group to a water molecule and reduces charge separation. Similarly, the transition state for the attack of the weak nucleophile, water, on the imine (VIII) will be stabilized by a general base which partially converts the water molecule into hydroxide ion and reduces the mutual repulsion of the two positive charges in VIII. It is not clear how hydrogen bonding in transition state VI, which is very similar to VIII, would provide appreciable stabilization of this transition state relative to the ground state or to other possible transition states. Thus, we see no conflict between "anthropomorphic" arguments, as commonly utilized by the organic chemist, and an analysis of a reaction in terms of transition-state theory.

These considerations are consistent with the simple generalizations that catalysis occurs where it is most needed and that reactions of this type generally proceed by pathways which avoid the formation of unstable intermediates.[14] These may be restated in the form of a rule, which we will call the Anthropomorphic rule, as follows. In general acid–base catalysis of reactions which involve proton transfer to or from nitrogen, oxygen, or sulfur, bases will react with protons which become more acidic and acids will react with atoms which become more basic in the transition state (and products). The degree of stabilization by such catalysis will be determined by this change in acidity (or basicity) compared to the basicity (or acidity) of the catalyst and by the stabilization of the transition state for the remainder of the reaction which is brought about by partial proton transfer.

In this discussion we have deliberately avoided discussion of the exact position of the proton in the transition state; this subject will be considered in a future communication. The possibility should be kept in mind that proton transfer proceeds through an intermediate water molecule.[31] In respect to the matters considered here it is only necessary to point out that Brønsted α or β values are measures of the stabilization of the *over-all* transition state by acids and bases of different strength; they are not necessarily exact indicators of the degree to which either proton transfer or the making and breaking of bonds to carbon has taken place in the transition state.

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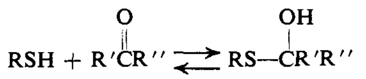
Thiol Addition to the Carbonyl Group. Equilibria and Kinetics[1]

Gustav E. Lienhard[2] and William P. Jencks

Contribution from the Graduate Department of Biochemistry,
Brandeis University, Waltham, Massachusetts 02154, and from the James Bryant
Conant Laboratory of the Department of Chemistry, Harvard University,
Cambridge, Massachusetts 02138. *Received May 4, 1966*

Abstract: Rate and equilibrium constants have been determined for the addition of a series of thiols to acetaldehyde and other carbonyl compounds to form the corresponding hemithioacetals and hemithioketals. The addition reactions occur by specific base catalyzed and general acid catalyzed pathways; no pH-independent reaction was detected. The solvent deuterium isotope effect on the rate of the hydronium ion catalyzed reaction, k_{H_2O}/k_{D_2O}, is 0.59; the isotope effect on the addition equilibrium, K_{H_2O}/K_{D_2O}, is 0.44. The Brønsted α value for general acid catalysis is large, on the order of 0.7. Evidence is presented that the unhydrated carbonyl compound is the reactive species. The acid-catalyzed reactions display a large sensitivity, but the base-catalyzed reactions almost no sensitivity to the basicity of the attacking species. It is suggested that the general acid catalyzed reaction involves proton donation to the carbonyl group and that the base-catalyzed reaction involves attack of the thiol anion on the carbonyl group. Possible roles of the acid catalyst in general acid catalysis are discussed.



$$\mathrm{RSH} + \mathrm{R'}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{R''} \rightleftharpoons \mathrm{RS{-}}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}\mathrm{R'R''} \tag{1}$$

In 1885 Baumann[3] reported the reaction of benzenethiol with pyruvic acid in benzene to form a crystalline addition compound, to which he ascribed the structure of a hemithioketal. Since that time a number of stable hemithioacetals and hemithioketals have been prepared by the reaction under mild conditions of thiols with aldehydes and ketones that contain electron-withdrawing groups (eq 1).[4] In the earlier work, the assignment of the hemithioacetal or hemithioketal structure to such compounds was generally based on their chemical composition and their ready dissociation under certain conditions into the component thiol and carbonyl compounds. More recently, this evidence for the α-hydroxy sulfide structure has been augmented: in the case of crystalline hemithioacetals prepared from phenylglyoxal by an examination of the infrared and nmr spectra of the compounds,[5] and in the case of the

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[1] Contribution No. 441 of the Graduate Department of Biochemistry, Brandeis University. Supported by grants from the National Science Foundation (GB-1648) and the National Institute of Child Health and Human Development of the National Institutes of Health (HD-01247).

[2] Part of this work was carried out by G. E. L. with support from a Public Health Service Fellowship from the National Institute of General Medical Sciences (1-F2-GM-18,818-01).

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vacuum-distillable hemithioacetals formed from formaldehyde and benzenethiol and benzyl mercaptan by the preparation of derivatives of the hemithioacetals.[6] In addition, compounds of the type $R_2C(SH)OH$ which are stable enough to be isolated by vacuum distillation have been made by reaction between hydrogen sulfide and a number of aldehydes and ketones with fluoro and chloro groups and have been thoroughly characterized.[7] Woodward, *et al.*, have prepared a stable internal hemithioacetal, the structure of which was proven by X-ray crystallography, as an intermediate in the synthesis of cephalosporins.[8]

Although the reaction of thiols with carbonyl compounds to form hemithioacetals and hemithioketals is thus clearly established, there has been no thorough study of the kinetics and equilibria of the reaction in aqueous solution with simple thiols and carbonyl compounds. A number of equilibrium measurements have shown that the tendency of thiols to add to the carbonyl group is considerably greater than that of hydroxyl compounds or most amines.[9,10] Addition reactions of thiols commonly proceed by reaction of the thiol anion, and Ratner and Clarke showed that the addition of N-acetylcysteine to formaldehyde is base catalyzed.[11] However, careful examination of Ratner and Clarke's data suggests that this reaction does not proceed exclusively by the base-catalyzed pathway at low pH, and preparative work has shown that thiol addition to the carbonyl group may occur also with acid catalysis.[12]

Experimental Section

Materials. The commercially available thiols were distilled under nitrogen before use. 2-Methoxyethanethiol, bp 109–110° (lit.[13] 112°), was prepared by the method of Chapman and Owen and also by that of Swallen and Boord.[14] Assay of these preparations by the method of Ellman[15] gave equivalent weights of 93 to 95 (mol wt 92). The aldehydes were distilled under nitrogen within a week of use and were stored under nitrogen in the refrigerator. Sodium pyruvate purchased from Nutritional Biochemicals Corp. was used without further purification. Commercial dichloroacetic acid and difluoroacetic acid were redistilled. Commercial cyanoacetic acid was twice recrystallized from benzene–acetone (4:6 by volume) and stored in a desiccator over silica gel.[16] Glass-distilled water containing 10^{-4} *M* disodium ethylenediaminetetraacetate (EDTA) was used throughout. The ionic strength was always maintained with potassium chloride. Solutions of the thiols and aldehydes were generally prepared by weight on the day on which they were used. Because of the volatility of ethanethiol its concentration in solution was measured just before use by the Ellman method.[15]

Equilibrium Constants. Equilibrium constants for the formation of the thiol addition compounds were determined by measuring the decreases in the carbonyl absorption in the region of 280 mμ in the presence of three or more concentrations of thiol at a constant pH, with a Zeiss PMQ II spectrophotometer equipped with a thermostated brass block. Each measurement was initiated by the addition of an aliquot from a temperature-equilibrated solution of the carbonyl compound to a temperature-equilibrated cuvette with a tight-fitting Teflon stopper that contained the thiol and buffer. The blank solution in the spectrophotometer was identical with the reaction solution, except that water was added in place of the aliquot of the solution of carbonyl compound. The change in absorbance with time was followed until the absorbance remained constant for at least 5 min. The apparent equilibrium constants for hemithioacetal or hemithioketal formation, K_{obsd} = [hemithioacetal or hemithioketal]/[hydrated + unhydrated carbonyl compound][thiol], were calculated from the absorbance changes and eq 2. In this equation, Δ is the difference between the equilibrium

$$K_{\mathrm{obsd}} = \frac{\Delta}{\epsilon_A + \epsilon_S - \epsilon_C} \Bigg/ \left(S_0 - \frac{\Delta}{\epsilon_A + \epsilon_S - \epsilon_C}\right)\left(A_0 - \frac{\Delta}{\epsilon_A + \epsilon_S - \epsilon_C}\right) \qquad (2)$$

values of the absorbance of the aldehyde alone and of the aldehyde plus thiol; ϵ_A, ϵ_S, and ϵ_C are the extinction coefficients in M^{-1} cm^{-1} of the unhydrated plus hydrated aldehyde, thiol, and hemithioacetal, respectively; A_0 and S_0 are the initial molar concentrations of the unhydrated plus hydrated aldehyde and the thiol, respectively. This equation is derived for our experimental conditions, in which the contents of the blank cuvette were identical with those of the reaction solution with the exception that the blank did not contain aldehyde. Except for methyl mercaptoacetate, ϵ_S was sufficiently small compared to ϵ_A to be negligible. Also, it was found that except for the reaction of acetaldehyde with methyl mercaptoacetate, constant values of K_{obsd} were obtained over a large range of thiol concentrations if ϵ_C was assumed to be negligible compared to ϵ_A. This is in agreement with the observation that simple monothioacetals do not absorb in the ultraviolet above 260 mμ.[17] In the case of methyl mercaptoacetate and acetaldehyde, successive approximations of ϵ_C were made until the data gave constant values of K_{obsd}. The values of 8.50, 0.75, and 1.35 M^{-1} cm^{-1} were found for ϵ_A, ϵ_S, and ϵ_C, respectively, at 280 mμ. In the study of general acid catalysis of hemithioacetal formation from acetaldehyde and 2-methoxyethanethiol, individual values of K_{obsd} were calculated for each buffer concentration from the initial concentrations of acetaldehyde and thiol and the equilibrium value of the absorbance at the end of the kinetic run.

A different method was used to determine the equilibrium constant for hemithioacetal formation from benzenethiol and isobutyraldehyde. It was found that this hemithioacetal has a $\lambda_{\max}$ at about 245 mμ (ε *ca.* 4900), whereas benzenethiol has $\lambda_{\max}$ at 236 mμ (ε 8100). This spectral shift is in agreement with the reports that in ethanol benzenethiol has $\lambda_{\max}$ 237 mμ (ε 7000)[18] and the monothioacetal, phenylmercaptomethyl methyl ether, has $\lambda_{\max}$ 247 mμ (ε 7950).[17] Consequently, the decreases in absorbance at 236 mμ of 10^{-4} *M* benzenethiol with varying concentrations of isobutyraldehyde were measured against blank solutions with the same concentrations of isobutyraldehyde and buffer as in the reaction solutions. In this case the careful use of tightly stoppered cuvettes was necessary because of the volatility of benzenethiol. The equilibrium constant K_{obsd} was obtained by use of eq 3 in which the symbols have the same meaning as in eq 2. This equation is a

$$\Delta = S_0(\epsilon_S - \epsilon_C) - \frac{1}{K_{\mathrm{obsd}}}\frac{\Delta}{A_0} \qquad (3)$$

simplified form because at 236 mμ ϵ_A is negligible with respect to ϵ_S and ϵ_C and because the concentration of isobutyraldehyde converted to the hemithioacetal is negligible in comparison to its total concentration. Plots of Δ against Δ/A_0 were linear over a large range of isobutyraldehyde concentrations. In 1 *N* hydrochloric acid and at pH 4.6, the value of $\epsilon_S - \epsilon_C$ is 5100 M^{-1} cm^{-1}.

