Aspects of the Kinetics of Hydrolysis of Acetals of Ketones[1]

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The rate constants are reported for the acid-catalyzed hydrolysis of the dimethyl acetals of acetone, butanone, 2-pentanone, 3-pentanone, 4-methyl-2-pentanone, 4-heptanone, 2-octanone, cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone. The hydrolytic reactions were conducted in 95% methanol–5% water at 15, 25, and 35°. Differences in rates for the series of acyclic ketones are small with the largest change being about a factor of 5. Activation parameters have been calculated for the above compounds and various linear free energy correlations attempted. Taft plots were poor but isokinetic plots of $\Delta H^\ddagger$ vs. $\Delta S^\ddagger$ were quite good with a slope, β, of 276 K and a correlation coefficient of 0.968. From previously measured equilibrium constants and the hydrolytic rate constants, rate constants were calculated for acetal formation for eight of the ketones. Rates parallel equilibria for both the formation reaction and for the hydrolysis reactions but the rates forward have an inverse relationship to the hydrolysis rates. It is concluded that steric factors control the small differences in rates observed for these reactions.

In an earlier paper,[3] rate constants and equilibrium constants were reported for the formation and hydrolysis of para-substituted benzaldehyde dimethyl acetals in 95% methanol–5% water at 15, 25, and 35°. This solvent was selected so that reaction rates could be determined for both the forward and reverse reaction under identical conditions. We now report a kinetic study for the hydrolysis of dimethyl acetals of selected ketones in the same solvent. These acetals are not hydrolyzed to completion under these conditions, with exceptions, and the reactions follow simple second-order kinetics (first order in acetal and first order in hydronium ion).

We were interested in the hydrolysis of acetals of ketones as a structural study for three particular reasons. First, these ketones form minimal amounts or no hemiacetals[4] in solution of methanol so the reaction kinetics remain clear of this possible complication.[5] Second, we have suggested[4] that the rates of acetal hydrolyses should correlate in classes for linear free energy correlations depending upon $\Delta S^\ddagger$ terms and these data have been unavailable. Third, we were interested in comparing rates and equilibria for this series as we have reported for the interconversion of para-substituted benzaldehydes and their dimethyl acetals.

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[6] and as previously reported.[3]

95% Methanol–5% Water–0.1 *m* Sodium Perchlorate was prepared in kilogram lots as previously reported[3] with the sodium perchlorate having been recrystallized three times from water and dried under vacuum at 120°. The salt did not change the pH of water for concentration changes from 0.02 to 0.1 *M*.

Acetals. The general procedure used for conversion of the ketones to their dimethyl acetals is essentially the same as that used by Kreevoy and Taft[7] for making diethyl acetals. Mixtures of 0.14 mol of the appropriate ketone, 0.146 mol of trimethyl orthoformate, 0.74 mol of methanol, and a crystal of *p*-toluenesulfonic acid were refluxed for 4 hr. One drop of 50% sodium hydroxide was added and 15 ml of hexane. The methanol layer was removed and the hexane layer was distilled on a Nester-Faust annular Teflon spinning band column. No attempts were made to optimize yields since we were interested in high-purity samples but yields of the center cuts were usually in the range of 50–70%. At no time was carbonyl absorption observed in infrared spectra of the acetals. The boiling points and refractive indices of these acetals follow: 2,2-dimethoxypropane, bp 83° (1 atm), $n^{20}\mathrm{D}$ 1.3770 [lit.[8] bp 80° (760 mm) $n^{25}\mathrm{D}$ 1.3748]; 2,2-dimethoxybutane, bp 105° (1 atm), $n^{20}\mathrm{D}$ 1.3930 [lit.[8] bp 50° (100 mm), $n^{24}\mathrm{D}$ 1.3915]; 2,2-dimethoxypentane, bp 37° (25 mm), $n^{20}\mathrm{D}$ 1.4005; 3,3-dimethoxypentane, bp 37° (25 mm), $n^{20}\mathrm{D}$ 1.4046 [lit.[8] bp 50° (63 mm), $n^{26}\mathrm{D}$ 1.4013]; 2,2-dimethoxy-4-methylpentane, bp 53° (29 mm), $n^{20}\mathrm{D}$ 1.4068 [lit.[8] bp 58° (35 mm), $n^{25}\mathrm{D}$ 1.4048]; 4,4-dimethoxyheptane, bp 79° (23 mm), $n^{20}\mathrm{D}$ 1.4135; 2,2-dimethoxyoctane, bp 37° (2 mm), $n^{20}\mathrm{D}$ 1.4186; 1,1-dimethoxycyclohexane, bp 65° (25 mm), $n^{20}\mathrm{D}$ 1.4397 [lit.[8] bp 56° (13 mm), $n^{24}\mathrm{D}$ 1.4373]; 1,1-dimethoxy-2-methylcyclohexane, bp 78° (25 mm), $n^{20}\mathrm{D}$ 1.4472; 1,1-dimethoxy-3-methylcyclohexane, bp 75° (25 mm), $n^{20}\mathrm{D}$ 1.4383; 1,1-dimethoxy-4-methylcyclohexane, bp 75° (25 mm), $n^{20}\mathrm{D}$ 1.4385. These structures showed all of the appropriate absorptions without extraneous bands for their NMR, ir, and Raman spectra.

