $\Delta\Delta G^{\ddagger}$ point is placed on zero but both the $\Delta\Delta H^{\ddagger}$ and $-T\Delta\Delta S^{\ddagger}$ values are superposed.

95% methanol–5% water. This result clearly agrees with the results of other workers for acetal hydrolysis in various solvents and particularly in water. While the results for water may indicate an A-1 mechanism for acetal hydrolysis, that conclusion is not appropriate for 95% methanol–5% water. Methanol and water have about equal reactivities for the alkoxycarbonium ion based upon Cordes' work[4] and upon our unpublished results for methanol–water mixtures of 0.2–0.8 mol fraction methanol. On this basis it is probably not meaningful to speak of a rate-determining step for this reaction in either direction for the solvent used. The significance of the entropies of activation for acetal formation and for acetal hydrolysis for this solvent is not immediately evident.

Quantitative correlations of the data of Table III by means of the Hammett linear free energy equation have been made for all three temperatures. Fair correlations were obtained for all three temperatures for the forward data, the reverse data, and the equilibrium data. The values are given in Table V along with the correlation coefficients. The correlations were made by a least-squares treatment of log k/k_0 (benzaldehyde reference) vs. σ or of log K/K_0 (benzaldehyde reference) vs. σ. Plots of the data revealed slight but real curvatures for all nine correlations in spite of the fact that the correlation coefficients were all 0.95 or better. Utilization of other σ's did not improve significantly the correlations.

The particular features of these results to be noted are that the ρ values are significantly negative over the temperature range studied for both directions and that $\rho_e = \rho_1 - \rho_2$ (as it must from $K_e = k_1'/k_2'$). To the extent that one can rely upon the sign of ρ as an indicator of the charge quality of the transition state,[4,16] then these results suggest that this transition state is the developing (or reacting) alkoxycarbonium ion. However, one cannot be very sure of this conclusion for the reasons given in our discussion of entropies of activation.

Table V
Hammett ρ Values for the Acetal Reaction for Rates and Equilibria[a]

	ρ values		
Calculated from	15°	25°	35°
Formation rate constants, k_1	−2.24 (0.997)	−2.15 (0.994)	−1.95 (0.995)
Reverse rate constants, k_2	−4.47 (0.982)	−4.29 (0.981)	−4.00 (0.979)
Equilibrium constants, K_e	2.25 (0.957)	2.14 (0.957)	2.05 (0.952)

[a] The numbers in parentheses are the correlation coefficients, r.

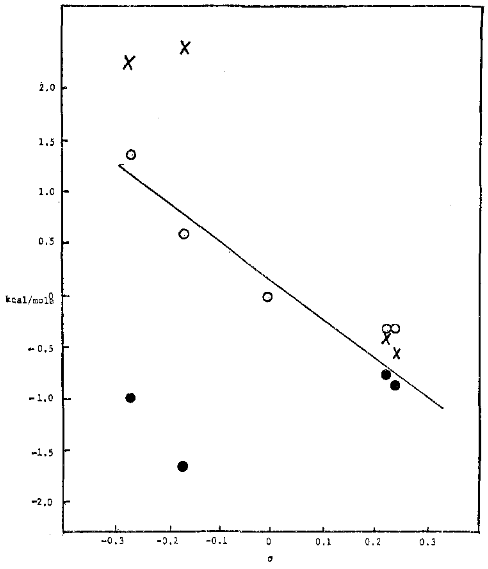


Figure 2. Plots of the equilibrium parameters for acetal formation vs. Hammett's σ: O, values for $\Delta\Delta G$; X, values for $\Delta\Delta H$; ●, values for $-T\Delta\Delta S$; only the $\Delta\Delta G$ point is placed on zero but both the $\Delta\Delta H$ and $-T\Delta\Delta S$ values are superposed.

For a plot of the activation parameters vs. σ (Figure 1) for the benzaldehydes in acetal formation we observe that the $\Delta\Delta G^{\ddagger}$ vs. σ is a sensibly linear plot but both $\Delta\Delta H^{\ddagger}$ and particularly $-T\Delta\Delta S^{\ddagger}$ vs. σ show considerably more scatter. The hydrolysis data provide similar correlations. In Figure 2 are shown similar plots for the equilibrium. In this case the $\Delta\Delta G$ vs. σ shows curvature but is made up of the two parts, $\Delta\Delta H$ vs. σ and $-T\Delta\Delta S$ vs. σ, both of which are largely scatter diagrams. For the rates in both directions, the slopes of the Hammett plots (see Figure 1) are determined predominantly by the changes in $\Delta H^{\ddagger}$ with structure. However, for equilibrium the slope of the Hammett plot (see Figure 2) is determined mainly by the changes in $-T\Delta S$ rather than by ΔH.[17]

References and Notes

(1) Grateful acknowledgment is given to the National Institutes of Health for a grant (R01-AM-1124) in support of this work.
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(3) Author to whom inquiries should be addressed.
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