ane and methanol. A pure sample, m.p. 257–258°, which was about 20% of the total initial material and may represent one of several stereoisomers, showed an infrared spectrum essentially identical with that of the initial product. The compound did not undergo acid hydrolysis or reaction with dinitrophenylhydrazine reagent.

Anal. Calcd. for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 67.99; H, 6.79; N, 9.93.

Acetal Formation for Ketones and Aromatic Aldehydes with Methanol[1]

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Equilibrium constants for acetal formation in methanol have been calculated for eight aromatic aldehydes, nine acyclic ketones, and seven cyclic ketones from spectrophotometric data at 10 and 25°. The values of ΔH, ΔG, and ΔS have also been calculated for these reactions. The method involves the determination of the absorbance of the carbonyl compound in neutral methanol and those in acidic methanol–water mixtures with the differences in absorbances representing the extent of acetal formation. The hemiacetal form does not interfere with acetal determination since when hemiacetal formation occurs, it does so in the neutral and acidic solutions. On the basis of the absorbance change with temperature in neutral methanol, hemiacetal formation has been detected for a few of the carbonyl compounds, but in general most of the compounds used in this study do not form hemiacetals in significant amounts in methanol. The data have been treated by a Taft linear free-energy correlation, but the results were not overly successful. It is suggested that for either equilibrium studies or for kinetic studies for the acetal reaction that a Taft treatment should not correlate the data on a single line for all types of carbonyl compounds because of ΔS (or ΔS^*) effects. Our data suggest that the equilibrium for acetal formation is controlled by the nucleophilic addition of methanol to the carbonyl group and not by the conversion of the hemiacetal to acetal stage. We find that rates parallel equilibria for acetal hydrolysis but bear an inverse relationship for acetal formation.

The equilibrium formation of acetals[3] from aldehydes has been the subject of numerous studies. The classical work of Adkins and his co-workers[4] has served to define the broad relationship between the structures of carbonyl compounds and of alcohols for the extent of formation of acetals. Generally, the reaction is believed to proceed through the formation of the corresponding hemiacetal.[4,5] While the equilibrium conversion of saturated aliphatic aldehydes with primary alcohols is quite good, the equilibrium for α,β-unsaturated aldehydes and aromatic aldehydes are less favorable. Ketones, in general, are not sufficiently converted to acetals to make the equilibrium technique useful to prepare acetals. Under proper operating conditions (low temperature and using an ion-exchange resin catalyst) certain ketones, such as acetone and cyclohexanone, are efficiently converted to acetals.[6,7] Many acetals of ketones can be made in good yields by acetal exchange.[8] The alcohol structure also has a marked influence on the equilibrium of acetals with the extent of conversion markedly decreasing in the order primary > secondary > tertiary.[4]

Much less is known about the relationship between the structures of carbonyl compounds and alcohols and the extent of hemiacetal formation. In part, the problem is complicated by the fact that hemiacetals cannot be isolated in general.[9] There is, however, a great deal of physical evidence which demonstrates the existence of simple hemiacetals in alcohol solutions, including studies by refractive indices,[10,11] by heats of solution,[12] and by the loss of carbonyl absorption in the ultraviolet[5,13,14] and infrared[5,15] regions of the spectrum.

While it is often assumed that all aldehydes and ketones form hemiacetals, Melchior apparently was the first to suggest that aromatic aldehydes do not form significant amounts of hemiacetals in the acetal equilibrium with methanol.[16] Wheeler suggested on the basis of an ultraviolet absorption study that cyclic ketones, such as cyclohexanone, form hemiacetals but not acetals in methanol and ethanol.[17] Subsequently it was demonstrated by a combination of chemical analyses and spectroscopic analyses that cyclohexanone in acidified methanol forms acetal predominantly and that Wheeler's erroneous conclusions were probably due to water as an impurity in the reaction mixtures.[18] The formation of the acetal is adequately confirmed by its isolation in significant yields.[6,7,18]

While thorough kinetic studies have been made for acetal hydrolysis,[19–21] only limited studies have been made for the kinetics of acetal formation.[22–24] Complications due to various extents and rates of formation

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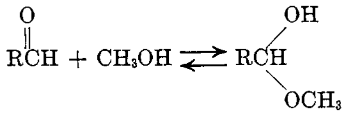
of hydrates and hemiacetals under conditions of acetal formation and hydrolysis have not been thoroughly explored. The kinetics and equilibria for hydrate formation have been evaluated by Bell and his coworkers,[25] but the reaction conditions used are rather different than for acetal studies. Studies on hydrate formation have not distinguished among the various possible hydrated forms such as the usual assumed *gem* diol, the hemihydrate,[26] or higher polymeric forms. Little has been done on the kinetics and equilibria for hemiacetal formation,[24,27,28] and practically nothing to define the structural limits permitting hemiacetal formation for either the carbonyl or alcohol moieties.

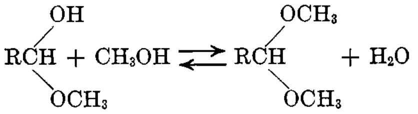
Because of the possibility of defining better some of the structural requirements for hemiacetal and acetal formation, equilibrium constants have been determined for acetal formation for those aldehydes and ketones which give low conversions to the acetals.

The Hemiacetal Problem

The technique we have used to determine the extent of the acetal reaction is essentially that of Melchior[16] and involves the measurement of the ultraviolet absorption due to the carbonyl group in neutral methanol and in acidic methanol for which the concentration of water is varied. The greater the amount of water, the less is the extent of acetal formation. Knowing the change in carbonyl absorbance due to acetal formation and knowing the concentrations of water and alcohol along with the stoichiometry, the equilibrium constant may be calculated.



$$RC(=O)H + CH_3OH \rightleftharpoons RCH(OH)(OCH_3) \quad (1)$$



$$RCH(OH)(OCH_3) + CH_3OH \rightleftharpoons RCH(OCH_3)_2 + H_2O \quad (2)$$

$$K_e = K_{e_1}K_{e_2} = \frac{a_{\text{acetal}}a_{H_2O}}{a_{\text{aldehyde}}a_{\text{MeOH}}^2}$$

Melchior assumed for the aromatic aldehydes which he studied in methanol that hemiacetal formation would, if possible, occur in the acid solution along with acetal formation but not in the neutral methanol. Thus the existence of hemiacetal would have been detected by a marked change in the calculated equilibrium constant for acetal formation. Inasmuch as the calculated equilibrium constants were very constant over a wide range of water–methanol concentrations, he concluded that hemiacetal did not form. However, since hemiacetal forms rapidly in neutral alcohol solutions as well as in basic or acidic systems, Melchior's technique is not capable of detecting the presence of hemiacetal.

The presence or absence of hemiacetal is immaterial to the determination of the extent of acetal formation if the same amount of hemiacetal is present in the neutral reference solution and in the acidified solutions. To the extent that various amounts of water in the methanol change the extent of hemiacetal formation, the extent of hydrate formation, or simple solvent effects which change the extinction coefficient, so will the method be in error.