Rate Measurements and Calculations. The reactions for acetal hydrolysis were monitored by measuring the appearance of the carbonyl group in the ultraviolet as a function of time. The wavelengths of absorption and the extinction coefficients have been previously reported.[4] A Beckman DU spectrophotometer with a modified cell compartment[9] was used in the manner previously described.[3]

The reactions were catalyzed by dichloroacetic acid–sodium dichloroacetate buffer with the ionic strength maintained essentially constant with 0.1 *m* sodium perchlorate. The particular concentrations of the acid and the salt used for the various kinetic runs and the measured pH values are reported in Table I along with the rate constants. The pH values were measured with a Corning Model 10 pH meter using a Corning Ag–AgCl combination electrode. Before each pH measurement the meter was standardized against an aqueous solution of pH 4.00 prepared with Coleman buffer tablets.

Second-order rate constants (first order in acetal and first order in hydronium ion) were calculated for acetal hydrolysis (k_2) as reported previously.[3,10] For the hydrolysis of the dimethyl acetals of acetone, butanone, cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone the back reaction was sufficient that we obtained ($k_1 + k_2$) values (the sum of the forward and reverse rate constants) as for the benzaldehyde series. These values along with our independently measured equilibrium constants[4] were used to obtain the rate constants. For the acetals of the other five ketones, the hydrolyses were all 99% complete or better at infinite time so that plots of log ($A_\infty - A_t$) vs. time provided k_2 (hydrolysis) values directly.

All rate constants were calculated by the method of least squares. The activation parameters E_a, $\Delta H^\ddagger$, $\Delta S^\ddagger$ and $\Delta G^\ddagger$ were calculated by the least-squares treatment of the rate constant–temperature data in the usual manner.[11] Error analyses for the values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated by the procedure recommended by Wiberg.[12] Linear free energy plots were made for visual inspection but the actual correlations were made by the method of least squares.

Results

Rate constants at 15.02, 25.39, and 35.04° were obtained for the acid-catalyzed hydrolysis of the dimethyl acetals and are summarized in Table I along with the activation parameters. These are shown in two series for acetals of acyclic ketones and acetals of cyclic ketones, each listed in order of increasing reactivity (25°). The reactions were conducted in 95% methanol–5% water which was 0.100 *m* in sodium perchlorate and the catalyst was dichloroacetic acid–sodium dichloroacetate buffer. This particular solvent mixture had been selected to enable the measurement of the rates for the forward and reverse reactions for the interconversion of benzaldehydes and their dimethyl acetals. These data also permitted the simultaneous determination of the equilibrium constants. One must simply be careful to obtain the proper rate constants for acetal hydrolysis depending upon correction for the back reaction, if any.