For a number of calculations it was necessary to know the equilibrium constant for the hydration of acetaldehyde in 1 *N* KCl at 25°. This constant can be calculated from the equation, K_{hyd} = [hydrated carbonyl compound]/[unhydrated carbonyl compound] = $(\epsilon - \epsilon_A)/\epsilon_A$, in which ε is the extinction coefficient of

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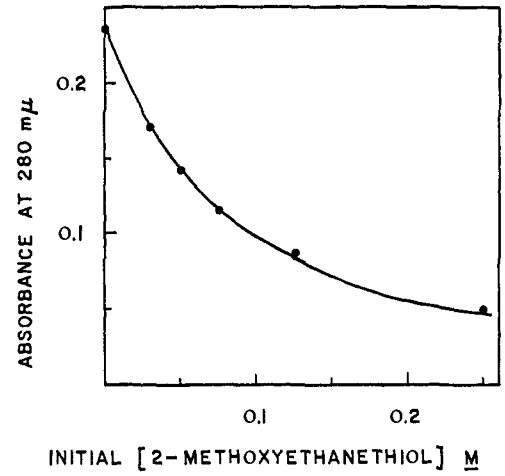

Figure 1. Hemithioacetal formation from acetaldehyde and 2-methoxyethanethiol. Equilibrium values of the absorbance at 280 mμ of solutions initially 0.03 M in acetaldehyde as a function of initial thiol concentration at 25°, ionic strength 1 M, 0.05 M acetate buffer, pH 4.6. The line was calculated from the average value of 17.4 M^{-1} for the equilibrium constant.

unhydrated acetaldehyde in water and ϵ_A is the extinction coefficient of the hydrated and unhydrated acetaldehyde at the same wavelength in 1 N KCl at 25°. The value of ϵ at 278 mμ was taken as 15.8 M^{-1} cm^{-1}, the average of values of 14.5 and 17.0 reported in the literature.[19] In order to determine ϵ_A, the absorbance at 278 mμ of a solution of acetaldehyde in 1 N potassium chloride and 0.05 M half-neutralized acetate buffer was measured at 25° in a tightly stoppered 1-cm cuvette against a buffer–potassium chloride blank. The concentration of acetaldehyde and its hydrate in this solution was accurately determined by assay with C. F. Boehringer and Soehne crystalline yeast alcohol dehydrogenase and nicotinamide–adenine dinucleotide.[20] The value of ϵ_A was found to be 8.55 M^{-1} cm^{-1}, and therefore K_{hyd} is 0.85 in 1 N potassium chloride at 25°. The same procedure was used for the determination of the values of K_{hyd} for acetaldehyde in the different concentrated buffers used to study general acid catalysis, except that the concentration of acetaldehyde in a stock solution was calculated from the absorbance at 278 mμ of an aliquot in 1 N potassium chloride at 25° and the known extinction coefficient. The value of K_{hyd} for acetaldehyde at 25° in D_2O with 1 N potassium chloride was measured by injecting with a micropipet in a cold room 0.010 ml of pure acetaldehyde into 3-ml solutions of 1 N KCl–0.003 N HCl–10^{-4} M EDTA in H_2O and D_2O that were in cuvettes with tightly fitting Teflon stoppers. The equilibrium values of the absorbance were measured at 25° against the appropriate blank. Five runs in H_2O gave an average absorbance of 0.485 ± 0.008; in D_2O, 0.451 ± 0.009. The value of K_{hyd} in deuterium oxide was calculated as described above and found to be 0.99. The deuterium isotope effect on the hydration equilibrium, $K_{hyd}(H_2O)/K_{hyd}(D_2O)$, is thus 0.86 in 1 N KCl at 25° which can be compared with the reported[19b] value of 0.84 in the absence of salts at 25°.

The extent of hydration of pivaldehyde in water was examined by the method of Bell and McDougall.[21] The spectral values found for pivaldehyde are λ_{max} 295 mμ (ϵ_{max} 15.4) in cyclohexane and λ_{max} 286 mμ (ϵ_{max} 15.1) in 0.01 N hydrochloric acid. Thus, K_{hyd} for pivaldehyde is less than 0.1.

Kinetic Measurements. In general the rates of hemithioacetal formation were followed by measuring the decrease in the carbonyl absorbance near 280 mμ with a sufficient excess of the thiol so that the reactions were pseudo first order. Reaction mixtures which contained all the components except the aldehyde were prepared in stoppered cuvettes (4 ml, 1 cm for pivaldehyde reactions, and 20 ml, 5 cm for acetaldehyde reactions) and were temperature equilibrated at 25°. The reactions were than initiated by the addition of an aliquot of a temperature-equilibrated aldehyde solution, which was rapidly mixed by inverting the stoppered cuvette several times, and were followed in a Zeiss PMQ II spectrophotometer with a thermostated cuvette compartment, usually against an appropriate blank cuvette. It was possible to obtain initial readings of the absorbance about 5 sec after the initiation of the reaction. The first-order rate constants were obtained from semilogarithmic plots of the difference between the absorbance at various times and the final equilibrium absorbance against time by use of the equation $k_{obsd} = 0.693/t_{1/2}$. In all cases the plots were linear for at least two half-times. The rate constants were generally obtained from duplicate rate determinations or from determinations at high and low buffer concentrations in buffers which do not affect the rate. In most instances final absorbances that were stable for at least five half-times were obtained, and these absorbances had the values expected on the basis of the equilibrium constants for the reactions. However, at pH 2 or below there was a relatively slow decrease in the absorbance beyond the expected equilibrium values for the reactions of pivaldehyde with mercaptoethanol and 3-methoxyethanethiol and of acetaldehyde with ethanethiol; oils subsequently separated from the reaction mixtures in the latter two cases. The oils may be the thioacetals, the formation of which is acid catalyzed.[3] These secondary reactions were sufficiently slow relative to hemimercaptal formation that linear, first-order plots were obtained by using the stable equilibrium absorbances expected from measurements at higher pH values.

The first-order rate constants were reproducible to within ±5% of the average value. In some experiments up to 10% of the thiol was used during the reaction; in these experiments the thiol concentrations at half-reaction were used in calculating the second-order rate constants.

Measurements of pH were carried out with a glass electrode and a Radiometer PHM-4b pH meter, which for measurements at low pH were standardized at pH 1.10 with 0.1 N HCl and at pH 2.10 with 0.01 N HCl–0.09 N KCl.[22] The apparent pK values (pK_a', Table II) of 2-methoxyethanethiol and ethanethiol at 25° and 1 M ionic strength were determined by spectrophotometric titration at 240 mμ with approximately 1.5×10^{-4} M thiol in dilute potassium carbonate buffers.[23] Those of 2-mercaptoethanol and methyl mercaptoacetate at 25° and 1 M ionic strength were determined by titration of 0.1 M solutions with standard sodium hydroxide. The concentrations of general acid in the reaction mixtures used to study general acid catalysis were corrected for dissociation of the acids by subtracting the hydrogen ion activities from the concentrations by weight of the general acids. These corrections were never more than 10% of the concentrations. The values of pK_a' for the general acids at 25° and 1 M ionic strength were calculated from the pH values of the reaction mixtures. The reaction mixtures for the experiments shown in Figure 4 were prepared so that the pH values were identical at the different concentrations of acid in each experiment; the points at zero buffer concentration were obtained in hydrochloric acid solutions at the same time that the rates with buffer were measured.

Product Analyses. By analogy with the known addition compounds of thiols with aldehydes and ketones (see introductory paragraphs), it was expected that the products of the reactions reported in this paper were the hemithioacetals and hemithioketals. The evidence that this is the case is that the equilibrium constants calculated from absorbance changes are constant over large concentration ranges only if it is assumed that the products of the reactions are the adducts of one molecule of thiol and one of carbonyl compound (Table I).

Results

Equilibrium Constants. The equilibrium constants for hemithioacetal and hemithioketal formation were determined by measuring the decreases in the carbonyl group absorbance of a constant concentration of aldehyde or ketone in the presence of increasing concentrations of thiol. Figure 1 shows such measurements at equilibrium for the reaction of acetaldehyde with 2-methoxyethanethiol at pH 4.6. The average value of the equilibrium constant, K_{obsd} = [hemithioacetal]/[unhydrated + hydrated carbonyl compound][thiol],

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Table I. Equilibrium Constants for Hemithioacetal and Hemithioketal Formation at 25° and 1 *M* Ionic Strength

Carbonyl compd (initial concn, *M*)	Thiol (initial concn, *M*)	Wave-length, mμ	pH	No. of measure-ments	K_{obsd},[a] M^{-1}	K_{hyd}[b]	K_{hemi},[c] M^{-1}
CH_3CHO (0.030)	$CH_3OCH_2CH_2SH$ (0.030–0.25)	280	4.6[d]	5	17.4 ± 1	0.85[e]	32
CH_3CHO (0.030)	$CH_3OCH_2CH_2SH$ (0.02–0.15)	278	4.6,[d] in D_2O	5	36.4 ± 4, in D_2O	0.99,[e] in D_2O	72
CH_3CHO (0.032)	CH_3OOCCH_2SH (0.018–0.27)	280	4.6[d]	6	32.7 ± 3	0.85[e]	60
CH_3CHO (0.034)	C_2H_5SH (0.014–0.058)	280	4.6[d]	3	19.6 ± 3	0.85[e]	36
$(CH_3)_2CHCHO$	$CH_3OCH_2CH_2SH$						
(0.025)	(0.083–0.23)	285	2.0[f,h]	5	12.8 ± 1	0.24[g]	16
(0.025)	(0.02–0.33)	285	4.3[d]	6	11.8 ± 1	0.24[g]	15
$(CH_3)_2CHCHO$	C_6H_5SH[i]						
(0.02–0.20)	(10^{-4})	236	1 *N* HCl[j]	7	14.8	0.24[g]	18
(0.01–0.38)	(10^{-4})	236	4.6[d]	10	14.8	0.24[g]	18
$(CH_3)_3CCHO$ (0.025)	$CH_3OCH_2CH_2SH$ (0.06–0.25)	286	4.6[d]	3	4.8 ± 0.7	<0.1[e]	4.8
$(CH_3)_3CCHO$	$HOCH_2CH_2SH$						
(0.025)	(0.05–0.97)	286	0.4 *N* HCl[k]	4	4.2 ± 0.5	<0.1[e]	4.2
(0.025)	(0.026–2.0)	286	4.6[d]	8	3.8 ± 0.5	<0.1[e]	3.8
CH_3COCOO^- (0.02)	CH_3OOCCH_2SH (0.05–0.28)	320	5.2[d]	5	5.2 ± 0.2	Not hydrated[l]	5.2
CH_3COCH_3 (0.05)	$CH_3OCH_2CH_2SH$ (0.52)	285	1.5[f]	1	<0.2[m]	Not hydrated[n]	<0.2

