isopropyl phosphate. Since phosphorylation by metaphosphate can be nonselective under the right conditions, its failure to phosphorylate 2-propanol is not likely to be due to an abnormal proportion of unproductive collisions in solution, but rather to an abnormally low chance of collision.

These considerations lead us to propose that the differences in reactivity observed between different alcohols may be due to nonstatistical distribution of solvent molecules in the solvation shell about the phosphoryl group. This *selective solvation* would be most pronounced for 2-propanol, the least effective ionizing solvent, which in consequence is totally excluded from the solvation shell of the phosphoryl group of both monoanions and dianions of phosphate monoesters. The differences will be less pronounced for the lower alcohols, and would be expected to be less for the monoanion than the dianion. Like other forms of selectivity, it will be expected to be reduced also at higher temperatures.

This picture accounts qualitatively for the results observed in mixed alcoholic solvents, if the reactivity of the metaphosphate intermediate is such that it does not survive long enough to penetrate its solvation shell. Clearly product distribution can no longer be regarded as a simple measure of metaphosphate formation.[60] We now regard nonselective phosphorylation in mixed alcohol–water solvents as sufficient, *but not necessary*, evidence for a metaphosphate intermediate.

Implications for Phosphate Transfer *in Vivo*. The transfer of the free phosphoryl group is a common and important process in living systems. We believe that our results indicate very clearly that the most effective way a simple phosphate derivative, XPO_3^{2-}, can be activated to transfer its phosphoryl group to another nucleophilic center

$$XPO_3^{2-} + Y \longrightarrow YPO_3^{2-} + X$$

is by modification of X, to convert it to a more effective leaving group. This would consist of either electrophilic or oxidative attack on X.[61] The process can be considerably further facilitated if solvation of the PO_3^{2-} group by hydrogen-bonding solvent molecules is reduced.

Acknowledgment. We wish to thank the Greek State Fellowship Foundation for the award of a Fellowship to A. G. V.

(60) Dr. J. D. Chanley (personal communication) informs us that he has reached a similar conclusion in a study of the solvolysis of acetyl phosphate.

(61) V. M. Clark, D. W. Hutchinson, A. J. Kirby, and S. G. Warren, *Angew. Chem. Intern. Ed. Engl.*, 3, 678 (1964).

Comparison of Mercaptide and Alkoxide Ions as Catalysts for Ketone Isomerization[1]

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Contribution from the Metcalf Chemical Laboratories, Brown University, Providence, Rhode Island. *Received August 1, 1966*

Abstract: In methanol solution, thioethoxide ion is from one-fifth to one-fifteenth as effective as methoxide ion in catalyzing the isomerization of (−)-menthone to (+)-isomenthone and of Δ^5- to Δ^4-cholesten-3-one. An improved method for dissecting catalysis by solutions of basic nucleophiles into contributions by nucleophile and lyate ions has been developed. The catalytic activity of thioethoxide ion is much greater than one would have anticipated from its basicity and the Brønsted β values for carboxylate ion catalysis of enolate ion (or enol) formation from acetone. In the functioning of enzymes, thiol groups require consideration as possible sites for proton donation or acceptance.

It is well known that many basic reagents have the capacity to remove an α-hydrogen atom from ketones, forming reactive intermediates which are enolate ions or enols. The rate of formation of these intermediates can be estimated from kinetic information on halogenation, hydrogen isotope exchange, or isomerization reactions. Many kinetic studies involving hydroxide ions, alkoxide ions, carboxylate ions, amines, and other types of bases have been made, but the reactivity of mercaptide ions in this type of reaction seems not to have been measured.

This paper reports the kinetics of the (−)-menthone (I)[3,4] ⇄ (+)-isomenthone (II) equilibration and of the isomerization of cholest-5-en-3-one (III) to cholest-4-en-3-one (IV), as catalyzed by methoxide and thioethoxide ions in methanol. Our results enable a comparison of the catalytic effectiveness of representative alkoxide and mercaptide ions.

The kinetics of acid-catalyzed menthone isomerization have been studied by many workers.[5b,6] Rates of isomerization as catalyzed by ethanolic ethoxide

(1) (a) Supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the donors of this fund. (b) Based on the Sc.M. thesis of L. A. R., Brown University, June 1965.