We were unable to use perchloric acid as the catalyst as was used for the benzaldehyde series[3] because at the catalyst concentration used for that series, the acetals of ketones hydrolyze too fast for accurate rate measurements in our system. The use of lower acid concentrations (below 10^{-4} *M*) was tried but was unsuccessful because of uncertainties in the acid concentrations. For these reasons it was necessary that a buffer system be used but we obtained consistent rate constants by utilizing measured pH values for $[H_3O^+]$.

The hydrolysis reaction is first order in acetal concentration and first order in hydronium ion concentration. The rate law at constant salt concentration is $k_{obsd} = k_2[H_3O^+]$. All rate constants are listed as k_2 for hydrolysis and are normalized to 1 *M* hydronium ion based upon pH measurements. The pH values measured in methanol–water are not the same as those measured in water.[1,13] For this reason we also have corrected the $[H_3O^+]$ based upon the liquid junction potentials reported by de Ligny.[14] These corrected rate constants are those given in parentheses in Table I with a correction factor of 3.98×10^3 because of the liquid junction potentials. These corrections are only approximate because of unknown effects of the perchlorate ion in our solutions on the liquid junction potentials. This correction does give, however, the correct order of magnitude for the $[H_3O^+]$ and does not affect the activation parameters or the linear free energy correlations.

All rate constants reported are the averages of at least three experiments but most generally are the averages of four experiments. Values were reproducible to within ± 2% and discordant data were eliminated by the *Q* test.[15]

For eight of the ketones we had previously reported equilibrium constants for dimethyl acetal formations.[4] For these ketones the equilibrium constants and the measured hydrolytic rate constants (k_2) were used to calculate the formation rate constants (k_1). These values are summarized in Table II.

Table I
Rate Data for the Hydrolysis of Acetals of Ketones[a]

Parent ketone of dimethyl acetal	Rate constants, k_2[b] 15.02°	25.39°	35.04°	E_a, kcal mol^{-1}	$\Delta G^{\ddagger}_{298}$, kcal mol^{-1}	$\Delta H^{\ddagger}_{298}$, kcal mol^{-1}	$\Delta S^{\ddagger}_{298}$, eu	Registry no.
Acetone	1.55[c] (6.18×10^3)	4.45[e] (18.1×10^3)	12.4[f] (49.4×10^3)	18.4	16.6	17.8	4.3	77-76-9
Butanone	2.48[c] (9.86×10^3)	7.82[e] (31.1×10^3)	20.0[f] (79.6×10^3)	18.5	16.2	17.9	5.7	3453-99-4
3-Pentanone	2.35[c] (9.35×10^3)	8.89[f] (35.4×10^3)	23.4[f] (93.2×10^3)	20.4	16.2	19.8	12.2	25636-49-1
2-Pentanone	3.14[c] (12.5×10^3)	8.97[e] (35.7×10^3)	29.8[f] (119×10^3)	19.9	16.2	19.3	10.5	55904-98-8
2-Octanone	2.72[c] (10.8×10^3)	9.46[f] (37.7×10^3)	27.5[f] (110×10^3)	20.5	16.1	19.9	12.8	54583-19-6
4-Heptanone	3.53[c] (14.1×10^3)	10.8[e] (43.0×10^3)	30.8[f] (123×10^3)	19.2	16.1	18.6	8.6	55904-99-9
4-Methyl-2-pentanone	8.08[f] (32.2×10^3)	25.4[e] (101×10^3)	64.4[g] (257×10^3)	18.4	15.5	17.8	7.7	1112-78-3
4-Methylcyclohexanone	0.167[d] (0.66×10^3)	0.542[c] (2.16×10^3)	2.03[d] (8.08×10^3)	22.1	17.7	21.5	12.8	18349-20-7
Cyclohexanone	0.169[d] (0.67×10^3)	0.67[c] (2.67×10^3)	2.20[f] (8.76×10^3)	22.8	17.7	22.2	15.0	933-40-4
3-Methylcyclohexanone	0.224[d] (0.89×10^3)	0.796[c] (3.17×10^3)	2.61[d] (10.4×10^3)	21.5	17.6	20.9	11.1	18349-16-1
2-Methylcyclohexanone	1.92[c] (7.6×10^3)	6.28[f] (25×10^3)	19.1[f] (76×10^3)	20.4	16.4	19.8	11.4	38574-09-3