[a] K_{obsd} = [hemithioacetal or hemithioketal]/[thiol][hydrated and unhydrated carbonyl compound]. This value is the average of the values calculated from each measurement ± the difference between the average and the extremes of the individual values. [b] K_{hyd} = [hydrated carbonyl compound]/[unhydrated carbonyl compound]. [c] K_{hemi} = [hemithioacetal or hemithioketal]/[thiol][unhydrated carbonyl compound] = $K_{obsd}(1 + K_{hyd})$. [d] With 0.1 *M* or less acetate buffer. [e] See Experimental Section. [f] With HCl buffer. [g] From the data in ref 19b, isobutyraldehyde in 1 *N* NaCl at 25°. [h] At this pH the establishment of equilibrium requires about 5 min and the final absorbance is stable for at least 10 min. [i] 0.6 *M* ethanol was present in the benzenethiol reaction mixtures. Control experiments showed that less than 4% of the isobutyraldehyde is present as the hemiacetal in 0.6 *M* ethanol. [j] The absorbance changes are complete within 30 sec and the equilibrium absorbance values are constant for at least 5 min. [k] At this pH the equilibrium values of the absorbances for hemithioacetal formation are reached within less than 10 sec of mixing the reactants. Then follows a further slow decrease in absorbance over several minutes and then at the lower concentrations of mercaptoethanol the separation of a water-insoluble liquid which may be one or more of the possible acetal compounds. The equilibrium constants were calculated from the absorbances extrapolated to the time of mixing. [l] M. Becker and H. Strehlow, *Z. Elektrochem.*, **64**, 813 (1960). [m] An upper limit. No change in absorbance from that of acetone without thiol occurred in 1.5 hr. [n] See ref 21.

derived from the data in Figure 1 (see Experimental Section), is 17.4 M^{-1}. The coincidence of the points in Figure 1 and the solid line which has been calculated from this value for the equilibrium constant demonstrates the validity of the equilibrium expression over the entire range of 2-methoxyethanethiol concentration. In a similar manner the other values of K_{obsd} given in Table I were obtained, with the exception that with benzenethiol the reaction was followed by measuring the absorbance changes of the thiol and the adduct. Each value of K_{obsd} was found to be constant over a wide range of reactant concentrations. Since some of the aldehydes used in this study are partially hydrated in aqueous solution, it was necessary to multiply K_{obsd} by $(1 + K_{hyd})$ in order to obtain K_{hemi}, the equilibrium constant for formation of the thiol adducts from the thiols and unhydrated carbonyl compounds. The values of K_{hemi} are given in the last column of Table I.

Kinetics of Hemithioacetal Formation. The pH dependences of the observed first-order rate constants for the reaction of acetaldehyde with excess methyl mercaptoacetate, 2-methoxyethanethiol, and ethanethiol are shown in Figure 2. These rate constants were obtained by following the decrease in the ultraviolet carbonyl absorption of acetaldehyde, as described in the Experimental Section. The concentrations of the thiols used in these experiments were such that with 2-methoxyethanethiol and ethanethiol approximately 50% of the acetaldehyde and its hydrate was converted to the hemithioacetal at equilibrium and with methyl mercaptoacetate 63% was converted. The reactions at the basic extreme were carried out in formate and acetate buffers, but correction for buffer catalysis was unnecessary because hemimercaptal formation is not catalyzed by these buffers (see Table IV for one example). The pH–rate profiles show that the reactions are both acid and base catalyzed. In each case the two observed rate constants at the acid extreme are directly proportional to the hydrogen ion activity and the two rate constants at the basic extreme are directly proportional to the reciprocal of the hydrogen ion activity. Rate constants could not be obtained over wider pH ranges, because beyond the extremes shown in Figure 2 the reactions are too fast for measurement by our method.

The complete rate law for hemithioacetal formation was derived from the pH–rate profiles as follows. At any constant pH value the kinetic scheme for the reaction is expressed by eq 4. The assumption that the

$$\mathrm{HO{-}\overset{|}{\underset{|}{C}}{-}OH} \underset{k_{hyd}}{\overset{k_{dehyd}}{\rightleftharpoons}} \mathrm{{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}} \underset{k_{-2}}{\overset{k_2[\mathrm{RSH}]}{\rightleftharpoons}} \mathrm{HO{-}\overset{|}{\underset{|}{C}}{-}SR} \qquad (4)$$

unhydrated carbonyl compound is the reactive species in hemithioacetal formation will be justified subsequently. If hemithioacetal formation is the rate-

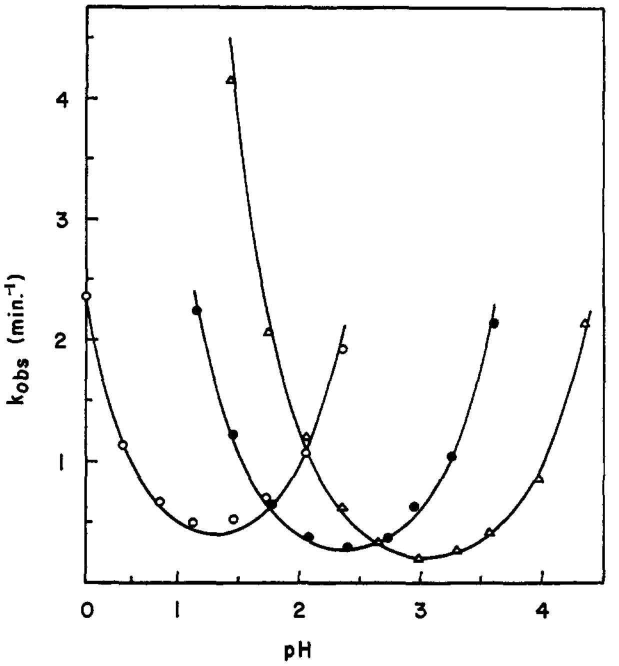

Figure 2. The effect of pH on the rate of hemithioacetal formation from acetaldehyde and thiols at 25° and 1 *M* ionic strength: methyl mercaptoacetate, ○; 2-methoxyethanethiol, ●; ethanethiol, △. The initial total concentration of acetaldehyde was about 0.01 *M* and that of the thiols was 0.060 *M* (ethanethiol 0.063 *M*). The buffers used were: below pH 2.9, hydrochloric acid; pH 2.9–4.0, 0.1–1 *M* potassium formate; pH 4.34, 0.325 and 0.65 *M* potassium acetate.

determining step in this scheme ($k_{hyd} > k_2$[RSH]), then the relationship between the observed first-order rate constant (k_{obsd}) and k_2 is given by eq 5, in which the

$$k_2 = k_{obsd}(1 + K_{hyd})\Big/\left([\mathrm{RSH}] + \frac{1}{K_{obsd}}\right) = k_{obsd}(K_{hemi} + K_{hemi}K_{hyd})/(K_{hemi}[\mathrm{RSH}] + 1 + K_{hyd}) \quad (5)$$

K's are the previously defined equilibrium constants, the values of which are known (Table I). The fact that, over the range of pH values shown in Figure 1 decreases in the carbonyl absorbance which obey the first-order rate equation are observed, is evidence that hemithioacetal formation is the rate-limiting reaction. If dehydration occurred slowly relative to the establishment of the acetaldehyde–hemimercaptal equilibrium (k_2[RSH] > k_{hyd}), a rapid initial decrease in absorbance followed by an increase in absorbance with time caused by dehydration of the hydrate would have been observed, since the reactions were initiated with an aqueous solution of acetaldehyde in equilibrium with its hydrate. Values of k_{hyd} under the conditions of the experiments shown in Figure 1 were calculated from the reported catalytic constants at 25° for the hydration of acetaldehyde[24] and, with one exception, were found to be at least five times, and generally more than ten times, larger than the corresponding k_2[RSH], calculated from k_{obsd} and eq 5. The one exception is the reaction of acetaldehyde with ethanethiol at pH 4.34 in 0.325 and 0.65 *M* acetate buffers, where the values of $k_{hyd}/k_2 \cdot$[RSH] are approximately 2.3 and 3.9, respectively. However, the fact that this twofold variation in buffer concentration caused less than a 10% change in k_{obsd} even though the dehydration of acetaldehyde is strongly catalyzed by acetate buffers indicates that even in this case hemithioacetal formation is almost completely rate determining.

The values of k_{H^+}, the third-order rate constant for hydronium ion catalysis of hemithioacetal formation, and k_{RS^-}, the rate constant for the reaction of thiol anion with the aldehyde, were calculated from the values of k_2 at the acidic and basic extremes of the pH–rate profile, respectively (Table II). If it is assumed that these two terms are the only significant ones in the rate law for hemimercaptal formation, the rate law can be expressed as

$$v = k_{H^+}a_{H^+}[\mathrm{RSH}][>\mathrm{C{=}O}] + k_{RS^-}[\mathrm{RS^-}][>\mathrm{C{=}O}] \quad (6)$$

and

$$k_{obsd} = \left(k_{H^+}a_{H^+} + k_{RS^-} \times \frac{K_{RSH}}{K_{RSH} + a_{H^+}}\right)\left(\frac{K_{hemi}[\mathrm{RSH}] + 1 + K_{hyd}}{K_{hemi} + K_{hemi}K_{hyd}}\right) \quad (7)$$

The solid lines in Figure 2 were calculated from eq 7 and show good agreement with the measured values of k_{obsd} in the intermediate pH range, with the exception that the calculated values are about 15% lower than the observed values for the methyl mercaptoacetate reaction. This agreement shows that the above rate law is sufficient to describe the pH–rate profiles and that the uncatalyzed reaction of the uncharged thiol with acetaldehyde is not a significant pathway for hemithioacetal formation.

Table II. Rate Constants for Hemithioacetal Formation at 25° and 1 *M* Ionic Strength

Aldehyde	Thiol	pK'_{RSH}[a]	k_{H^+},[b] M^{-2} min^{-1}	k_{RS^-},[c] M^{-1} min^{-1}
CH_3CHO	CH_3OOCCH_2SH	7.83	84	1.41×10^7
CH_3CHO	$CH_3OCH_2CH_2SH$	9.50	530	2.82×10^7
CH_3CHO	C_2H_5SH	10.25	1960	2.83×10^7
$(CH_3)_3CCHO$	$HOCH_2CH_2SH$	9.51	200[d]	5.8×10^6[d]
			228[e]	6.4×10^6[e]
	$CH_3OCH_2CH_2SH$	9.50	180[d]	5.6×10^6[d]

[a] At 25° and 1 *M* ionic strength. [b] $k_{H^+} = k_2/a_{H^+}$, where k_2 is defined by eq 5 and k_{H^+} is an average calculated from k_{obsd} at the two lowest pH values in Figure 2. [c] $k_{RS^-} = k_2((K'_{RSH} + a_{H^+})K'_{RSH}) \approx k_2(a_{H^+}/K'_{RSH})$ where k_2 is defined by eq 5 and k_{RS^-} is an average calculated from k_{obsd} at the two highest pH values in Figure 2. [d] From k_{obsd} measured by pivaldehyde disappearance. [e] From k_{obsd} measured by pivaldehyde appearance.

The data in Table III show the dependence of k_{obsd} for hemithioacetal formation from acetaldehyde and 2-methoxyethanethiol upon the thiol concentration at pH 2.36, where the contributions from the acid- and base-catalyzed pathways are equal. The fact that k_2 calculated by eq 5 from this data is constant shows that at any pH the forward rate of hemithioacetal formation is first order with respect to the thiol and is thus further evidence in support of the above rate law.