Hine[29] has found by an n.m.r. study that acetone forms a hydrate to the extent of about 0.16% in 80% water–20% acetone and forms a hemiacetal to an extent of about 0.3% in methanol. For *p*-chlorobenzaldehyde he could find little evidence for hemiacetal formation in CH_3OD. The n.m.r. spectrum was sufficiently complex to prevent a clear-cut decision for hemiacetal formation for cyclohexanone. However, a time study of the absorbance of cyclohexanone in methanol provided unequivocal evidence for hemiacetal formation. Sufficient cyclohexanone was added by a microsyringe to 3.0 ml. of methanol in a ultraviolet cell to give about a 0.1 *M* solution at about 25°. Measurements of the absorbance on a Carey Model 14 spectrophotometer were started within 15 sec. of dissolution and were followed continuously until the absorbance became constant. The absorbance decreased by about 12% in a first-order reaction with a half-life of about 5 min. Repetition provided three values of 12.6, 12.0, and 12.0% hemiacetal. In another experiment the absorbance in neutral methanol was followed with time to 40 sec. whereupon 0.030 ml. of 0.137 *M* $NaOCH_3$ was added. At 25 sec., the absorbance decrease was only about 1%, but at 50 sec. the full 12% decrease was more than 90% complete.

We have verified Hine's results for cyclohexanone, obtaining in a single run a 10.4% conversion for hemiacetal formation with a carefully prepared solution following the absorbance change with time on a Beckman DU spectrophotometer. We calculate a first-order rate constant of 77.7×10^{-5} sec.$^{-1}$, a $t_{1/2}$ of 92.5 sec., and $K_e = 4.7 \times 10^{-3}$ l. mole^{-1} for hemiacetal formation at 25°.

These interesting results were surprising to us inasmuch as we concluded earlier that hemiacetal formation for cyclohexanone in methanol should be considerably less than this amount.[18] Furthermore, Anteunis, Alderweireldt, and Acke recently reported on n.m.r. study of acetal formation for cyclobutanone, cyclopentanone, and cyclohexanone in methanol and concluded that none of the three ketones formed a hemiacetal.[30] We had looked purposely for hemiacetal formation in neutral and basic methanol solutions by ultraviolet absorption studies and found the same extinction coefficients for both types of solutions and that the solutions followed Beer's law for considerable variations in concentrations of ketones, However, we failed to measure absorbances as soon as the solutions were mixed, because we tried to be careful in having accurately prepared solutions and thus the hemiacetal equilibrium was established before we measured the absorbances.

We are not sure as to why our previous studies failed to reveal the presence of hemiacetal because the absorbances for cyclohexanone were measured in dioxane free of methanol and water.[18] For the system studied, the extent of acetal formation was about ten times the

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TABLE I

ABSORBANCE AND TEMPERATURE FOR CARBONYL COMPOUNDS IN NEUTRAL METHANOL

	Compound	M	Absorbance		ϵ, at 25°	λ_{max}, mμ
			10°	25°		
I.	Anisaldehyde	5.85×10^{-4}	0.956	0.940	16,050	275
	p-Acetamidobenzaldehyde	3.46×10^{-5}	0.693	0.686	19,830	292
	3,4,5-Trimethoxybenzaldehyde	4.54×10^{-5}	0.463	0.460	10,120	285
	Furfural	7.58×10^{-5}	1.056	1.056	13,930	271
	Benzaldehyde	7.06×10^{-4}	0.820	0.819	1,160	281
	p-Tolualdehyde	3.81×10^{-5}	0.611	0.610	16,000	262
	Acetophenone	3.43×10^{-4}	0.388	0.380	1,107	278
	Acetone	5.16×10^{-2}	0.662	0.670	13.0	280[a]
	2-Butanone	5.39×10^{-2}	0.957	0.957	17.8	272
	3-Pentanone	2.94×10^{-2}	0.599	0.600	20.4	275
	3-Methyl-2-hexanone	2.57×10^{-2}	0.742	0.740	28.8	282
	Cyclopentanone	1.46×10^{-2}	0.269	0.268	18.3	288
	2-Methylcyclohexanone	2.68×10^{-2}	0.509	0.513	19.1	285
	Cyclopentadecanone	1.24×10^{-2}	0.386	0.386	31.1	288
	Dicyclopropyl ketone	2.37×10^{-2}	0.848	0.842	35.4	267
II.	*p*-Bromobenzaldehyde	5.69×10^{-5}	0.753	0.833	14,650	258
	Cyclohexanone	9.40×10^{-2}	1.270	1.360[b]	14.5	288[a]
	3-Methylcyclohexanone	2.34×10^{-2}	0.369	0.394	16.9	284
	4-Methylcyclohexanone	2.84×10^{-2}	0.378	0.411	14.5	283
	4-*t*-Butylcyclohexanone	4.22×10^{-2}	0.601	0.638	15.1	284

[a] Not λ_{max} but the wave length that was used. [b] The value of the absorbance for this same solution at 40° was 1.417.

extent of hemiacetal formation. Thus, for the most concentrated solution the extent of hemiacetal formation was only about 3% while for the most dilute solution it should have been about 10%. We did have considerable variation in the value of K_x by ultraviolet analysis and in addition the temperature variation was sufficiently large to obscure, in part, the presence of hemiacetal. In any event, the conclusion that acetal formation in methanol is the predominant reaction is valid, but the acetal is accompanied by a small amount of hemiacetal.

Evidence for the formation of hemiacetal in our systems is indicated by the change of the absorbances of the carbonyl compound in methanol with temperature. The hemiacetal equilibrium is markedly dependent upon the temperature as is the acetal equilibrium.[4,7] For cyclohexanone in methanol we found the molar extinction coefficient at 288 mμ changed from 13.5 to 14.5 to 15.1 as the temperature was changed from 10 to 25 to 40°. On the other hand, the absorbance for acetone in methanol was the same at 10 and 25° within experimental error. The absorbances at 10 and 25° for the various aldehydes and ketones used in this work are shown in Table I. The first group of compounds are those for which the absorbances did not increase significantly as the temperature was raised and therefore formed little or no hemiacetal. The second group all show a marked increase in the absorbance as the temperature was raised, indicating the presence of measurable amounts of hemiacetal. We tentatively conclude that acyclic aliphatic ketones, most aromatic aldehydes (excepting those with electronegative substituents), aromatic ketones, and most cyclic ketones excepting cyclohexanones (and perhaps cyclobutanone) do not form more than trace amounts of hemiacetal (about 1% or less) for dilute solutions of the carbonyl compound in methanol. The extent of hemiacetal formation may be less for alcohols other than methanol, but this point remains to be demonstrated. Cyclohexanones without α-alkyl substituents show definite hemiacetal formation, up to about 10% for 0.1 M solutions in methanol (the extent for acetal formation for these same solutions approaches 90%). Considerably more work must be done to make these conclusions valid and studies are in progress to define more accurately the structural limits of hemiacetal formation for aldehydes and for ketones.