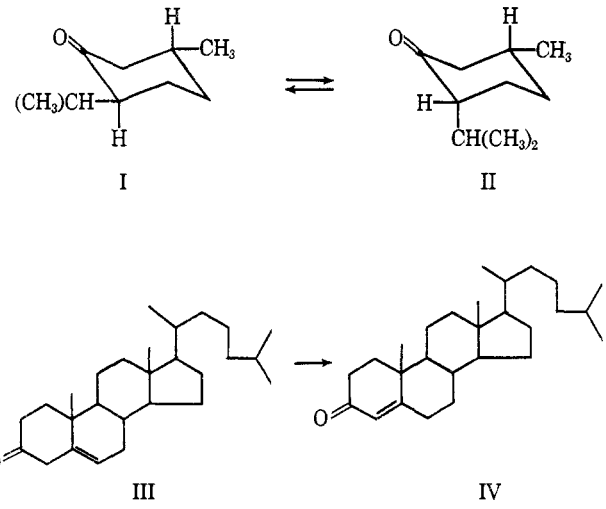
(2) University of California, Santa Cruz.

(3) The official *Chemical Abstracts* name of menthone is *p*-menthan-3-one.

(4) For a discussion of conformations, see C. Djerassi, P. A. Hart, and C. Beard, *J. Am. Chem. Soc.*, **86**, 85 (1964).

(5) (a) C. Tubandt, *Ann.*, **339**, 41 (1905); (b) *ibid.*, **354**, 259 (1907); (c) C. Tubandt, K. Mohs, W. Tubandt, and H. Weinhausen, *ibid.*, **377**, 284 (1910).

(6) P. D. Bartlett and J. R. Vincent, *J. Am. Chem. Soc.*, **55**, 4992 (1933); R. P. Bell and E. F. Caldin, *J. Chem. Soc.*, 382 (1938); A. Weissberger, *J. Am. Chem. Soc.*, **65**, 102, 245, 402 (1943); **67**, 1622 (1945); F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).



I II III IV

have been reported by Tubandt and co-workers[5] and by Gruse and Acree.[7] Tubandt[5] also gave some attention to the catalytic effects of sodium methoxide in methanol and in methanol–water mixtures, and of other alkoxide ions in the corresponding alcohols as solvents.

The mechanisms of enolization, enolate ion formation, and isomerization of Δ^4- and Δ^5-3-keto steroids have been extensively investigated by Ringold with Malhotra and other co-workers, mainly by product studies and use of isotopic tracers.[8] These studies have included rate determinations on isomerizations catalyzed by hydrochloric acid,[8d] an enzyme,[8d] and potassium *t*-butoxide in *t*-butyl alcohol.[8e] III and IV were often involved in these studies, thought not in the rate determinations. Kinetics of some similar isomerizations, again not involving III, as catalyzed by acid and by enzymes have been reported by Nes, *et al.*[9]

Except for some preliminary measurements in these laboratories by Stauffer,[10] we are unaware of any kinetic studies of mercaptide ion catalyzed ketone isomerization. It is interesting, however, that Tubandt[5b] conducted a few kinetic runs on menthone isomerization with thioethoxide solutions for the purpose of evaluating equilibrium constants for reactions of alkoxides with ethanethiol, such as reaction 1, below.

Evaluation of Mercaptide Ion Catalysis. In this work, methanolic thioethoxide solutions were prepared by mixing measured amounts of sodium methoxide with measured excesses of ethanethiol. If equilibrium

$$CH_3O^- + C_2H_5SH \rightleftharpoons CH_3OH + C_2H_5S^- \quad (1)$$

1 lay entirely to the right, interpretation of rate data would be simple and straightforward. However, a significant concentration of methoxide ions is present at equilibrium. Because methoxide is more effective than thioethoxide ion as a catalyst for ketone isomerization, the small concentration of methoxide ions can catalyze an appreciable fraction of the isomerization. Indeed, one must be on guard against the possibility that the observed catalysis is wholly due to the lyate ion.