[a] The reactions were conducted in 95% methanol–5% water with 0.1 *m* $NaClO_4$ and dichloroacetic acid–sodium dichloroacetate buffer. [b] k_2 is the rate constant for acetal hydrolysis normalized to 1 *M* H_3O^+ using observed pH values. The values in parentheses are normalized to 1 *M* H_3O^+ using corrected pH values. [c] The buffer ratio of [acid]/[salt] = 0.01/0.01; av pH 3.24. [d] The buffer ratio of [acid]/[salt] = 0.03/0.01; av pH 2.80. [e] The buffer ratio of [acid]/[salt] = 0.002/0.01; av pH 3.97. [f] The buffer ratio of [acid]/[salt] = 0.004/0.02; av pH 3.93.

Discussion

The first and most obvious effect observed for these systems is that the rate changes are small for a change of the alkyl groups. This small structural effect was first suggested by Kreevoy and Taft[7] in their classic work on acetal hydrolysis and is to be expected if all alkyl groups have about the same σ's.[16] A number of linear free energy correlations were attempted without much success for our data for the acyclic ketone series at all three temperatures. The 15° data, as a typical example, were used for an unsuccessful Taft correlation giving $\rho^* = -0.91$ with a correlation coefficient of 0.72. Omitting the value for the dimethyl acetal of 4-methyl-2-pentanone did not improve the correlation to an acceptable level.

Interestingly, an isokinetic plot[17] of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ for the hydrolysis of the dimethyl acetals of the acyclic ketones gave a good correlation. Least-squares treatment of the data gave $\beta = 276$ K and a correlation coefficient of 0.968. When the value of the dimethyl acetal of 4-methyl-2-pentanone was omitted, $\beta = 266.7$ K and the correlation coefficient was 0.996. The fact that we obtain a good isokinetic plot but a poor Taft plot is in agreement with the arguments presented by Ritchie and Sager.[16]

The hydrolysis data for the dimethyl acetals of the four

Table II
Rate and Equilibrium Constants[a] for Dimethyl Acetal Formation and Hydrolysis Reactions, 25°

Ketone[b]	$K_e \times 10^3$ [d]	k_2, l. mol^{-1} sec^{-1} [c]	k_1, l. mol^{-1} sec^{-1} [d]
Acetone	0.40	4.45	0.48
Butanone	0.13	7.82	0.28
3-Pentanone	0.034	8.89	0.082
2-Octanone	0.048	9.46	0.12
Cyclohexanone	6.7	0.67	1.22
2-Methylcyclohexanone	0.20	6.28	0.34
3-Methylcyclohexanone	3.4	0.80	0.73
4-Methylcyclohexanone	6.1	0.54	0.90

[a] These equilibrium constants were determined for the ketones dissolved in various mixtures of methanol-water at 25°.[4] [b] The corresponding dimethyl acetals were hydrolyzed. [c] k_1 is the rate constant for acetal formation and k_2 is for acetal hydrolysis. [d] $k_1 = k_2K_e\,[\mathrm{MeOH}]^2/[\mathrm{H_2O}]$. See ref 3.

cyclic ketones also correlate reasonably well by an isokinetic treatment of $\Delta H^\ddagger$ vs. $\Delta S^\ddagger$. The correlation provided β = 201 K and a correlation coefficient of 0.91. The largest effect observed for this particular series is that due to replacing a hydrogen by methyl on the 2 position of the cyclohexane ring, for which the rate increases by a factor of about 10. Moving the methyl group to the 3 or to the 4 position has a very small effect on the rate relative to cyclohexanone dimethyl acetal.

It is possible that the linear correlation between $\Delta H^\ddagger$ and $\Delta S^\ddagger$ indicates a small steric factor operating to control the rates relative to structure. We would not strongly promote the identity, but we do present some evidence which rules out the control of rates by a polar effect.