The Acetal Equilibrium

On the basis of absorbance studies at 10 and 25° for aldehydes and ketones in neutral methanol and in acidic methanol–water solutions we have calculated equilibrium constants for acetal formation for seven aromatic aldehydes, for nine acyclic ketones, and for seven cyclic ketones. These values along with those of the thermodynamic functions for the reactions are given in Table II.

The important errors due to variations in activity coefficients as the solvent system is changed have been discussed by Melchior.[16] Because of these types of errors, Melchior chose to express his equilibrium constants in mole fractions. Inasmuch as we have used dilute solutions of the carbonyl compounds, we have expressed our results in terms of molar concentrations. There are valid objections to this because the water concentrations are varied from as low as 0.01 M to as high as 2 M and we do not know the activity coefficients for the components in this system. However, the results are not sufficiently precise and probably not sufficiently accurate to warrant the utilization of water and methanol activities even if they were available.

In general, we made up a single solution of the given carbonyl compound in methanol and then used aliquots of this to obtain from three to six solutions having various amounts of water to shift the equilibrium. The absorbance values for the neutral solutions were always checked against values obtained in Beer's law plots and found to agree within ±2%. The values of the calculated equilibrium constants for a series agreed within ±5% for most of the systems and many were within ±1%. Duplication of a series by a given ex-

TABLE II

EQUILIBRIUM CONSTANTS FOR ACETAL FORMATION IN ANHYDROUS METHANOL[a]

	$K \times 10^3$, l. mole^{-1}		ΔH,[b]	ΔG_{298},[b]	ΔS,[b]	
Carbonyl compound	10°	25°	kcal./mole	kcal./mole	cal./deg. mole	$\Sigma\sigma^*$[c]
		A. Aromatic Aldehydes				
p-Bromobenzaldehyde	43.1 ± 0.2	28.7 ± 0.2	−4.7	2.1	−23	1.32
Benzaldehyde	23.7 ± 0.5	14.2 ± 0.5	−5.7	2.5	−28	1.09
o-Anisaldehyde[d]	20.5 (2°)	9.4	−5.5	2.8	−28	...
Furfural	12.3 ± 0.6	7.4 ± 0.3	−5.6	2.9	−29	0.96
p-Tolualdehyde	10.5 ± 0.2	6.6 ± 0.2	−5.2	3.0	−28	0.92
3,4,5-Trimethoxybenzaldehyde	9.2 ± 0.3	5.9 ± 0.2	−5.0	3.0	−27	1.06
p-Acetamidobenzaldehyde	7.3 ± 0.4	4.7 ± 0.2	−4.8	3.2	−27	0.89
p-Anisaldehyde	2.1 ± 0.08	1.5 ± 0.05	−3.8	3.9	−26	0.73
Salicylaldehyde[d]	2.72 (2°)	1.3	−5.5	3.9	−30	...
p-Nitrobenzaldehyde	...	0[e]	...	...	...	...
		B. Acyclic Ketones				
Acetone	0.65 ± 0.01	0.40 ± 0.02	−5.4	4.6	−34	0.0
2-Butanone	0.20 ± 0.01	0.13 ± 0.01	−4.9	5.3	−34	−0.10
2-Octanone	...	0.048 ± 0.002	...	5.9	...	−0.15
3-Pentanone	0.052 ± 0.002	0.034 ± 0.002	−4.7	6.1	−36	−0.20
Acetophenone	0.035 ± 0.002	0.025 ± 0.002	−3.9	6.3	−34	0.60
3-Methyl-2-hexanone[f]	0.021 ± 0.002	0.015 ± 0.003	−3.8	6.6	−35	−0.21
3,5-Dimethyl-4-octanone	...	0.0096	...	6.8	...	−0.42
α,α'-Dichloroacetone	...	0[e]	...	...	...	...
Dicyclopropyl ketone	...	0	...	...	...	...
		C. Cyclic Ketones				
Cyclohexanone[g]	12.9 ± 0.9	6.7 ± 0.4	−7.3	3.0	−34	
4-Methylcyclohexanone	11.5 ± 0.6	6.1 ± 0.4	−7.1	3.0	−34	
4-*t*-Butylcyclohexanone	10.0 ± 0.4	5.9 ± 0.2	−5.9	3.0	−30	
3-Methylcyclohexanone	5.5 ± 0.3	3.4 ± 0.2	−5.4	3.4	−29	
Cyclopentanone	0.66 ± 0.02	0.46 ± 0.02	−4.0	4.5	−29	
2-Methylcyclohexanone	0.32 ± 0.01	0.20 ± 0.01	−5.2	5.0	−34	
Cyclopentadecanone[f]	0.021 ± 0.002	0.014 ± 0.003	−5.8	6.7	−42	

[a] Determined by the Melchior technique.[16] [b] The values of ΔH are precise to at least ±0.5 kcal. and those of ΔG to ±0.2 kcal. based on the measured values of K. The values of ΔS are precise to about ±1 e.u. [c] Values from H. H. Jaffé [*Chem. Rev.*, **53**, 254 (1953)] and from R. W. Taft, Jr. ("Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, New York, N. Y., 1956, p. 619) except for the furan ring and *p*-acetamido groups, which were estimated from a σ correlation as recommended by Jaffé. [d] These values were calculated from Melchior's[16] mole fraction data making the appropriate volume corrections for known densities of methanol–water mixtures (N. A. Lange, Ed., "Handbook of Chemistry," 10th Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1961, p. 1184). [e] Hemiacetal formation and hydrate formation as well as acetal formation. [f] The thermodynamic values are questionable because of the poor reproducibility of K_e. [g] Duplication of these determinations by another student gave poor reproducibility between three series of measurements. However, the calculated thermodynamic properties agreed within 2% of the above values. Typical values were: $K_e = (9.8 \pm 0.1) \times 10^{-3}$ at 10°, $(5.4 \pm 0.1) \times 10^{-3}$ at 25°, and $(3.2 \pm 0.1) \times 10^{-3}$ at 40°; $\Delta H = -7.4$ kcal./mole, $\Delta G_{298} = 3.1$ kcal./mole, $\Delta S_{298} = -35.2$ e.u.

perienced individual usually gave precision within ±10%. Because of the many possible indeterminate errors that can occur in performing these experiments, all of the results were obtained only after considerable experience by each of the authors in preparing the solutions and measuring the absorbances. For these reasons we cannot expect our results to be more accurate than ±10%.

One significant error in our results could arise if the absorbance of the carbonyl compound in methanol is different than in methanol–water mixtures owing to solvent effects, or to variable extents of hemiacetal or hydrate formation. However, we found that the absorbance of cyclohexanone in methanol was the same in methanol–water mixtures for which the water content was varied from 0.107 to 0.533 M. Inasmuch as cyclohexanone should be as sensitive to this type of error as any of the carbonyl compounds, we have assumed in all cases that the differences in absorbances between the neutral anhydrous methanol and the acidic methanol–water mixtures is proportional to the amount of acetal.