If both thioethoxide and methoxide ions are catalytically active, eq 2 obtains, where k_ψ is the observed

$$k_\psi = k_S[C_2H_5S^-] + k_O[CH_3O^-] \quad (2)$$

pseudo-first-order rate coefficient and k_S and k_O are second-order coefficients for catalysis by the sulfur and oxygen anions, respectively. For equilibrium 1

$$K_1 = \frac{[C_2H_5S^-]}{[CH_3O^-][C_2H_5SH]} \quad (3)$$

Substitution into eq 2 gives

$$\frac{k_\psi}{[C_2H_5S^-]} = k_S + \frac{k_O}{K_1}\frac{1}{[C_2H_5SH]} \quad (4)$$

A plot of $k_\psi/[C_2H_5S^-]$ against $1/[C_2H_5SH]$ should be linear with intercept k_S and slope k_O/K_1. The methoxide catalytic coefficient, k_O, can be evaluated separately, and thus K_1 can be estimated from the slope.[11]

Derivation of eq 4 involves no assumptions except that activity coefficients approach unity closely enough to be disregarded. However, in using this method for evaluating k_S and K_1 one commonly assumes concentrations for C_2H_5SH and $C_2H_5S^-$ as though reaction 1 had gone fully to completion. If the methoxide concentration at equilibrium is more than, say, 5% of the thioethoxide concentration, the constants evaluated can be significantly in error.

A treatment involving fewer assumptions makes use of the definition, $[CH_3O^-]_{st} = [CH_3O^-] + [C_2H_5S^-]$. From this definition and eq 3

$$[CH_3O^-] = \frac{[CH_3O^-]_{st}}{1 + K_1[C_2H_2SH]}$$

Substituting for both $[C_2H_5S^-]$ and $[CH_3O^-]$ in eq 2

$$k_\psi = \frac{k_S K_1[C_2H_5SH][CH_3O^-]_{st} + k_O[CH_3O^-]_{st}}{1 + K_1[C_2H_5SH]}$$

Rearranging

$$k_\psi = k_S[CH_3O^-]_{st} + \frac{(k_O[CH_3O^-]_{st} - k_\psi)}{[C_2H_5SH]}\frac{1}{K_1} \quad (5)$$

According to eq 5, a plot of k_ψ *vs.* $(k_O[CH_3O^-]_{st} - k_\psi)/[C_2H_5SH]$ should have intercept $k_S[CH_3O^-]_{st}$ and slope $1/K_1$. Inasmuch as k_O can be determined separately and $[CH_3O^-]_{st}$ (necessarily constant within a set of experiments) is known from the way the experiments were set up, one need only assume a value for $[C_2H_5SH]$ in order to determine both k_S and K_1. In practice, one starts with the assumption that equilibrium 1 lies wholly to the right, uses the resulting K_1 value for a more accurate estimate of $[C_2H_5SH]$, repeats the plot to get a new K_1 value, and iterates until further iteration causes no significant change in the slope or intercept.

We have found occasion to use both methods in the present work.

Experimental Section

(−)-Menthone (I), bp 43.5–44.5° (1 mm), $[\alpha]^{28}D$ −29.3° (neat), was prepared in 81% yield by sodium dichromate oxidation of (−)-menthol;[12] in methanol, $[\alpha]^{26}D$ −27.1° (0.308 g/ml).

(7) W. A. Gruse and S. F. Acree, *J. Am. Chem. Soc.*, **39**, 376 (1917).
(8) (a) H. J. Ringold and S. K. Malhotra, *ibid.*, **84**, 3402 (1962); (b) S. K. Malhotra and H. J. Ringold, *ibid.*, **85**, 1538 (1963); (c) *ibid.*, **86**, 1997 (1964); (d) *ibid.*, **87**, 3228 (1965); (e) G. Subrahmanyan, S. K. Malhotra, and H. J. Ringold, *ibid.*, **88**, 1332 (1966).
(9) W. R. Nes, E. Loeser, R. Kirdani, and J. Marsh, *Tetrahedron*, **19**, 299 (1963).
(10) James F. Stauffer, Sc.B. Thesis, Brown University, 1962.
(11) *Cf.* J. W. Baker and A. J. Neale, *J. Chem. Soc.*, 3225 (1954).
(12) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2952 (1961).

Cholest-5-en-3-one (III) was prepared by bromine addition to cholesterol, oxidation to the ketone, and finally debromination with zinc, after Fieser.[13] The observance of certain precautions was found necessary in order to obtain a high purity product: thorough washing of the cholesterol dibromide with acetic acid and of 5α,6β-dibromocholestan-3-one with methanol, until the filtrates were colorless, and rigorous drying of the ether solution of cholest-5-en-3-one before evaporation. The product obtained had mp 124–128°; both its ultraviolet absorption at 241.5 mμ and thin layer chromatography indicated about 5% contamination by cholest-4-en-3-one. (The R_f value of the minor spot was identical with that for an authentic sample of the Δ^4-ketone, prepared after Fieser.[13]) The Δ^5-ketone was stored under nitrogen in the refrigerator.