Values of k_{H^-} and k_{RS^-} for the reaction of pivaldehyde with 2-mercaptoethanol and 2-methoxyethanethiol were obtained by determining k_{obsd} with 0.24 *M* thiol

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[24] R. P. Bell, M. H. Rand, and K. M. A. Wynne-Jones, *Trans. Faraday Soc.*, **52**, 1093 (1956).

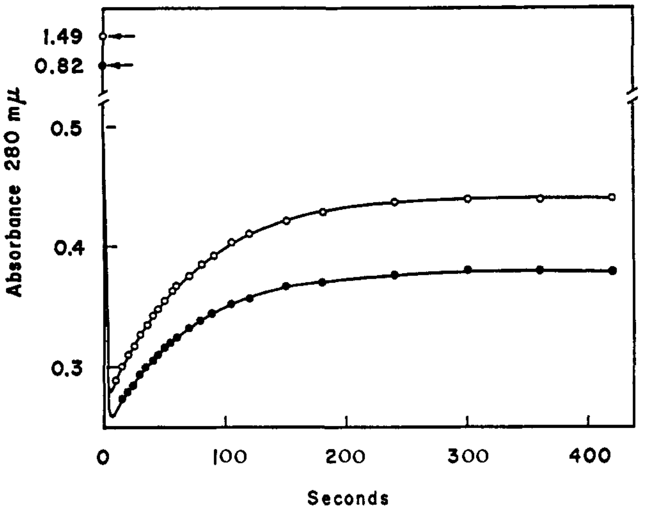

Figure 3. The reaction of acetaldehyde with 0.1 M (●) and 0.2 M (○) mercaptoethanol in 0.02 M acetate buffer, pH 5.08, ionic strength 1.0 M, at 25°. The arrows indicate the absorbance of the same amount of acetaldehyde and its hydrate in the absence of thiol.

and 0.025 M pivaldehyde at 286 mμ over the pH range from 1.45 to 3.62 (Table II). The data were treated as described for the acetaldehyde reactions, except that K_{hyd} is negligible for pivaldehyde. The values of k_{obsd} for these reactions at intermediate pH values agree with those calculated from $k_{\mathrm{H^+}}$ and $k_{\mathrm{RS^-}}$. The rates of the reverse reaction were measured at 286 mμ over the pH range from 1.18 to 3.84 by following the appearance of pivaldehyde after the addition of 0.20 ml of a solution containing 0.25 M 2-mercaptoethanol pivaldehyde hemithioacetal, 0.50 M 2-mercaptoethanol, and 0.125 M pivaldehyde in 1.7 M ethanol and 0.05 M acetate buffer (50% acetate) to 2.8 ml of reaction buffer. From the observed first-order rate constants at the pH extremes which were obtained in these experiments, the values of $k_{\mathrm{H^+}}$ and $k_{\mathrm{RS^-}}$ were calculated in the same way as described for the acetaldehyde reactions. These values of $k_{\mathrm{H^+}}$ and $k_{\mathrm{RS^-}}$ are in tolerable agreement with those derived from the measurements of pivaldehyde disappearance (Table II).

Table III. Dependence on Thiol Concentration of the Rates of Hemithioacetal Formation from Acetaldehyde and 2-Methoxyethanethiol at pH 2.36[a]

CH_3OCH_2-CH_2SH, M[b]	Acetaldehyde and its hydrate, M[b]	k_{obsd}, min^{-1}	k_2,[c] M^{-1} min^{-1}
0.06	0.01	0.31	4.9
0.12	0.01	0.45	4.8
0.25	0.03	0.81[d]	5.1

[a] Measured at 280 mμ in HCl buffer at 25° and 1 M ionic strength with 5-cm cuvettes. [b] Initial concentrations. [c] Calculated from k_{obsd} by eq 5. [d] Measured with the reaction mixture in a 1-cm cuvette.

From a comparison of the rate constants for acetaldehyde dehydration[24] and the values of $k_{\mathrm{RS^-}}$, it is apparent that, at pH values more alkaline than those in Figure 1, the dehydration of acetaldehyde should become the rate-determining step in hemithioacetal formation from acetaldehyde hydrate (k_2[RSH] > k_{hyd}). This prediction was verified by the observation that upon the addition of a small aliquot of a solution of acetaldehyde equilibrated with its hydrate in 1 N KCl at 25° to a solution of 2-mercaptoethanol in 1.0 N KCl–0.02 M acetate buffer, pH 5.08, at 25° there is an instantaneous drop in the absorbance at 280 mμ (complete within 5 sec of mixing) to a value much less than that expected for the acetaldehyde alone and that this drop is followed by a slower increase in the absorbance which finally reaches a stable equilibrium value (Figure 3). The initial drop in absorbance is explained by the establishment of the equilibrium between acetaldehyde and its hemithioacetal at a rate which is too fast to measure at this pH; the subsequent increase in absorbance is caused by the slower dehydration of the hydrate, which leads to the establishment of equilibrium among all reacting species. Under these conditions, with excess mercaptoethanol, the absorbance changes obey the first-order rate equation and the relationship between k_{obsd}, k_{hyd}, and k_{dehyd} derived from the kinetic scheme (eq 4) is

$$k_{\mathrm{obsd}} = k_{\mathrm{dehyd}} + k_{\mathrm{hyd}}/(1 + K_{\mathrm{hemi}}[\mathrm{RSH}]) \quad (8)$$

A value of 18.5 M^{-1} for K_{hemi} was obtained from the equilibrium absorbances. A plot of k_{obsd} against $1/(1 + K_{\mathrm{hemi}}[\mathrm{RSH}])$ gave 0.75 min^{-1} for k_{dehyd} and 0.57 min^{-1} for k_{hyd}, values which are in good agreement with the values of 0.71 and 0.61 min^{-1} calculated from k_{obsd} for acetaldehyde hydration in the absence of thiol and K_{hyd}. These experiments prove directly that acetaldehyde rather than its hydrate is the reactive species in base-catalyzed hemithioacetal formation. Dehydration is also the rate-determining step in the addition of thiols to formaldehyde[10] and to methylglyoxal[25] hydrates.

General Acid Catalysis of Hemithioacetal Formation. In Figure 4, the dependence of the apparent second-order rate constants (k_2) for hemithioacetal formation from 2-methoxyethanethiol and acetaldehyde upon the concentration of general acids present in the reaction mixtures is shown. The values of k_2 were calculated from the observed first-order rate constants (k_{obsd}) in the buffers by use of eq 5. Since the values for K_{hyd} and K_{obsd} were changed somewhat by the buffers, which were present in concentrations as high as 2.5 M, the values of K_{obsd} and K_{hyd} were determined for each buffer concentration (see Experimental Section), and these individual values were used in calculating the factor $(1 + K_{\mathrm{hyd}})/([\mathrm{RSH}] + 1/K_{\mathrm{obsd}})$. The difference between k_2 calculated with the individual values of this factor and k_2 calculated with the equilibrium constants in Table I (K_{hyd} and K_{obsd} in 1 N potassium chloride and dilute buffer) was never greater than 10% of k_2. The findings that the rates of hemithioacetal formation at constant pH increase proportionally with the increase in buffer concentration and that the slopes of the plots of k_2 against acid concentration are the same at different pH values indicate that the reaction is catalyzed by the acidic species of the buffer.

The third-order catalytic constants taken from the slopes of the plots together with the apparent pK values of the acids at 25° and 1 M ionic strength are: dichloroacetic acid, 28 M^{-2} min^{-1}, 1.3; difluoroacetic acid,

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(25) E. E. Cliffe and S. G. Waley, *Biochem. J.*, 79, 475 (1961).

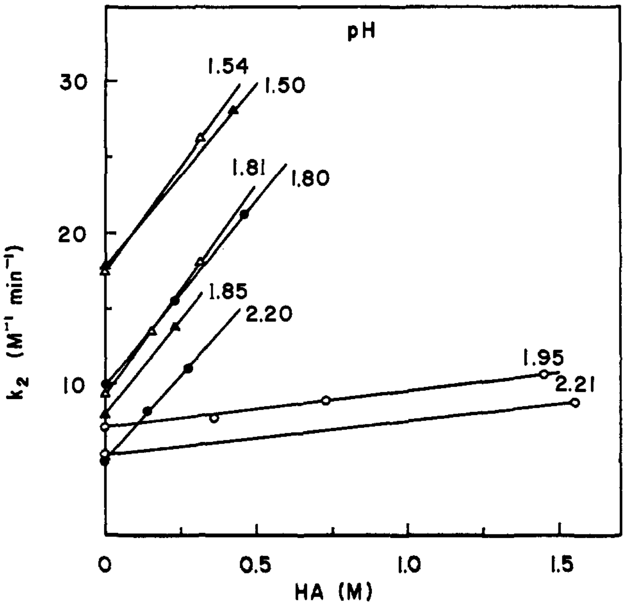


Figure 4. Dependence of the apparent second-order rate constants for hemithioacetal formation from 2-methoxyethanethiol and acetaldehyde upon general acid concentration at 25° and 1 M ionic strength. The buffers, with the approximate per cent acid at the pH values, were: ○, potassium cyanoacetate (61%, 2.21 and 72%, 1.95); ●, potassium dihydrogen phosphate (28%, 2.20 and 48%, 1.80); △, potassium dichloroacetate (25%, 1.81 and 37%, 1.54); ▲, potassium difluoroacetate (18%, 1.85 and 32%, 1.50). The values of k_2 were calculated from k_{obsd} by use of eq 5. The initial concentrations were 0.060 M 2-methoxyethanethiol and 0.010 M total acetaldehyde.

Table IV. The Effect of Ionic Strength, Organic Solvents, and Carboxylate Buffers on the Rates of Hemithioacetal Formation from Acetaldehyde and 2-Methoxyethanethiol at 25°

Solvent	pH	k_{obsd},[a] min^{-1}	K_{obsd},[b] M^{-1}	K_{hyd},[b]	f,[c] M^{-1}	$k_2 = k_{obsd}f$, M^{-1} min^{-1}
0.022 N HCl	1.75	0.42	19.1	1.00	18.3	7.7
1 N KCl, 0.02 N HCl	1.75	0.66	17.2	0.85	16.1	10.6
2 N KCl, 0.015 N HCl	1.75	0.76	18.1	0.75	15.6	11.8
1 N KCl, 2 N acetic acid, 0.012 N HCl	1.75	0.58	17.7	0.68	14.9	8.7
0.045 N HCl	1.40	0.81	18.1	1.00	17.9	14.5
1 N KCl, 0.040 N HCl	1.40	1.26	18.1	0.85	16.5	20.8
1 N KCl, 2 N acetonitrile, 0.042 N HCl	1.40	1.43	19.5	0.62	14.7	21
0.1 N potassium formate buffer, 0.98 N KCl	2.98[d]	0.64	17.4[f]	0.85[f]	16	10.2
1 N potassium formate buffer, 0.8 N KCl	2.94[d]	0.61	17.4[f]	0.85[f]	16	9.8
0.2 N potassium formate buffer, 0.9 N KCl	3.59[e]	2.10	17.4[f]	0.85[f]	16	33.6
1 M potassium formate buffer, 0.5 N KCl	3.63[e]	2.13	17.4[f]	0.85[f]	16	34.1

[a] Measured at 280 mμ with initial concentrations of 0.060 M 2-methoxyethanethiol and 0.01 M acetaldehyde and its hydrate in 5-cm cells. [b] For the solvents used. [c] $f = (1 + K_{hyd})/([RSH] + 1/K_{obsd})$. [d] About 80% formic acid. [e] About 50% formic acid. [f] These values were not measured for the solvent used; they are the ones obtained in dilute buffer with 1 N KCl at 25°.