The results for the aromatic aldehydes are given in section A and of Table II and are arranged in order of decreasing values of K_e. Also included are the results for *o*-anisaldehyde and salicylaldehyde which were calculated from Melchior's data to demonstrate that our results are in sensible agreement with his results. One can see that as the electron-attracting ability of the *para* substituent is increased, the value of K_e increases. For the series, ΔG parallels ΔH, and ΔS remains essentially constant. The entropy values for this series are significantly and consistently less negative than for the ketones which have been studied. The entropy loss for all of these systems is, as an order of magnitude, about what one should expect for the loss of translational energy for 1 mole.

Replacement of the methyl groups of acetone by ethyl and higher groups effects a marked decrease of the equilibrium constant as may be seen in section B, Table II. The effect is more severe when methyl is replaced by phenyl or by an alkyl group with branching on the α-carbon atom. When both methyl groups are replaced by cyclopropyl groups, acetal formation is completely prevented.

α,α'-Dichloroacetone failed to give a constant value of K_e as the amount of water was varied owing to the formation of hemiacetal. That hemiacetal formation

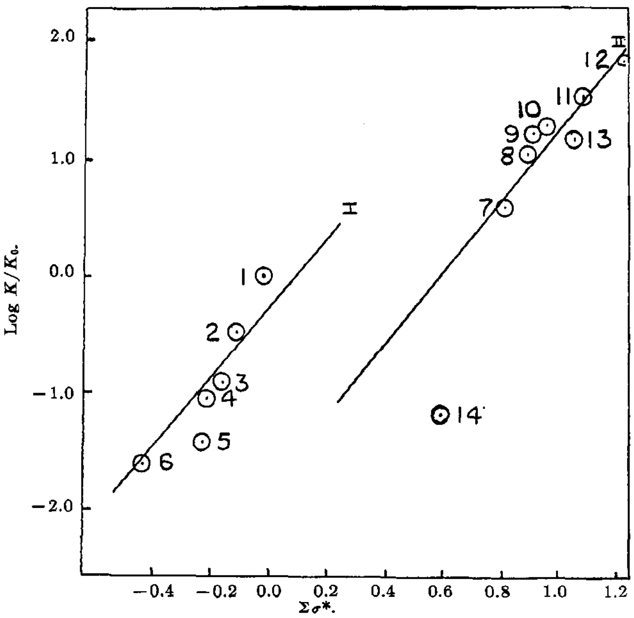

Figure 1.—Plot of log K/K_0 vs. $\Sigma\sigma^*$ for dimethyl acetal formation for R_1R_2CO. K_0 is the equilibrium constant for acetone. The points are 1, CH_3, CH_3; 2, CH_3, C_2H_5; 3, CH_3, n-C_6H_{13}; 4, C_2H_5, C_2H_5; 5, CH_3, sec-C_4H_9; 6, sec-C_4H_9, 2-C_5H_{11}; 7, H, p-$CH_3OC_6H_4$; 8, H, p-$CH_3CONHC_6H_4$; 9, H, p-$CH_3C_6H_4$; 10, H, C_4H_3O; 11, H, C_6H_5; 12, H, p-BrC_6H_5; 13, H, 3,4,5-$(CH_3O)_3C_6H_2$; and 14, CH_3, C_6H_5.

occurred was deduced from the fact that the absorbance of the ketone was higher in basic methanol solution than in acidic methanol and that the initial absorbance reading in neutral methanol was higher than in basic methanol but then gradually decreased until it was equal to the absorbance in acidic methanol. The absorbance change in neutral methanol was undoubtedly due to a trace of hydrogen chloride from the hydrolysis of the chloro ketone. The approximate value of K_e for hemiacetal formation was 1×10^{-4} and that over-all for acetal formation was 1×10^{-6}.

The series of cyclic ketones given in section C, Table I, show a definite decrease in K_e due to branching on the α-carbon. K_e for cyclohexanone is about 30 times as great for that for 2-methylcyclohexanone, but the effect is much less when the branching is on the 3-position and nearly vanishes for branching on the 4-position. Interestingly, the 4-alkyl groups have essentially no effect on equilibria compared to the effect by hydrogen and the difference between hydrogen, methyl, and t-butyl is about the same as the experimental error. The influence of α branching on K_e observed for the cyclic compounds is similar to that observed for 3-methyl-2-hexanone and 3,5-dimethyl-4-octanone (section B, Table II).

Our results for dimethyl acetal formation for cyclopentanone and cyclohexanone are significantly different from the results Anteunis, *et al.*,[30] obtained by n.m.r. analysis. For cyclopentanone, our value of K_e is about 5 times as large as theirs (46×10^{-5} compared to 9.4×10^{-5}), but the values of ΔH (ours −4.0, theirs −3.5) and ΔS (ours −28.9, theirs −30.3) agree rather well. For cyclohexanone, they obtained $K_e = 6.5 \times 10^{-3}$ at 27° while we found $K_e = 6.7 \times 10^{-3}$ at 25°. However, the values of ΔH (ours −7.3, theirs −14.6) and ΔS (ours −34.5, theirs −59.1) are so markedly different that we repeated the equilibrium determination a number of times at 10, 25, and 40°. While our values of K_e varied as much as 20% between any given two series of determinations, the results were very consistent within any series and the values of ΔH varied less than ±2% and ΔS varied less than ±1% between series. As a further crosscheck we calculated mole fraction equilibrium constants from our data for cyclohexanone to obtain values for K_x of 0.168 at 25° and 0.310 at 10°. These compare quite well with the values obtained by short-path cell measurements for concentrated solutions.[18,31]

Inasmuch as our values for acetal formation (for which K_e values vary by about four powers of 10) give calculated ΔH values in the range of from about −4 to −7 kcal./mole and ΔS values are in the range of −25 to −36 e.u., we believe our values for cyclohexanone are fairly reliable. As a final confirmation of this position, we experimentally measured ΔH in a crude calorimeter at 20° for cyclohexanone and methanol and obtained a value of −8.9 kcal./mole; this value has been independently confirmed (see Experimental Section). Therefore, we believe that the variation of K_e with temperature found by Anteunis is much too large, resulting in very high values for ΔH and ΔS. If this is true, then their arguments for evidence of the twist conformation for cyclohexanone are invalidated. If our results have validity, then the values of ΔS for cyclic ketones are not significantly different from those of acyclic ketones. It is only for the aromatic aldehydes that we find significantly lower values for ΔS than for other series studied.