In a paper on rates and equilibria for the benzaldehyde–dimethyl acetal interconversion,[3] a striking relationship was noted between rates forward and reverse and between equilibria. For that system having substantially negative ρ's the rates parallel each other in both directions ($\rho_{25°}$ = −2.15 for rates of acetal formation; $\rho_{25°}$ = −4.29 for rates of acetal hydrolysis) but these rates have an inverse relationship for the equilibria for acetal formation ($\rho_{25°}$ = +2.14). This effect is expected if the polar effect is the predominant source of stabilization of the transition state.

For the hydrolysis of dimethyl acetals of ketones, just the opposite effect is observed. The data of Table II show an inverse relationship of the acetal formation rates to the acetal hydrolysis rates for substituent changes; thus, the formation rates parallel the formation equilibria and the hydrolysis rates parallel the hydrolysis equilibria.

The transition state is positively charged for these acetals just as it is for the benzaldehyde acetals and for both directions of reaction. These positively charged transition states should be stabilized by electron-donating groups for either direction if the polar effect is the predominant source of stabilization. The fact that the formation and hydrolysis rates are not parallel for changes in alkyl substituents suggests that the predominant control is not by polar effects. Furthermore, if one accepts the arguments of Ritchie and Sager[16] that all alkyl groups have the same polar qualities then one is left with the main possibility of a steric effect controlling the small changes in rates which are observed.

It is evident that there is at least a qualitative relationship between the forward and reverse rates and the sizes of the alkyl groups. In the formation reaction the steric effect operates to retard the rates and equilibria because the larger the group the less favored is the change from sp^2 geometry to the developing sp^3 geometry of the transition state or of the product acetal. Just the opposite should be and is observed for acetal hydrolysis. With a bulkier alkyl group change, such as isobutyl in place of methyl, there is a particularly large enhancement in rate just as Kreevoy and Taft observed for the neopentyl and *tert*-butyl groups.[7]

We have suggested[4] that one should not expect all classes of carbonyl compounds to have their rates of acetal hydrolysis lie on a single linear free energy correlation line. It did not seem that aromatic aldehydes should correlate on the same line with aliphatic ketones and with aliphatic aldehydes as Kreevoy and Taft[7] were able to accomplish by the use of a hyperconjugation parametric term on the Taft equation for the rates of hydrolysis of diethyl acetals. The reason for our suggestion was that the contributions of $\Delta S^\ddagger$ to $\Delta G^\ddagger$ were unknown and could distort the validity of the correlations. We reported that ΔS values were about −24 to −28 eu for the equilibrium formation of dimethyl acetals of aromatic aldehydes while ΔS values were about −30 to −36 eu for both cyclic and acyclic ketones. We suggested that a similar effect might be observed for the entropies of activation for acetal hydrolysis.

We have reported $\Delta S^\ddagger$ values for the hydrolysis of dimethyl acetals of para-substituted benzaldehydes to be near zero (−1 to +4 eu).[3] These values are in line with what one would expect for a unimolecular process even though that may not be the case for this system. As can be seen in Table 1, $\Delta S^\ddagger$ values for the hydrolysis of the dimethyl acetals of ketones are considerably more positive than for the dimethyl acetals of substituted benzaldehydes. These values vary from near zero to nearly +15 eu and are all positive. On this basis we reemphasize our previous point[4] that parametric corrections should not be made for linear free energy correlations in the absence of activation parameters. Our results were obtained in 95% methanol–5% water while Kreevoy and Taft worked in 50% water–dioxane and it may be that comparisons between results for the two different solvents should not be made. However, we think that the conclusions made are valid since the ρ values obtained for ketal hydrolysis are not significantly different (theirs −3.60 and ours −4.29).

It appears to us that the so-called hyperconjugation term of Kreevoy and Taft may be an entropic contribution to the free energy of activation, at least for ketal hydrolysis. This effect may be steric in origin as Wiberg has suggested.[18]

References and Notes

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