25 M^{-2} min^{-1}, 1.15; phosphoric acid, 23 M^{-2} min^{-1}, 1.7; cyanoacetic acid, 2.4 M^{-2} min^{-1}, 2.4.

Because high concentrations of buffer were needed to demonstrate clearly the rate enhancements (Figure 4), it was important to make certain that the rate increases were not due to solvent effects. Consequently the effects of organic solvents and variations in ionic strength were determined in the pH range where the catalysis is observed. It was found that the apparent second-order rate constant for hemimercaptal formation in 1 N KCl at constant pH decreases about 20% with 2 N acetic acid (pK 4.7) and remains the same with 2 N acetonitrile and also that a change in the ionic strength from 1 to 2 M results in a rate increase of about 10% (Table IV). These variations are small compared to the increases in rate of 60 to 120% observed with the 1 M buffers of phosphoric, difluoroacetic, and dichloroacetic acids (Figure 4). Thus, these acids are acting as general acid catalysts, and their catalytic rate constants are probably accurate to within ±20%. Since 2 M acetic acid slows the reaction, the fact that 2 M buffers of cyanoacetic acid increase the rate by about 50% is evidence for its action as a general acid catalyst as well. However, its catalytic constant can only be considered a crude estimate, which the inhibition by acetic acid suggests may be as much as 100% too low.

The Brønsted plot of the logarithms of the third-order catalytic constants against the pK_a values of the acids shows at its center a cluster of the points for phosphoric, dichloroacetic, and difluoroacetic acids and at its extremes the points for cyanoacetic acid and the hydronium ion. The points do not fall on a straight line so that a unique value of the slope, α, is not determined, but the results do indicate that the value of α is large. A line drawn through the points for the carboxylic acids has a slope of 1.0, which is reduced to 0.7 if it is assumed that the rate constant for cyanoacetic acid is low by a factor of 2 because of a solvent effect; a line through the points for the hydronium ion and the strong carboxylic acids has a slope of 0.4. The absence of detectable catalysis by formic and acetic acids also indicates that the value of α is large.

At higher pH values, with weaker general acids (0.8 N formic acid and pH 2.94, Table IV), no general acid catalysis is observed. It is obscured by the base-catalyzed reaction pathway, which at higher pH values occurs at a rate much greater than the acid-catalyzed pathways. The absence of a rate enhancement at pH 3.6 in 1 M formate buffer with 0.5 N potassium formate (Table IV) shows that there is no significant general base catalysis of hemithioacetal formation by formate ion.

Kinetic Deuterium Isotope Effect. The rate of hydronium ion catalyzed hemithioacetal formation from 2-methoxyethanethiol and acetaldehyde in water was found to be 0.59 of the rate in deuterium oxide solution (Table V).

Discussion

Equilibria of Thiol Addition. The equilibrium constant for the addition of a molecule of thiol to acetone is at least 100-fold smaller than for addition to acetal-

Table V. Kinetic Deuterium Isotope Effect in the Hydronium Ion Catalyzed Reaction of 2-Methoxyethanethiol and Acetaldehyde at 25° and 1 M Ionic Strength

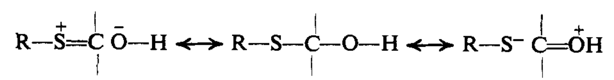
Solvent	k_{obsd},[a] min^{-1}	K_{hyd},[b]	K_{hemi},[c] M^{-1}	k_2,[d] M^{-1} min^{-1}	k'_{H^+},[e] M^{-2} min^{-1}
H_2O, 0.02 N HCl	1.65	0.85	32	10.3	515
H_2O, 0.03 N HCl	2.38	0.85	32	14.8	493
D_2O,[f] 0.02 N DCl	2.21	0.99	72	16.6	830
D_2O,[f] 0.03 N DCl	3.50	0.99	72	26.2	873

[a] Determined at 280 mμ with initial concentrations of 0.030 M acetaldehyde and its hydrate and 0.25 M 2-methoxyethanethiol in 1-cm cuvettes. The values are averages of duplicate determinations. [b] See Experimental Section. [c] From Table I. [d] Calculated from K_{hyd} and K_{hemi} with eq 5. [e] $k'_{H^+} = k_2/[H_3O^+]$. [f] Greater than 98% D_2O.

dehyde, which is in turn some 20-fold smaller than for addition to formaldehyde hydrate.[10] This order is similar to that for hydration equilibria[21] and presumably reflects in large part the hyperconjugative and steric effects of methyl substituents. The order of decreasing equilibrium constants in the series $CH_3CHO > (CH_3)_2CHCHO > (CH_3)_3CCHO$ also reflects steric effects.

There is only a twofold variation in the equilibrium constants for hemithioacetal formation from acetaldehyde and three thiols which vary in pK over a range of 10^2. This finding shows that the equilibrium, $RS^- + {>}C{=}O^+H \rightleftharpoons RS{>}COH$ is altered by the variations in the structure of R ($-CH_2CH_3$, $-CH_2OCH_3$, $-CH_2COOCH_3$) almost quantitatively to the same extent as the analogous equilibrium, $RS^- + H_3O^+ \rightleftharpoons RSH + H_2O$. Thus, the inductive effects of the substituents in the thiols have nearly the same effect upon the strength of the S–C bond which is formed in the hemithioacetals as upon the S–H bond in the thiols.

The much larger tendency of thiols than of water to add to the carbonyl group[9] is again evident in this series. This high affinity of thiols for the carbonyl group is not predicted from the usual tables of average bond energies.[26] For example, hemithioacetal formation from acetaldehyde and thiols should be unfavorable by 11 kcal/mole, according to the average bond energies.[26] A possible explanation for this discrepancy is that the hemithioacetal is stabilized by double bond–no bond resonance of the type



$$R-\overset{+}{S}=\underset{|}{\overset{|}{C}}\ \bar{O}-H \longleftrightarrow R-S-\underset{|}{\overset{|}{C}}-O-H \longleftrightarrow R-S^-\ \underset{|}{\overset{|}{C}}=\overset{+}{O}H$$

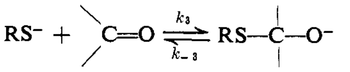
I II

Hine has made a convincing case for the importance of such resonance in the stabilization of compounds with two or more fluorine or oxygen atoms attached to the same carbon atom.[27]

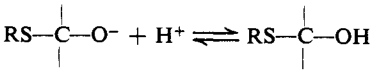
In the formation of a hemithioacetal the S–H bond of the thiol disappears and an O–H bond is formed. The observation that the equilibrium constant for this reaction is 2.27 times larger in deuterium oxide than in water is explained, in part, by the difference in the stretching frequencies of the S–H and O–H bonds. The S–H stretching frequencies of thiols generally lie between 2550 and 2600 cm^{-1}, regardless of structure or the degree of hydrogen bonding.[28] The difference between these values and that of approximately 3400 cm^{-1} for the O–H bond gives calculated values of K_{D_2O}/K_{H_2O} in the range 1.4–1.7 according to the treatment of Bunton and Shiner and depending on the assumptions which are made regarding the stretching frequencies within hydrogen bonds to the solvent.[29] This is smaller than the observed isotope effect, which suggests that the difference between the bending frequency of O–H (about 1420 cm^{-1} for alcohols[28]) and that of S–H (the in-plane deformation frequency of S–H has been observed at 832 cm^{-1} by Raman spectroscopy[30]) also contributes to the isotope effect. A deuterium isotope effect of about 2 in the hemithioacetal equilibrium is also expected on the basis of measurements made by Hobden, *et al.*, of the equilibrium constants for isotopic hydrogen exchange in the systems ethanethiol–water and 1-pentanol–water.[31] Their data show that the equilibrium constant for the distribution of deuterium between liquid pentanol and liquid ethanethiol at 25°, $K = [C_5H_9OD][C_2H_5SH]/[C_5H_9OH][C_2H_5SD]$, is 2.5.

Base-Catalyzed Hemithioacetal Formation. The results of the kinetic study of the base-catalyzed formation of hemithioacetals show that the unhydrated carbonyl compound is the reactive species. A mechanism consistent with the kinetic data is one in which the rate-determining step is the attack of the thiol anion upon the carbonyl group to form the hemithioacetal anion, a step which is preceded and followed by faster proton-transfer reactions (eq 9–12). The

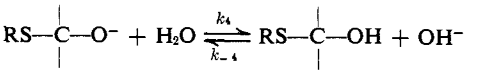
$$RSH \rightleftharpoons RS^- + H^+ \tag{9}$$



$$RS^- + {>}C{=}O \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} RS-\underset{|}{\overset{|}{C}}-O^- \tag{10}$$



$$RS-\underset{|}{\overset{|}{C}}-O^- + H^+ \rightleftharpoons RS-\underset{|}{\overset{|}{C}}-OH \tag{11}$$



$$RS-\underset{|}{\overset{|}{C}}-O^- + H_2O \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} RS-\underset{|}{\overset{|}{C}}-OH + OH^- \tag{12}$$

rate constant for reaction 9 is 32 sec^{-1} for mercaptoethanol,[32] which indicates that reaction 9 is not rate-determining under the conditions of our measurements. The ratio k_{-3}/k_4 is equal to $k_3K_A/K_{hemi}k_{-4}K_w$, in which K_A is the acidic dissociation constant of the thiol. The rate of reaction 12 is presumably diffusion-controlled in the reverse direction[33] so that $k_{-4} = \sim 10^{10}\ M^{-1}$ sec^{-1}. Substitution indicates that reaction 12 proceeds at an adequate rate with weakly acidic thiols, but becomes significantly slow compared to the back reaction of eq 10 as the thiol becomes more acidic; for methyl mercaptoacetate $k_{-3}/k_4 = \sim 0.6$. The rate of reaction 11 is probably adequate to give rapid protonation of the intermediate under the condi-

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[26] J. S. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 32.

[27] J. Hine, *J. Am. Chem. Soc.*, **85**, 3239 (1963).

[28] L. J. Bellamy in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, p 47; J. T. Edsall, *Biochemistry*, **4**, 28 (1965); R. N. Jones and C. Sandorfy in "Technique of Organic Chemistry," Vol. 9, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp 432, 546.

[29] C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 42, 3207, 3214 (1961).

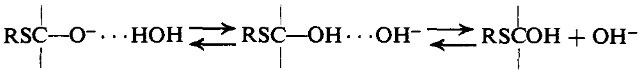
[30] N. Sheppard, *J. Chem. Phys.*, **17**, 79 (1949).

[31] F. W. Hobden, E. F. Johnston, L. H. P. Weldon, and C. L. Wilson, *J. Chem. Soc.*, 61 (1939).

[32] M. M. Kreevoy, D. S. Sappenfield, and W. Schwabacher, *J. Phys. Chem.*, **69**, 2287 (1965).