The values for cyclohexanone obtained by Anteunis may show a variation from ours because they used a calibration curve for the ketone and acetal obtained at a single temperature but applied the corrections for reaction mixtures at other temperatures. We suggest this as a significant error because of hemiacetal formation, the extent of which varies with temperature. In addition, the n.m.r. spectra for this system are complex and the methoxyl hydrogens of the hemiacetal apparently are covered up by the acetal absorption.[29]

We have tried a number of linear free-energy correlations of our data such as the Taft equation[32] or ΔG *vs.* ΔH.[33] While we have had some success with these correlations, particularly by using certain assumptions, we are not satisfied with the results. We find that a Taft plot of log K/K_0 (where K_0 is the equilibrium constant for the formation of acetone dimethyl acetal) against $\Sigma\sigma^*$ for the acyclic ketones and aromatic aldehydes gives two lines having about the same slope as shown in Figure 1. The points for the acyclic ketones lie along one line (I) and the points for aromatic aldehydes lie along the other line (II); the two lines being displaced by about 0.5 unit for $\Sigma\sigma^*$. All of these compounds are similar in that they do not form significant amounts of hemiacetals and so we considered the possibility that in going from acetone to the benzaldehydes it might be appropriate not to correct $\Sigma\sigma^*$ for replacing a methyl group by hydrogen.[19] Using this curve-fitting assumption in the treatment of our data displaced the points for the aromatic aldehydes to the

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(31) R. Garrett and D. G. Kubler, unpublished results.

(32) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 3120 (1952); **75**, 4231 (1953).

(33) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p. 325.

left onto the line for the ketones. A least-squares treatment gave $\rho^* = +3.05 \pm 0.25$ with a correlation coefficient of 0.963 and a probable error of 0.27 log units. We did not include acetophenone in the series because it deviated very far from the line.

Beyond the fact that ρ^* has a positive value we are not convinced of any other significance for this correlation. However, a comparison of certain aspects of our correlation for the equilibrium formation of dimethyl acetals with the correlation of Kreevoy and Taft[19] for the rates of hydrolysis of diethyl acetals is informative.

Correlation of their data by the equation $\log k/k_0 = \rho^*\Sigma\sigma^*$ provided three lines (their Figure 1); the lower line was for acetals of aliphatic aldehydes, the middle line was for acetals of methyl ketones and the upper line for acetals of α,β-unsaturated aldehydes with all lines having about the same negative slope. Because the line for the acetals of α,β-unsaturated aldehydes was over 4 log units higher than that for the acetals of aliphatic aldehydes they assumed a significant resonance effect was operating in the transition state (the line for the acetals of ketones is about 2 log units higher than for the acetals of aliphatic aldehydes). By applying a parameter for the number of α-hydrogens on any given acetal compared to the six on acetone diethyl acetal, they were able to bring the line for acetals of ketones down to that of the acetals of aliphatic aldehydes. Excellent correlation of the data was obtained. Unfortunately, application of this parameter did not improve the line for the acetals of α,β-unsaturated aldehydes compared to the other lines. Interestingly, each of their lines are separated by about 0.5 $\Sigma\sigma^*$ units as we have found for the equilibria for acetal formation and the separation is in the same direction.

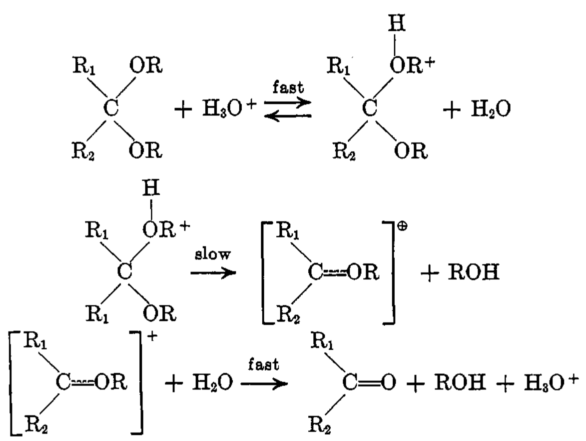
While Kreevoy and Taft successfully treated the rate data for the hydrolysis of 20 acetals by the assumption of a resonance effect due to hyperconjugation, and one cannot gainsay the effectiveness of the correlation, we are not convinced that the explanation is necessarily correct. That this could be explained by an alternative model, such as a steric effect as one example, has been pointed out by Wiberg.[34] If one invokes the idea of hyperconjugation for stabilization of a positively charged transition state, one should observe a manyfold increase in stabilization of the transition state when there is unsaturation adjacent to the reaction site. Thus ethyl acetals of α,β-unsaturated aldehydes should hydrolyze significantly faster than acetone diethyl acetal and not slower as found by Kreevoy and Taft (acetone diethyl acetal hydrolyzed 2.5 times as fast as the ethyl acetal of crotonaldehyde, 5 times as fast as the ethyl acetal of cinnamaldehyde, 100 times as fast as the ethyl acetal of benzaldehyde, and 67,000 times as fast as the ethyl acetal of *p*-nitrobenzaldehyde[35]). One can rationalize this slower rate for unsaturated acetals if it is assumed that there is a large negative inductive effect for the unsaturated systems, but such an explanation could not be easily supported. Kreevoy has proposed that the transition state for unsaturated acetals resembles the ground state acetal more than the alkoxycarbonium ion with little resonance stabilization of the transition state.[36] Alternatively, he suggests that for saturated acetals the transition more closely resembles the alkoxycarbonium ion than the ground state acetal so there is considerable positive charge on the transition state and hyperconjugation can come into play. We do not wish to argue with this concept although we would point out that this is simply a proposal without an experimental basis except that ethyl acetals of ketones hydrolyze nearly as fast or faster than the acetals of most α,β-unsaturated aldehydes. One should note that if the magnitude of charges on the transition states of two series markedly differ, there should be different ΔS^* values for each series and hence the results should not correlate along a single line, although the lines might well be parallel as is true for the acetal hydrolysis data. The values of ΔG^* and ΔS^* for structural variations of the carbonyl moiety have not been determined for either acetal formation or hydrolysis.

On the basis of our equilibrium results we would not expect the rate data for aromatic aldehydes to correlate with the data for acyclic ketones because ΔS is approximately 7 e.u. less negative for the former class for acetal formation and there is likely to be a similar effect for ΔS^*. We would expect the same situation for the hydrolytic data for the acetals of saturated aldehydes since the correlation line is displaced about 0.5 of a $\Sigma\sigma^*$ unit from the line for acetals of ketones.[19] We suggest that the acetal data may correlate in classes (*i.e.*, saturated aldehydes, acyclic ketones, α,β-unsaturated aldehydes, aromatic aldehydes, etc.) rather than by a single line for all aldehydes and ketones and this is because of differences in entropy factors.

The basic argument against using the various parametric corrections for linear free-energy correlations which has been applied to this and other reactions is that these corrections may obscure the contribution of ΔS^* to ΔG^* which is one of the most important aspects of such correlations.

Implications for the Mechanism

The background details for the mechanism of acetal hydrolysis are given by Kreevoy and Taft.[19] More recent studies have been concerned with defining solution effects for acetal hydrolysis.[20,21] The mechanism usually given for this reaction is illustrated below.



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[34] K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons' Inc., New York, N. Y., 1964, p. 419. See also P. R. Wells, *Chem. Rev.*, **63**, 200 (1963).

[35] M. M. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, **79**, 4016 (1957).

[36] M. M. Kreevoy, *Tetrahedron*, **5**, 233 (1959).