Reagent grade **methanol** was dried by the magnesium metal method[14] and stored with protection from the atmosphere by Drierite and soda lime. Commercial **ethanethiol** was distilled and a middle cut was taken.

Kinetic Measurement of Cholest-5-en-3-one Isomerization, Catalyzed by Sodium Methoxide. Solutions of the ketone in methanol and of sodium methoxide in methanol were thermally equilibrated in the thermostat bath. (Because the ketone dissolves slowly in methanol, a solution in ethyl ether was prepared and 1 ml was diluted to 25 ml with methanol.) Equal volumes were mixed in a thermostated flask by means of pipets precooled to thermostat temperature. The initial concentration of ketone in the reaction mixture was about 1×10^{-4} *M*. A portion of the reaction mixture was placed in a silica cell in the thermostated cell compartment of a Cary 14 spectrophotometer and absorbance at 242 mμ was recorded. The increase in absorbance followed a first-order law. Substantially equal rate coefficients were obtained at equal sodium methoxide concentrations with a fresh sample of the Δ^5-ketone and with an old sample that assayed only about 85% Δ^5-ketone. Infinity absorbances showed that isomerization to the Δ^4-ketone was complete and that methanol addition to the C=C double bond had not occurred.

Kinetic Measurement of Cholest-5-en-3-one Isomerization, Catalyzed by Sodium Thioethoxide. Equal volumes of a solution of the ketone in methanol and of a freshly prepared solution of sodium thioethoxide in methanol (prepared by combining a solution of sodium methoxide with a solution of excess ethanethiol), both at thermostat temperature, were thoroughly mixed and 5-ml aliquots were dispensed by pipet into 10-ml volumetric flasks immersed in the thermostat bath. The initial concentration of ketone in the reaction mixture was about 1×10^{-4} *M*. At recorded times, the aliquots were quenched by addition of 1 ml of a 0.055 *M* solution of acetic acid in methanol. The quenched solutions were diluted to the mark with methanol and absorbance at 242 mμ was determined by means of the Cary 14 spectrophotometer. The increase in absorption followed a first-order law. Infinity absorbances, corrected for absorbance due to ethanethiol, indicated that isomerization to the Δ^4-ketone was complete and that addition of methanol or ethanethiol to the C=C double bond had not occurred.

Kinetic Measurement of (−)-Menthone Isomerization, Catalyzed by Sodium Methoxide. Reaction solutions were prepared at the temperature of the thermostat bath. The concentration of (−)-menthone in reaction solutions was about 0.1 *M*. A portion of reaction solution was placed in the jacketed cell of a Perkin-Elmer 141 photoelectric polarimeter; water from the thermostat was circulated through the jacket. Rotation at 436 mμ was recorded as a function of time and pseudo-first-order coefficients were reckoned in the usual way from "infinity" rotations after ten or more half-lives.

Kinetic Measurement of (−)-Methanone Isomerization, Catalyzed by Sodium Thioethoxide. Essentially the same procedure was followed. Sodium thioethoxide solutions were freshly prepared before each run.

Results

Kinetic study of the methoxide-catalyzed isomerizations of (−)-menthone and cholest-5-en-3-one was straightforward. Results are displayed in Tables I and II, respectively. Extrapolation of our measurements on menthone isomerization to 20° gives an overall second-order rate coefficient of 5.36×10^{-3} l. mole^{-1} sec.$^{-1}$ From Tubandt's data at the same temperature,[5b] 6.08×10^{-3} l. mole sec^{-1} is calculated.

For the thioethoxide-catalyzed isomerization of (−)-menthone, measurements at each of five temperatures were made with two or more concentrations of excess ethanethiol. The rate coefficients measured are presented in Table III. At each temperature, these data were treated according to eq 5 in order to estimate k_S, the catalytic coefficient for thioethoxide ion, and K_1 (defined by eq 3). The resulting values are listed in Table IV. Treatment of the data according to eq 4 gave nearly the same values.