[33] M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

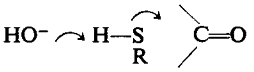
tions of our experiments, but it would be expected that at higher pH values and with acidic thiols the protonation step would become kinetically significant. It is probable that the carbonyl group is initially hydrogen bonded to water so that the proton-transfer process can occur as shown in eq 13; in this case the diffusion-



$$RSC{-}O^{-}\cdots HOH \rightleftharpoons RSC{-}OH\cdots OH^{-} \rightleftharpoons RSCOH + OH^{-} \qquad (13)$$

controlled separation of $RSCOH\cdots OH^-$ is likely to become kinetically significant with more acidic thiols. The rate of the proton-transfer step of the thiol (eq 9)[32,33] is also not adequate to maintain an equilibrium concentration of thiol anion at more alkaline pH values, so that the reaction of eq 9 may also become rate limiting under alkaline conditions. The similarity of the rate constants for the reactions of thiol anions which vary 250-fold in basicity (Table II) is evidence that diffusion-controlled steps do not become significant in these reactions under the conditions of our measurements, because the magnitude of the over-all rate constants requires that any rate-determining, diffusion-controlled step (*e.g.*, eq 12) be preceded by an unfavorable equilibrium step (*e.g.*, eq 10) and any such equilibrium would be expected to be different for thiol anions of different basicity.

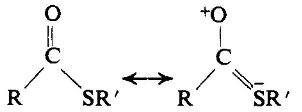
A mechanism in which hydroxide ion removes the proton as the thiol attacks the carbonyl group (mechanism 14) is improbable in view of the absence of



(14)

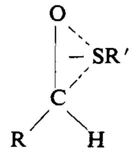
catalysis of the reaction by bases other than hydroxide ion and the fact that the third-order rate constant for such a reaction with methyl mercaptoacetate would have to be 3.5×10^{11} M^{-2} sec^{-1}. This is larger than the rate constant for a diffusion-controlled bimolecular reaction,[33] and it does not appear possible to divide this reaction into a series of bimolecular reactions which would proceed at less than diffusion-controlled rates.

The fact that the rate constants for the reaction with acetaldehyde increase only twofold with a 250-fold increase in the basicity of the thiol anion is surprising. The slope of a plot of log k against pK for the reaction of thiol anions with p-nitrophenyl acetate[34] is only about 0.4, compared to 0.8 for several other series of nucleophilic reagents,[35] but the corresponding slopes for the reactions with an oxime acetate,[36] acrylonitrile,[37] and ethylene oxide[38] are approximately 0.86, 0.38, and 0.36, respectively. The very small value of this slope for acetaldehyde would not seem to be an expression of a similarity of the transition state to reactants,[39] in view of the fact that the equilibrium constant for the reaction of eq 10 is almost certainly unfavorable. Baker and Harris have pointed out that the low basicity and stretching frequency of the carbonyl group of thiol esters suggest an important contribution of the resonance form (III) in which there is electron donation



III

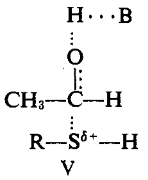
from the oxygen atom to the d orbitals of sulfur.[40] This and other evidence for the utilization of the d orbitals of sulfur suggest that in the transition state for the addition of the thiol anion to acetaldehyde, back-bonding from the carbonyl group (IV) may



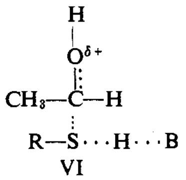
IV

stabilize the transition state and account for the absence of substitutent effects on the rate. A back-interaction of π electrons with sulfur has been suggested by Friedman, *et al.*,[37] as an explanation for the larger nucleophilicity of sulfur anions than of amines of comparable basicity toward acrylonitrile.

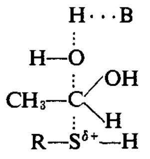
Acid-Catalyzed Formation of Hemithioacetals. The finding that the formation of the hemithioacetals is catalyzed by phosphoric acid and by strong carboxylic acids suggests that the catalysis by hydronium ion is also general acid catalysis or its kinetic equivalent. Possible transition states for the rate-determining step of these acid-catalyzed reactions with acetaldehyde are V–VIII, in which B is water, phosphate monoanion, or carboxylate ion. Transition states V and VI depict general acid catalysis and the kinetically equivalent specific acid–general base catalysis, respectively, of the attack of the thiol upon the unhydrated carbonyl group of acetaldehyde. Transition states VII and VIII show the same types of catalysis for the nucleophilic displacement of water from acetaldehyde hydrate by the thiol. Mechanisms in which proton transfer *alone* is the rate-determining step are unlikely for reasons which will be discussed in a later section. Estimates of the rate of the proton-transfer steps[33] suggest that proton transfer can occur faster than the observed over-all reaction rate. The following arguments suggest that the direct nucleophilic displacement mechanisms (transition states VII and VIII) are improbable. (1) All known substitution reactions of carbonyl hydrates and



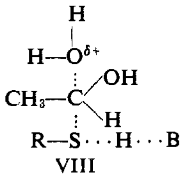
V



VI



VII



VIII

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[34] J. R. Whitaker, *J. Am. Chem. Soc.*, **84**, 1900 (1962); J. W. Ogilvie J. T. Tildon, and B. S. Strauch, *Biochemistry*, **3**, 754 (1964).

[35] T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, **80**, 2265 (1958); W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960).

[36] J. J. O'Neill, H. Kohl, and J. Epstein, *Biochem. Pharmacol*, **8**, 399 (1961).

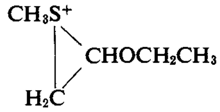
[37] M. Friedman, J. F. Cavins, and J. S. Wall, *J. Am. Chem. Soc.*, **87**, 3672 (1965).

[38] J. P. Danehy and C. J. Noel, *ibid.*, **82**, 2511 (1960).

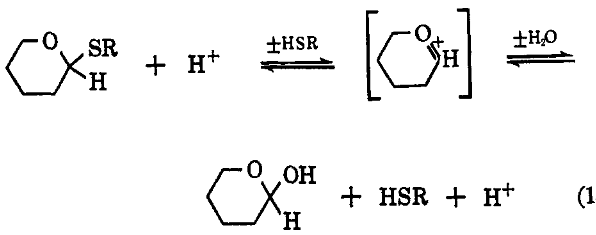
[39] G. S. Hammond, *ibid.*, **77**, 334 (1955); J. E. Leffler, *Science*, **117**, 340 (1953).

[40] A. W. Baker and G. H. Harris, *J. Am. Chem. Soc.*, **82**, 1923 (1960).

hemiacetals, including the base-catalyzed addition of thiols, proceed by an elimination–addition mechanism with addition to the free carbonyl group.[9] (2) The third-order rate constant for the acid-catalyzed addition of $CH_3OCH_2CH_2SH$ to acetaldehyde in water is 400 times larger than the second-order rate constant for the acid-catalyzed hydrolysis of $CH_3SCH_2CH(OCH_2CH_3)_2$ in 50% dioxane–water.[41] It has been proposed[41] that the latter reaction proceeds by intramolecular nucleophilic participation of the sulfur atom to give the intermediate



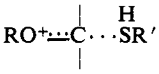
Since intramolecular reactions ordinarily exhibit larger rate constants than their intermolecular analogs, this suggests that the intermolecular addition of thiol to acetaldehyde does not proceed by nucleophilic attack of thiol on acetaldehyde hydrate. (3) There is suggestive evidence that the hydrolysis of cyclic monothioacetals proceeds by an A1 mechanism with expulsion of the exocyclic thiol[42] (eq 15). According to the



(15)

principle of microscopic reversibility, the reverse reaction would then proceed by addition of thiol to a carbonium ion, rather than by nucleophilic attack of thiol on saturated carbon. If the attack on a hemiacetal does not occur by direct nucleophilic displacement, it is unlikely that attack on a hydrate occurs by nucleophilic displacement either.

The transition state for monothioacetal hydrolysis by an A1 mechanism implies complete protonation in a



$$RO^{+}\cdots\overset{|}{\underset{|}{C}}\cdots\overset{H}{S}R'$$

prior equilibrium step (*i.e.*, the Brønsted $\alpha = 1.0$) and is similar to VI except for the substitution of an alkyl group for hydrogen. If it is accepted that monothioacetal hydrolysis proceeds by an A1 mechanism, then the value of α should be 1.0 for a reaction which proceeds through transition state VI. The fact that the addition of thiols to acetaldehyde is subject to detectable general acid catalysis means that α is not equal to 1.0 and that VI is not the correct transition state for this reaction. A similar argument supported by more extensive data has been used against preequilibrium protonation of the carbonyl group in the addition of ROH and HOH to aldehydes.[9]

The relationship between the Brønsted parameter, α, and the nucleophilic reactivity of the compound which is attacking the carbonyl group has been discussed previously[9,43,44] in terms of equations derived from the Brønsted and Swain–Scott equations. The experimental data for a series of nucleophilic reagents of widely varying reactivity show values of α which are in agreement with transition state I and with the predictions of other structure–reactivity correlations.[39] It is convenient to rearrange the equations in the forms

$$pK_2 - pK_1 = c_2(s_2 - s_1) \tag{16}$$

$$n_k = c_2(\alpha_0 - \alpha_k) \tag{17}$$

in which n is a measure of nucleophilic reactivity and is often proportional to the basicity of the nucleophile, s is a measure of sensitivity to nucleophilic reactivity, the pK's refer to catalyzing acids, c_2 is the negative of the previously defined C_2, and the other subscripts refer to individual reaction series. Equation 16 states that if a substrate is made more reactive because of catalysis by a stronger acid, its sensitivity to the nucleophilicity of the attacking reagent will decrease. If this is accepted, the conclusion of eq 17 follows with no further assumptions other than the original assumption of the applicability of the Brønsted and Swain–Scott relationships. Equation 17 states that as the nucleophilicity (basicity) of the attacking reagent increases, the sensitivity to the strength of the catalyzing acid, α, decreases. For the addition of thiols to acetaldehyde, this relationship is illustrated by the fact that the addition of the highly nucleophilic thiol anion occurs without detectable acid catalysis (*i.e.*, $\alpha = 0$), while the addition of the very weakly basic free thiol shows a high sensitivity to acid catalysis with a large value of α.

The analogous equations for general base catalysis are

$$pK_2 - pK_1 = c_5(s_1 - s_2) \tag{18}$$

$$n_i c_5 = \beta_0 - \beta_i \tag{19}$$

in which the Brønsted β is a measure of the sensitivity of the reaction to the strength of the catalyzing base. The interpretation of these equations is similar to that for acid catalysis and states that the sensitivity to general base catalysis, β, will decrease as the nucleophilicity of the attacking reagent increases. For a given series of reactions $\alpha = 1 - \beta$, depending on whether the reaction is interpreted as general acid catalysis (mechanism V) or general base catalysis of attack on the conjugate acid of the substrate (mechanism VI), and these relationships predict opposite behavior for the two mechanisms. If mechanism VI held, the observed value of α should increase (*i.e.*, β decreases) as the reactivity of the nucleophilic reagent is increased. We know of no data for general acid catalysis of carbonyl addition reactions which are in accord with this prediction. Swain and Worosz have reached this same conclusion for the reaction of amines with carbonyl compounds by applying the "solvation rule" and the "reacting-bond rule."[45]

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[41] J. C. Speck, Jr., D. J. Rynbrandt, and I. H. Kochevar, *J. Am. Chem. Soc.*, 87, 4979 (1965). The rates of acid-catalyzed hydrolysis of acetals in water and 50% dioxane–water are about the same. For example, the second-order rate constants for acetaldehyde diethyl acetal are 15.2 M^{-1} min^{-1} in 50% dioxane–water at 25° and 44 M^{-1} min^{-1} in water at 20°: J. N. Brønsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 25, 59 (1929).