To the extent that this mechanism for acetal hydrolysis is valid, one can invoke microscopic reversibility to insure the mechanism for acetal formation. However, the above mechanism does not reveal the nature of the steps after the rate-determining step for hydrolysis, and these steps are important to understanding acetal formation. Furthermore, one could not be sure that the mechanism does not change when the conditions for acetal hydrolysis are changed to those for acetal formation, nor could one be sure that the mechanism is the same for those carbonyl structures which form hemiacetals as for those which do not.

Because there is so little kinetic and other mechanistic data available for acetal formation, we are determining the kinetics of the formation and of the hydrolysis of dimethyl acetals in methanol–water mixtures for several of the aldehydes and ketones used in the equilibrium study. In particular, we wish to unravel the relationship between rates and equilibria for this system and the influence of structures on ΔS^*, While the equilibrium parallel the kinetics for the hydrolysis of acetals (σ^* is negative), our preliminary studies of the kinetics of acetal formation indicate an inverse relationship with equilibria.[37] This inverse relationship is to be expected if the rate-determining step involves the formation of the oxocarbonium ion but the equilibria is controlled by a separate step.

Inasmuch as ρ^* has a positive value for equilibria for acetal formation, and because there are only trace amounts of hemiacetal present in the systems studied, *the equilibrium must be controlled by the nucleophilic addition of alcohol to the carbonyl group and not by the etherification stage.* That is to say, the over-all equilibrium constant is the product of two equilibria; the first of these must be smaller and variable (hemiacetal formation) and the second be larger and more constant (hemiacetal-to-acetal conversion) for structural variations. As a structural analogy to the hemiacetal-to-acetal conversion, one should expect alcohols having structures like the carbonyl compounds to be converted significantly to their methyl ethers. To verify this conclusions we are evaluating the acid-catalyzed formation of the methyl and ethyl ethers of benzyl alcohol.[38] These studies have not been completed, but it appears that the conversions to benzyl methyl ether are essentially complete for benzyl alcohol and methanol at 60, 90, or 100°. The reaction is very slow even at the higher temperature and with high mole ratios of methanol to benzyl alcohol and 0.4 wt. % of sulfuric acid as a catalyst. We ascertained the extent of reaction by water analysis and verified the analytical method by infrared analyis for benzyl methyl ether content. These results lend some validity to the conclusion that the hemiacetal-to-acetal conversion does not control the over-all equilibrium.

Experimental Section

Purification of Reactants.—Methanol was purified by the method of Lund and Bjerrum.[39] Each portion was distilled (on a column of 30 theoretical plates) until the transmittance was 97% or better measured against distilled water at 250 mμ before collecting the product. The water content was determined for each batch by the Karl Fischer method. In all cases the water content was less than 0.010% and was usually about 0.005% or less. Storage of the methanol for periods as long as 6 months did not change significantly the spectral qualities or the water content. Ordinarily, a batch of about 3 l. was prepared and was used in less than a week.

Aldehydes and Ketones.—The aldehydes and ketones were all commercial products and standardly were extracted with dilute aqueous bicarbonate solution (except for the water-soluble ketones) prior to other purification steps. In all cases the final purification was performed just prior to use. We have found it necessary to use the bicarbonate extraction to remove traces of acidity from the carbonyl compounds even for several of the ketones. If this is not done, the solutions of the carbonyl compounds in neutral methanol often slowly decreased in absorbance on standing. The sources, the methods of purification, and observed physical properties are given in Table III.

TABLE III

PROPERTIES OF CARBONYL COMPOUNDS

Compound	Source[a]	Method of purification[b]	B.p. (mm.) or m.p., °C.	$n^{25}\text{D}$
Acetone	F	1	55–55.5 (atm.)	1.3542
2-Butanone	F	1	77.5–78 (atm.)	1.3753
3-Pentanone	EK	3	99–100 (atm.)	...
3-Methyl-2-hexanone	COC	2	45–45.5 (20)	1.4064
2-Octanone	F	2	...	1.4127
3,5-Dimethyl-4-octanone	COC	2	76–77 (12)	1.4207
α,α'-Dichloroacetone	EK	3	172 (atm)	...
Dicyclopropyl ketone	COC	2	67 (20)	1.4640
Cyclopentanone	EK	2	129.5 (atm.)	1.4342
Cyclohexanone	EK	2	55 (22)	1.4466
2-Methylcyclohexanone	COC	2	57 (15)	1.4442
3-Methylcyclohexanone	COC	2	60 (15)	1.4422
4-Methylcyclohexanone	COC	2	60 (15)	1.4418
4-*t*-Butylcyclohexanone	COC	2	53–54	...
Cyclopentadecanone	A	4	60–61	...
Furfural	EK	2	65 (20)	1.5214
Benzaldehyde	EK	2	62 (10)	1.5416
p-Tolualdehyde	A	2	81 (10)	...
p-Anisaldehyde	EK	2	117–117.5 (10)	1.5680
p-Acetamidobenzaldehyde	A	5	155–157	...
p-Bromobenzaldehyde	A	5	60–61	...
p-Nitrobenzaldehyde	A	5	102–104	...
3,4,5-Trimethoxybenzaldehyde	A	5	74.6–75.2	...
Acetophenone	EK	2	85 (10)	1.5312

[a] F, Fisher Scientific Co.; EK, Eastman Kodak Co.; COC, Columbia Organic Chemicals Co.; and A, Aldrich Chemical Co. [b] Method 1: compound was distilled, recrystallized as sodium iodide addition compound, distilled from the addition compound, and redistilled. Method 2: compound was washed with dilute sodium bicarbonate solution, then with water, dried and distilled, collecting only the middle portion. Method 3: compound was fractionally distilled, collecting only the middle fraction. Method 4: compound was recrystallized from methanol–water. Method 5: compound was recrystallized from water and dried under vacuum at 60°.

In all cases except for *p*-tolualdehyde, *p*-nitrobenzaldehyde, and α,α'-dichloroacetone, the solutions gave reproducible extinction coefficients and followed Beer's law over the concentration ranges used in the equilibrium studies. The absorbance values for the reference solutions and the reaction mixtures remained constant over the 6- to 8-hr. periods used for the measurements. In all cases the addition of a trace of mineral acid to a solution of the aldehyde or ketone in methanol effected an immediate decrease in the absorbance value. The dimethyl acetals of most of the aldehydes and ketones used in this work have been prepared for hydrolytic kinetic studies. The absorbances of these acetals in methanol at the same concentration levels used for the aldehydes and ketones were essentially zero. This means that the acetal form does not contribute to the measured absorbances, except for *p*-nitrobenzaldehyde.

Acid Solution.—A stock solution of aqueous hydrochloric acid was prepared and standardized (1.070 N). This solution was used for preparing the acid solutions of aqueous methanol in all of the equilibrium studies. A weighed amount of the 1.070 N acid was added to an appropriate volumetric flask and diluted to

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(37) J. M. Bell, B. J. Cox, D. G. Kubler, and R. G. Zepp, unpublished results.

(38) We wish to thank Dr. D. F. DeTar and Dr. J. L. Kice for suggesting this experimental work.