[42] C. Bamford, B. Capon, and W. G. Overend, *J. Chem. Soc.*, 5138 (1962); R. L. Whistler and T. Van Es, *J. Org. Chem.*, 28, 2303 (1963).

[43] E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, 84, 4319 (1962).

[44] L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, 88, 2225 (1966).

[45] C. G. Swain and J. C. Worosz, *Tetrahedron Letters*, No. 36, 3199 (1964).

While these considerations argue against transition state VI and are in accord with mechanism V, the possibility should be kept in mind of a cyclic proton-transfer mechanism and the occurrence of proton transfer through intervening water molecules.[29,46] In the acid-catalyzed thiol addition reaction, the proton which is initially on the thiol may be accepted by the conjugate base of the catalyst before the diffusion-controlled separation of the products. This may be called a "one encounter," as opposed to a "concerted" mechanism.

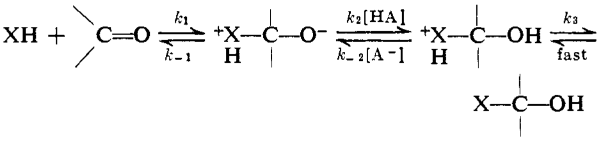
The acid-catalyzed addition of thiol to acetaldehyde occurs faster in deuterium oxide than in water, with a k_H/k_D ratio of 0.59, in spite of the fact that the reaction is general acid catalyzed. Similar inverse isotope effects have been observed for the dehydration steps of oxime[47] and semicarbazone[48] formation and the isotope effects for acid-catalyzed acetaldehyde hydration,[49] semicarbazide addition,[43] and glucose mutarotation[50] are only 1.3, 1.2, and 1.37, respectively. The interpretation of such isotope effects will be mentioned below and it will only be pointed out here that an inverse isotope effect does not rule out general acid catalysis and that in the case of the thiol addition reaction there is an equilibrium isotope effect which favors addition of the deuterated thiol and which does not exist in the other reactions.[19b,48] The fact that the equilibrium constant for hemithioacetal formation is 2.27 times larger in deuterium oxide than in water means that the kinetic isotope effect for the acid-catalyzed decomposition of the hemithioacetal, k_{H_2O}/k_{D_2O}, is 1.31.

In contrast to the situation with thiol anions, the reactivity of thiols for acid-catalyzed addition to acetaldehyde increases with increasing basicity of the thiol (Table II). The basicity of the substituted thiols is not known, but is presumably inversely proportional to their acidity and a plot of the rate constants for the acid-catalyzed reaction against the pK values of the thiols is linear with a slope of 0.56. There are few data of this kind in the literature, but it has been reported[51] that the rate of acid-catalyzed addition of substituted benzamides to formaldehyde exhibits a ρ value of -1.1, which is similar to the ρ value for the basicity of these amides.[52] It is of interest that the third-order rate constant for the acid-catalyzed addition of ethanethiol to acetaldehyde is about the same as that for the addition of water,[24] in spite of the fact that the basicity of thiols is some five orders of magnitude less than that of water.[53] This indicates that the free thiol group is an extremely effective nucleophilic reagent toward the carbonyl group. The fact that most addition reactions of thiols are observed to proceed rapidly by base-catalyzed pathways is only a reflection of the still greater nucleophilicity of the thiol anion and the ease of its formation from the free thiol. The anion of methyl mercaptoacetate adds to acetaldehyde more rapidly than hydroxide ion,[24] although it is some 10^8 less basic than hydroxide ion.

The Role of Proton Transfer in General Acid–Base Catalysis. In reactions which involve only proton transfer, usually to or from a carbon atom, the role of the catalyst as a nucleophilic agent or leaving group and the mechanism of the reaction may be considered in the same framework as other displacement reactions. In a large class of reactions which involve catalysis of proton transfer to or from oxygen, nitrogen, or sulfur, the situation is far more complex, because the principal energy barrier to the reaction is some reaction other than the proton transfer itself. General acid catalysis of the addition of thiols and other nucleophilic reagents to the carbonyl group is a typical example of this class of reaction. The complexity of these reactions arises from the multiplicity of atomic motions and energies which make up the reaction coordinate. For the addition of HX to $>C{=}O$ the over-all reaction involves the removal of a proton from HX and the addition of a proton to $>C{=}O$ to form $X-\overset{|}{\underset{|}{C}}-O-H$, and the energy profiles for these proton transfers not only influence the (larger) energy barrier for the formation of the X–C bond and breaking of the carbonyl double bond, but are themselves influenced by the latter processes. Proposals as to the nature of general acid–base catalysis, and the proton-transfer process in these reactions, have ranged all the way from a process divided into two separate steps in which the proton transfer itself is the rate-determining step to a fully "concerted" process in which proton transfer occurs at the same time as the energetically more difficult step.[9,29,33,43,54–57] We wish to restate the problem, as we understand it, at this time.

The kinetics of the general acid catalyzed addition of HX to a carbonyl group require that the transition state be made up of the elements of HX, $>C{=}O$, and HA. For purposes of discussion, it will be assumed that the role of the catalyst is to transfer a proton to the carbonyl group, but similar considerations apply to other mechanisms. The following cases may be considered.

(1) The proton transfer alone is rate-determining and follows a rapid and reversible addition of XH to $>C{=}O$ (eq 20, *cf.* ref 9 and 54). This requires that $k_{-1} > k_2[\text{HA}]$ in order that the first step be at equilibrium. At high acid concentrations, this mechanism is unlikely in any case in which the acid, HA, is sufficiently strong that proton transfer to the intermediate, $HX^+-\overset{|}{\underset{|}{C}}-O^-$, is favored by the equilibrium because such a proton transfer will be diffusion controlled,[33] and



$$\text{XH} + {>}\text{C}{=}\text{O} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^{+}\underset{\text{H}}{\text{X}}-\overset{|}{\underset{|}{\text{C}}}-\text{O}^- \underset{k_{-2}[\text{A}^-]}{\overset{k_2[\text{HA}]}{\rightleftharpoons}} {}^{+}\underset{\text{H}}{\text{X}}-\overset{|}{\underset{|}{\text{C}}}-\text{OH} \underset{\text{fast}}{\overset{k_3}{\rightleftharpoons}} \text{X}-\overset{|}{\underset{|}{\text{C}}}-\text{OH} \quad (20)$$

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(46) M. Eigen, *Discussions Faraday Soc.*, **39**, 7 (1965).

(47) A. Williams and M. L. Bender, *J. Am. Chem. Soc.*, **88**, 2508 (1966).

(48) B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

(49) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960).

(50) W. H. Hamill and V. K. La Mer, *J. Chem. Phys.*, **4**, 395 (1936).

(51) M. Imoto and M. Kobayashi, *Bull. Chem. Soc. Japan*, **33**, 1651 (1960).

(52) J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Can. J. Chem.*, **38**, 1518 (1960); K. Yates and J. B. Stevens, *ibid.*, **43**, 529 (1965).

(53) E. M. Arnett, *Progr. Phys. Org. Chem.* **1**, 223 (1963).

(54) (a) A. R. Butler and V. Gold, *J. Chem. Soc.*, 2305 (1961); (b) Y. Pocker, *Proc. Chem. Soc.*, 17 (1960); (c) S. L. Johnson, *J. Am. Chem. Soc.*, **84**, 1729 (1962).

(55) (a) R. P. Bell and B. De B. Darwent, *Trans. Faraday Soc.*, **46**, 34 (1950); (b) C. A. Bunton and R. H. DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965); (c) A. J. Kresge and R. J. Preto, *J. Am. Chem. Soc.*, **87**, 4593 (1965); (d) E. H. Cordes *Progr. Phys. Org. Chem.*, in press; (e) H. Zimmerman and J. Rudolph, *Angew. Chem. Intern. Ed. Engl.*, **4**, 40 (1965); (f) R. P. Bell, *Discussions Faraday Soc.*, **39**, 16 (1965).

(56) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, **87**, 1553 (1965).

(57) J. J. Weiss, *J. Chem. Phys.*, **41**, 1120 (1964).

the reverse of step 1 cannot occur at a rate which is faster than diffusion controlled. Furthermore, the rate of such a reaction would show no dependence on the strength of the catalyzing acid. The same step must be rate determining in both directions of the overall reaction. Thus, the reaction of A^- with $HX^{+}\text{–}\overset{|}{\underset{|}{C}}\text{–}OH$ would be rate determining when the reaction proceeds from right to left, and if the equilibrium for proton transfer were in the opposite direction from that indicated above, this reaction would be diffusion controlled and would proceed at a rate independent of the basicity of A^-. Although an example of this type of rate-determining proton transfer has not been demonstrated, it is approached in the base-catalyzed thiol-addition reaction and may occur with less basic thiol anions than those examined here.

(2) If case 1 does not hold, the addition of HX to the >C=O group provides the greater part of the energy barrier in the rate-determining step, and the problem is to define the behavior of the proton which is initially on HA and is finally on the oxygen atom. To approach this problem, it would be desirable to know how much time elapses between the instant a pair of molecules which are going to react come together in solution and the instant that the transition state is reached, and the amount that the character of the carbonyl oxygen atom changes during this interval. In other words, is it more probable that the (many) >C=O and XH molecules in a low-energy state will be brought to the transition state by one or a few (rare) high-energy collisions, or that the (rare) HX···>C=O pairs which have been brought to a high-energy state by many low-energy collisions suffer one (of many) further low-energy collisions to reach the transition state. Without an answer to this question, it is not possible to decide whether the proton of an HA molecule which is hydrogen bonded to the carbonyl group can reach an equilibrium state in respect to HX···>C=O immediately before the transition state, or even whether it is possible for a molecule of HA to diffuse to the reacting complex between the time of first contact and the transition state. A definite answer to this question for reactions in solution is apparently not availble at the present time. It is probable, but not proved, that the HA molecule is hydrogen bonded to the carbonyl group before reaction with HX occurs; if this is the case, the diffusion of HA does not have to be considered and only the behavior of the proton is in question. The following limiting cases may be considered.

(a) The proton is in a stable potential well, does not itself undergo movement, and facilitates the reaction only by the stabilization which results from hydrogen bonding. The potential curve for the proton, the shape of which is dependent on the basicity of >C=O and the acidity of HA, is shown in Figure 5A. The species IX and X undergo reaction with XH with rate constants

$$\begin{tikzcd} {>}C{=}O{-}\overset{+}{H}\cdots A \arrow[r, shift left, "K"] \arrow[d, "k_1[HX]"] & {>}C{=}O\cdots H{-}A \arrow[l, shift left] \arrow[d, "k_2[HX]"] \\ \text{product IX} & \text{product X} \end{tikzcd}$$

k_1 and k_2, respectively. Although the concentration of IX is very low, k_1 will be very large. The over-all deuterium isotope effect for this reaction will be a function of the isotope effect on the equilibrium constant for the formation of the hydrogen-bonded complex, the equilibrium constant, K, and the relative magnitudes of k_1 and k_2. The relative catalytic efficiency of acids of different strength, as expressed by the Brønsted coefficient, α, will be a function of the same factors.