(39) H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

the mark with methanol. Final adjustment of the volume was made in the constant-temperature bath.

Carbonyl Solutions.—The freshly purified carbonyl compound was weighed into a volumetric flask, previously flushed with nitrogen, and then diluted to the mark with methanol. In most instances the final adjustment of the volume was made at 25° in the constant-temperature bath, but in a few cases the adjustment was made at room temperature. In all cases room temperature was 26 ± 2° and this error is not significant because of the relative method of determining the carbonyl absorbances for the solutions. For acetone we had some difficulty in obtaining reproducible extinction coefficients for each freshly prepared solution owing to volatility losses while weighing.

Reaction Mixtures.—To each of several volumetric flasks there were added equal volumes (pipet) of the carbonyl compound in methanol. Into all but one of these flasks (the reference solution) there were pipetted various volumes of the standard solution containing water, methanol, and hydrogen chloride. The solutions were filled to the mark with methanol with the final adjustment of the volume made at 25° in the constant-temperature bath. The solutions were stored in the constant-temperature bath which was maintained at 25 ± 0.01°. Water was circulated to the Beckman DU spectrophotometer which was equipped with thermospacers, and the temperature in the cell housing was determined to be 25 ± 0.05°. For the 10° runs the bath was maintained at 8 ± 0.02° and the temperature in the cell housing was 10 ± 0.1°. A stream of dry air was passed through the cell compartment to prevent fogging of the cells. Portions of the solutions were transferred to ground-glass-stoppered quartz cells and then measured against methanol. In all cases the acetal equilibrium was attained in less then 30 min., and we did not observe drifting of the values with time.

After the readings were made at 25° the bath temperature was adjusted to 8° (10° in the DU cell compartment) and the new absorbance values were measured. The absorbance readings were checked several times at appropriate intervals to be sure the reactions were at equilibrium. In most instances we found the absorbance values for the reference solutions to be the same at 25 and 10°, but occasionally the values were significantly lower at 10°. In certain instances that this occurred we found that some reaction had occurred in the reference solution, and fresh solutions were prepared to obtain satisfactory values at both temperatures. In other cases the absorbance change with temperature was due to hemiacetal formation. The data for acetophenone and methanol, as a typical example, are shown in Table IV.

In two cases the absorbance reading of the solutions changed in an erratic fashion regardless of how the compounds were purified or how carefully the solutions were prepared. These situations are discussed individually.

p-**Tolualdehyde.**—In the initial attempts to determine the equilibrium constant for acetal formation for *p*-tolualdehyde it was found that the absorbance reading was greater with solutions containing aqueous acid than for neutral methanol. This suggested to us that the aldehyde contained traces of acid which catalyzed the formation of acetal, and when aqueous acid was added the acetal equilibrium was reversed. We were not successful in eliminating the difficulty in spite of repeated extractions with sodium bicarbonate solutions and water, followed by redistillation with a nitrogen purge. The absorption change in neutral methanol occurred extremely rapidly and we could not detect any change even when we added 1 drop of the aldehyde to methanol and directly transferred the solution to a cell to measure the absorbance. We found that these solutions followed Beer's law (less than 0.1% variation in ϵ for a sixfold concentration change), but the value of ϵ was markedly increased by the addition of a trace of sodium hydroxide to the methanol prior to adding the aldehyde. However, the value of ϵ depended upon how the aldehyde and sodium hydroxide were added to the methanol and varied from 353 and 13,500. When a standard solution of the aldehyde in methanol was diluted volumetrically with increasing amounts of water the value of ϵ increased and leveled at 16,000; this value was duplicable. This value was then used to calculate the concentration of tolualdehyde for the equilibrium solutions.

p-**Nitrobenzaldehyde.**—Solutions of *p*-nitrobenzaldehyde in methanol gave duplicable values of ϵ 10,900. When aqueous acid was added, the absorbance reading decreased immediately but was essentially constant regardless of the amount of aqueous acid present as shown in Table V.

TABLE IV

EQUILIBRIUM DATA FOR ACETOPHENONE AND METHANOL

Solution[a]	Vol. of HCl solution,[b] ml.	A (at 278 mμ)	M_{MeOH}[c]	M_{H_2O}[d]	$\frac{A_0 - A}{A}$[e]	K_e[f] $\times 10_5$
1	0.0	0.380	...	...	...	...
2	1.0	0.259	24.52	0.0280	0.467	2.17
3	2.0	0.296	24.50	0.0560	0.284	2.65
4	5.0	0.345	24.48	0.140	0.1015	2.37
5	7.0	0.351	24.45	0.196	0.0826	2.70
6	10.0	0.361	24.40	0.280	0.0526	2.47
						Av. 2.5
1	0.0	0.388	...	...	...	...
2	1.0	0.227	24.98[g]	0.0285	0.710	3.24
3	2.0	0.277	24.95	0.0571	0.401	3.68
4	5.0	0.338	24.92	0.1425	0.148	3.40
5	7.0	0.347	24.90	0.1995	0.118	3.79
						Av. 3.5

[a] Each solution was made in a 25-ml. volumetric flask. To each flask there was added 2.00 ml. (pipet) of 3.44×10^{-4} M acetophenone in methanol. [b] Pipet addition of the stated volume of 1.3113 g. of 1.070 N hydrochloric acid in 100 ml. of methanol solution. Each milliliter of solution contained 0.0126 g. of water. [c] Calculated from the difference between 25 ml. and the known volume of added and/or formed constituents and assuming the densities of the methanol and water to be additive. This is not true, but the error by this assumption is much less than the experimental errors. For at least two different systems we weighed in all constituents and found the error to be considerably less than 1% for K_e. [d] For this system the molarity of the water was not significantly changed by the amount of water formed by reaction. The aliphatic ketones in many cases had conversions in excess of 90% and were sufficiently concentrated to change the value of the water molarity. For those cases the appropriate corrections were made. [e] $(A_0 - A)\alpha M_{\text{acetal}}$ and $A\alpha M_{\text{aldehyde}}$, so that $(A_0 - A)/A = M_{\text{acetal}}/M_{\text{aldehyde}}$. [f] $K_e = (A_0 - A)M_{H_2O}/AM_{\text{MeOH}}^2$. [g] The total volume of the system at 10° was determined by using the volume change for mixtures of methanol and water. This volume was used for calculating the molarity of methanol and of water.

TABLE V

Flask[a]	Vol. of acid,[b] ml.	A (at 265 mμ)
1	0.00	1.02[c]
2	1.00	0.933
3	2.00	0.931
4	5.00	0.940
5	7.00	0.935
6	10.00	0.941

[a] All solutions made at 25° in 25-ml. volumetric flasks: 0.0444 g. of the aldehyde was diluted to 50 ml. in methanol followed by dilution of 10 ml. of the first solution to 50 ml. To each flask there was added 2.0 ml. of the final solution ($M = 9.4 \times 10^{-5}$, ϵ 1.09×10^4). [b] To a 50-ml. flask there was added 5.070 g. of 1.070 N hydrochloric acid in water and the mixture was diluted to the mark with methanol. [c] This value was constant (25°) for over 24 hr.