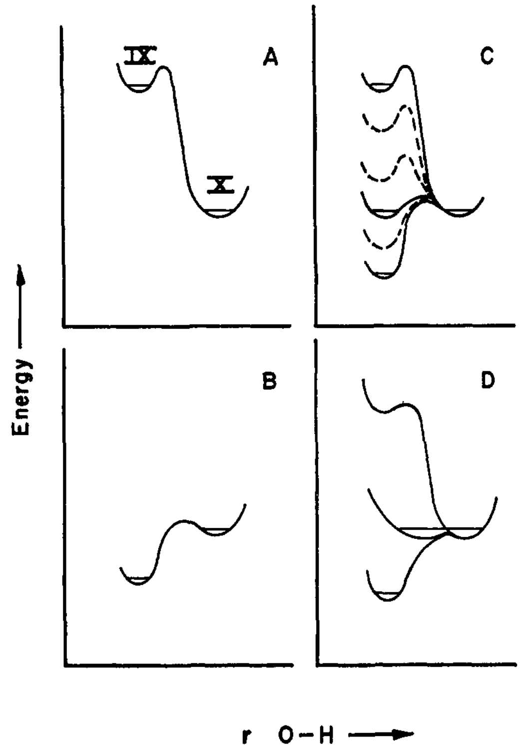

Figure 5. Schematic energy diagrams to indicate the state of the proton in general acid catalysis of addition to the carbonyl group.

(b) The proton is certainly not completely motionless in the transition state. Even if it is fixed in the lower energy potential well of Figure 5A and it is assumed that the transition state is reached in a single collision, the preferred mode of reaction should be that in which the proton approaches the carbonyl group

$$H\overrightarrow{X}\cdots{>}\overleftarrow{C}{=}\overrightarrow{O}\cdots\overleftarrow{H}\text{–}\overrightarrow{A}$$

rather than that in which it is furthest from the carbonyl group.

$$H\overrightarrow{X}\cdots{>}\overleftarrow{C}{=}\overrightarrow{O}\cdots\overrightarrow{H}\text{–}\overleftarrow{A}$$

Immediately after the transition state, the basicity of the carbonyl oxygen atom will be greatly increased so that the shape of the potential well for the proton will be changed to that shown in Figure 5B, and the proton will jump to the oxygen atom.

(c) The proton undergoes translation toward the carbonyl oxygen atom and is at the top of a potential barrier in the transition state. Swain, *et al.*, have suggested that this is unlikely for a symmetrical transition state because the observed small deuterium isotope effects for such reactions suggest that the proton has not lost its zero-point energy.[56] Such a mechanism requires that the energy lost in raising the proton to this transition state be gained in lowering the energy of the potential barrier for formation of the X–C bond.

(d) If the transition state is reached relatively slowly in a number of collisions, the potential wells for the proton will change as the carbonyl oxygen atom increases in basicity (Figure 5C). In the course of this change, the barrier for proton transfer, which is initially large, will progressively decrease. The size of the barrier at the moment the transition state is reached is not known, but it is certainly small. Since the rate of proton-transfer processes between oxygen and nitrogen atoms is limited by diffusion (10^{10}–10^{11} M^{-1} sec^{-1}), the proton-transfer process itself must be even faster, on the order of 10^{12} sec^{-1}, and there is other evidence that proton transfer in a hydrogen-bonded system is extremely fast and may occur by tunneling.[33,55,57,58] There have been many explanations proposed for the low deuterium isotope effects which are often seen in proton-transfer reactions.[29,55,56,59] It is difficult to predict the isotope effect under conditions in which the time scale is so short that stable potential wells for the proton are unlikely to exist and the proton transfer is not itself rate determining. To the extent that the proton can be located in a potential well and the zero-point energy maintained, the isotope effect will be small.[29,56] As the oxygen atom becomes more basic and the potential surface for the proton changes rapidly, the proton may fall into the new potential well, and there is theoretical and experimental evidence that the isotope effect for hydrogen transfer becomes small as the energy for the transfer becomes favorable and the energy barrier becomes small.[60]

(e) The barrier to proton transfer may effectively disappear so that the proton is in a single potential well in the transition state as shown in Figure 5D. (The shape of the curve in the figure should not be interpreted literally.) A single potential well has been proposed on experimental grounds for strong hydrogen bonds and on theoretical grounds even for relatively weak bonds, and it is expected that the single potential well will be approached as the acidity and basicity of the reacting pair become more favorable.[61]

The Brønsted coefficient, α, is an experimental measure of the extent to which a reaction is catalyzed by acids of different strength and is frequently extrapolated to serve as a measure of the "amount" of proton transfer in the transition state. While this extrapolation is undoubtedly roughly correct, it may not be possible to define the precise location of the proton in the transition state, and it is apparent that α will have somewhat different meanings for the different mechanisms described above, so that α may not necessarily be an exact measure of the amount of proton transfer for different reactions. For a reaction catalyzed by two acids of different strengths, it would be expected that the potential energy–distance curves and, hence, the amount of proton transfer would be different in the transition state, even though both acids correspond to the same value of α.[62] Furthermore, the nature of the nucleophilic reagent HX (for example, the relative importance of basicity and polarizability) may influence the relative amount of stabilization of the transition state by acids of different strength at a given optimal degree of proton transfer.

There has been some discussion as to the extent to which these reactions are "stepwise" or "concerted," with both of these terms often being used in different senses by different authors. We suggest (in contrast to a recently expressed view[56]) that it is profitable to think of these reactions as concerted in the sense that: (a) the proton is not motionless in the transition state, and it has almost certainly moved toward the carbonyl oxygen atom, compared to its position in the starting material; (b) the potential energy of the proton in the transition state, to the extent that this can be defined, is affected by the change in the properties of the groups between which it is being transferred, and the potential energy of this other part of the reaction is itself affected by the position of the proton; and (c) there does not appear to be good reason to regard the proton transfer and the rest of the reaction as occurring in separate steps, any more than the approach to the transition state of any other reaction is thought of as occurring in discrete steps.

Enzymatic Reactions. A number of enzymatic reactions in which a thiol ester is formed from an aldehyde and a sulfhydryl group appear to occur by the addition of the sulfhydryl group to the aldehyde followed by hydride transfer from the hemithioacetal to an acceptor.[63] These include the conversion of methylglyoxal and glutathione to S-lactoylglutathione, a reaction catalyzed by the enzyme glyoxalase I, in which the ketone carbonyl of the methylglyoxal is the hydride acceptor;[25] the reaction of glyceraldehyde 3-phosphate with the enzyme glyceraldehyde 3-phosphate dehydrogenase to form a thiol ester with a sulfhydryl group of the enzyme, a process in which nicotinamide–adenine dinucleotide is the hydride acceptor;[64] and the formation of thiol esters from coenzyme A or glutathione and simple aliphatic aldehydes, with hydride transfer to nicotinamide–adenine dinucleotide.[65] Cliffe and Waley have shown that under some conditions the rate of the glyoxalase I reaction is independent of the enzyme concentration and approximates that for the dehydration of methylglyoxal.[25] The kinetic studies reported here indicate that, in general at pH values near neutrality, the addition of thiols to aldehydes occurs much more rapidly than the addition of water. Thus, it seems likely that conditions could be found under which the rates of the other enzymatic reactions of this type are independent of enzyme concentration, being controlled by the rate of aldehyde

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dehydration. Alternatively, some of these enzymes may catalyze the dehydration of their aldehyde substrates.

Acknowledgments. We are grateful to S. H. Bauer, M. Eigen, S. Golden, E. Grunwald, and M. Kreevoy for helpful comments or discussions.

Kinetics of the Addition of Grignard Reagents to Ketones. The Addition of Methylmagnesium Bromide to 2,4-Dimethyl-4′-methylmercaptobenzophenone[1]

Stanley G. Smith[2] and George Su

Contribution from the W. A. Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61801. *Received April 6, 1966*

Abstract: The rate of addition of methylmagnesium bromide to 2,4-dimethyl-4′-methylmercaptobenzophenone in diethyl ether at 25.0° has been measured for Grignard concentrations from 0.04 to 1.5 *M*. The ultraviolet spectrum of reacting solutions has been interpreted in terms of a complex in equilibrium with the Grignard reagent and ketone which gives rise to the formation of addition products.

Because of wide applicability in synthesis, the reactions of Grignard reagents have received extensive study.[3] An understanding of the mechanism of, *e.g.*, the addition of Grignard reagents to ketones depends in part on knowledge of the nature of the Grignard reagent as well as the composition of the transition state and potential intermediates.[4,5]

Recent magnesium exchange data,[6,7] X-ray studies,[8] and molecular weight determinations[9] on various Grignard reagents in ether have been interpreted in terms of a monomeric reagent, RMgX, at low concentrations[9] (<0.1 *M*). Attributing all deviations of observed molecular weights[9] in ether from theoretical values to association suggests[9d–f] that dimerization becomes important at concentrations above *ca.* 0.1 *M*,[9d–f] the extent of association being a function of the specific reagent. Measurements of Smith and Becker[10] of the heat of reaction (3.6 kcal/mole) of diethylmagnesium with magnesium bromide were interpreted[10] as indicating that, for this reagent in ether, equilibrium strongly favors the formation of the Grignard, EtMgBr, at 0.1 *M*.

Most of the various species conceivably present in an ether solution of a Grignard reagent have been implicated in many of the diverse[3,9d,11–13] proposals which have been made for the mechanism of the addition reaction with ketones. For example, Becker[12] has recently formulated the reaction as proceeding by way of a low concentration of a 1:1 complex between ketone and dimeric methylmagnesium bromide, based on an initial rate which is first order in benzophenone and first order in methylmagnesium bromide in tetrahydrofuran. It was suggested[12] that the complex rearranged to form product in a rate-determining step. Similar mechanisms have been suggested by Mosher[13] and others[3] in ether solvent.

To explain the reported observation that the reaction of methylmagnesium iodide with acetone is zero order in ketone,[14] the high reactivity of dialkylmagnesium compounds, as well as the tendency of magnesium halides to decrease reaction rates,[12] House[15] has suggested that the addition reaction occurs by way of a 1:1 complex between the ketone and the dialkylmagnesium in equilibrium with the Grignard reagent in ether.

In a modification of Swain's[16] early suggestion, Ashby[9c] has suggested that the monomeric reagent, RMgX, is involved. His proposed mechanism employs a rate-determining attack of ketone on monomeric Grignard displacing an ether of solvation followed by rapid reaction with a second monomeric Grignard forming a complex which rearranges to product. Reaction by way of dissociated Grignard species has also been suggested by Ashby.[9d]

In a previous communication[5] we reported spectroscopic[4] and kinetic studies in support of the addition mechanism (eq 1) involving rapid complex formation

$$\text{ketone} + \text{Grignard} \overset{K}{\rightleftharpoons} \text{complex} \xrightarrow{k} \text{product} \qquad (1)$$

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[1] Research supported by a grant from the National Science Foundation.

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