To investigate further what was occurring in this system we performed some qualitative experiments comparing the influence of acid and of base on the absorbance of the aldehyde in methanol. The presence of base significantly lowered the absorbance reading compared to neutral methanol, and the presence of acid reduced the absorbance reading still further. However, *p*-nitrobenzaldehyde dimethyl acetal was prepared and found to have a significant absorbance in methanol at 265 mμ (ϵ 1.02×10^4). The hemiacetal and hydrate forms for *p*-nitrobenzaldehyde are expected to have extinction coefficients essentially like that of the acetal. When the complete absorbancy curve (210–280 mμ) was run for *p*-nitrobenzaldehyde in methanol there was not a K band characteristic of the carbonyl group. Addition of a trace of HCl in methanol to the aldehyde in methanol effected a decrease in the absorbance at 265 mμ of the solution by about 16% while addition of a trace of base effected a change of about 8%. On the basis of these facts we conclude that *p*-nitrobenzaldehyde exists predominantly as the hemiacetal in methanol solutions. Thus the Melchior technique is not applicable for the measurement of the extent of acetal formation, not because of hemiacetal or hydrate formation but because these derivative forms all have significant extinction coefficients. The absorbance of a solution of the aldehyde in 80% dimethyl sulfoxide–20% water diminished by about 4% when a trace of acid or base was added, indicating some hydrate formation.

Cyclohexanone Methyl Hemiacetal.—Methanol at room temperature (24.5°) was added nearly to the mark of a 10.00-ml. volumetric flask and then 0.0512 g. of refined cyclohexanone was added, the flask was quickly filled to the mark with methanol and thoroughly mixed. A sample was transferred to a 1-cm. quartz cell and readings were taken as rapidly as possible. With zero time as the time at which cyclohexanone was added, the following results were obtained, time, sec. (absorbance): 62 (0.820), 97 (0.810), 122 (0.800), 151 (0.795), 177 (0.792), 210 (0.785), 237 (0.780), 273 (0.778), 348 (0.772), 780 (0.766), ∞ (0.766). From the expression for a first-order reaction in both directions for an equilibrium,[40] $k_1tA_0/2.303(A_0 - A_\infty) = \log [(A_0 - A_\infty)/(A - A_\infty)]$, where A_0 is the absorbance at $t = 0$, A_∞ is the absorbance at $t = \infty$, A = absorbance at $t = t$, and k_1 is the specific rate constant for hemiacetal formation, it is seen that a plot of $\log (A - A_\infty)$ *vs.* t will give a straight line of slope equal to $-2.303(A_0 - A_\infty)/k_1A_0$. A plot of $\log (A - A_\infty)$ against t was extrapolated to $t = 0$ to give $A - A_\infty = 0.089$ (and $A_0 = 0.855$) and the slope was -3.25×10^{-3} sec.$^{-1}$. The calculated rate constant was 77.7×10^{-5} sec.$^{-1}$ and $t_{1/2} = 92.5$ sec. The molarity of the methanol was about 24.6, so $K_e = M_{\text{hemiacetal}}/M_{\text{ketone}}M_{\text{MeOH}} = (A_0 - A_\infty)/A_\infty M_{\text{MeOH}} = 4.7 \times 10^{-3}$ l. mole^{-1}.

Etherification Studies. Benzyl Alcohol–Methanol.—A mixture was made of 23.487 g. (0.735 moles) of methanol, 15.425 g. (0.143 mole) of benzyl alcohol and 0.1604 g. of concentrated sulfuric acid, (0.4% by weight of the reactants). Analysis of the mixture for water by the Karl Fischer method gave a value of 0.15%. Portions of the mixture were sealed in glass ampoules and placed in an oil bath controlled at 90 ± 0.1°. Ampoules were removed and chilled in ice and the contents were analyzed for water content. The water compositions obtained were 25.6 hr., 1.46%; 116.5 hr., 3.07%; 170.3 hr., 3.78%; 332.2 hr., 4.62%, and 885 hr., 6.60%. Preliminary runs had demonstrated that approximately 700 hr. was needed to obtain complete etherification at 90° for a 5:1 mole ratio mixture and for the given catalyst concentration. The final value of water concentration corrected for the initial amount of water represents a conversion of benzyl alcohol to benzyl methyl ether of 97.8%.

In order to verify the analytical system, two other reaction mixtures, each containing about 0.5 wt. % of sulfuric acid, were analyzed by Karl Fischer for water content and by infrared analysis for benzyl methyl ether content: (I) a 5:1 mole ratio of methanol to benzyl alcohol, 1225 hr. at 60°; and (II) a 10:1 mole ratio of methanol to benzyl alcohol, 809 hr. at 60°. Reaction mixture I contained 2.06% water by the Karl Fischer method which represents a 28.7% conversion of benzyl alcohol to ether. Analysis of the reaction mixture by infrared in carbon tetrachloride solution for benzyl methyl ether content (using the antisymmetric ether stretch at 1098 cm.$^{-1}$) gave a value of 11.7% which represents a 27% conversion. For solution II, the water analysis gave 1.33% water and a calculated conversion of 27.5%. Infrared analysis for ether content gave 8.4% ether and a calculated conversion of 29.3%.

The infrared analytical method was evaluated by running solutions of each of the reactants in carbon tetrachloride to be sure there were no overlapping bands for the 1098-cm.$^{-1}$ band of benzyl methyl ether. Benzyl alcohol has a weak band at 1080 cm.$^{-1}$ which also appeared as a shoulder on the 1098-cm.$^{-1}$ band of benzyl methyl ether. Using various synthetic mixtures of benzyl alcohol, benzyl methyl ether, methanol, and water, an accuracy of about ±5% for ether content was demonstrated. Current studies of this system utilizing g.l.p.c. analysis verify our conclusions that the reaction goes significantly toward completion.

Heat of Reaction for Cyclohexanone and Methanol.—The heat of reaction at 20° for cyclohexanone and methanol was determined in a 1-qt. Dewar flask insulated with about 3 in. of vermiculite. The flask was closed by means of a cork stopper through which were inserted a Beckmann thermometer and a motor-driven stirrer. The heat capacity of the calorimeter was determined by measuring the heat of solution of ammonium chloride (C_s = 70 cal./deg.). The temperature decrease due to the heat of solution of 4.83×10^{-2} moles of cyclohexanone in 395 ml. of methanol was found to be −0.127 and −0.125°. The heat rise due to the heat of reaction of 4.83×10^{-2} moles of cyclohexanone in 395 ml. of methanol was found to be +1.513 and +1.517°. From these data, utilizing the heat capacity of methanol and that the reaction was 98% complete (calculated from K_e), gave a calculated value of $\Delta H = -8.9$ kcal./mole.

Independently, Tamplin determined the value of ΔH for this reaction in a precision ice calorimeter[41] and obtained a value of $\Delta H = -8.77$ kcal./mole.[42]

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