The isomerization of (−)-menthone is really an equilibration. The equilibrium mixture comprises

Table I. Kinetics of Isomerization of (−)-Menthone in Methanol, Catalyzed by Sodium Methoxide

Temp, °C	[$NaOCH_3$], *M*	$10^4 k_\psi$,[a] sec^{-1}	$10^3 k_\psi$/[$NaOCH_3$],[a] l. $mole^{-1}$ sec^{-1}
25.2	0.036	3.02	0.84
30.4	0.036	4.80	1.33
35.3	0.036	7.10	1.97
40.3	0.012	3.50	2.92
	0.024	6.83	2.85
	0.036	10.5	2.90
45.7	0.036	15.4	4.28

[a] Rate coefficients for equilibration are equal to the sum of forward and reverse rate coefficients.

Table II. Kinetics of Isomerization of Cholest-5-en-3-one in Methanol, Catalyzed by Sodium Methoxide

Temp, °C	[$NaOCH_3$], *M*	$10^3 k_\psi$,[a] sec^{-1}	k_ψ/[$NaOCH_3$], l. $mole^{-1}$ sec^{-1}
0.5	0.01	3.12; 3.26	0.319
	0.02	6.50; 6.75	0.331
	0.03	9.88	0.329
9.6	0.01	5.68	0.568
13.4	0.01	7.15	0.715
15.2	0.01	7.96	0.796
18.9	0.01	9.81	0.981

[a] Duplicate entries represent duplicate runs.

Table III. Measured Rate Coefficients for Isomerization of (−)-Menthone in Methanolic Solutions of Sodium Thioethoxide

Temp, °C	[$NaOCH_3$]$_{st}$,[a] *M*	[C_2H_5SH]$_{st}$,[a] *M*	$10^4 k_\psi$, sec^{-1}
25.2	0.100	0.189	0.98
	0.100	0.243	0.82
30.4	0.100	0.189	1.57
	0.100	0.243	1.30
35.3	0.100	0.135	3.36
	0.100	0.162	2.74
	0.100	0.189	2.45
	0.100	0.216	2.20
	0.100	0.243	2.05
40.3	0.100	0.189	3.83
	0.100	0.216	3.45
	0.100	0.243	3.23
45.7	0.100	0.189	6.05
	0.100	0.243	5.05

[a] Concentrations as if no reaction of $NaOCH_3$ with C_2H_5SH had occurred.

(13) L. F. Fieser, *J. Am. Chem. Soc.*, 75, 5421 (1953).
(14) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed, D. C. Heath and Co., Boston, Mass., 1941, p 360.

Table IV. Calculated Rate and Equilibrium Constants from Isomerization of (−)-Menthone in Methanolic Solutions of Sodium Thioethoxide[a]

Temp, °C	$10^4 k_S$,[b] l. mole^{-1} sec^{-1}	K_1,[c] l. mole^{-1}
25.2	5.34	180
30.4	8.75	190
35.3	13.8	180
40.3	20.8	170
45.7	32.2	150

[a] Calculation according to eq 5. [b] See footnote *a*, Table I. [c] K_1 is defined by eq 3.

about 70% (−)-menthone and 30% (+)-isomenthone.[15] The observed rate coefficients, as recorded in Tables I, III, and IV, represent the sum of forward and reverse coefficients. If we were in possession of exact information as to the composition of the equilibrium mixture in methanol, we could dissect the observed rate coefficients into forward and reverse components, but its exact composition is not known. However, the fact that the same final rotation was observed (at equal menthone concentrations) in both methoxide- and thioethoxide-catalyzed isomerizations shows that the ratio of forward and reverse coefficients is the same with either catalyst. Therefore the ratios of catalytic coefficients for equilibration are identical with the ratios for forward or reverse rates.

Rate measurements on isomerization of cholest-5-en-3-one as catalyzed by thioethoxide ion were complicated by the relatively high extinction coefficients of this ion and of ethanethiol at 242 mμ. Absorption by the thioethoxide ion is particularly strong, and precluded following the reaction rate by direct photometric measurements on the reacting solution. A procedure involving photometric analysis of acid-quenched aliquots of the reacting solution was feasible, but the appreciable absorption of the thiol restricted kinetic determinations to solutions of rather low total thiol content. The measurements made are recorded in Table V. Treatment of the data according to eq 5

Table V. Measured Rate Coefficients for Isomerization of Cholest-5-en-3-one in Methanolic Solutions of Sodium Thioethoxide

Temp, °C	$[NaOCH_3]_{st}$,[a] M	$[C_2H_5SH]_{st}$,[a] M	$10^4 k_\psi$,[b] sec^{-1}
−5.3	0.0100	0.0185	6.95
	0.0100	0.0212	6.21
	0.0100	0.0239	5.76
−0.5	0.0100	0.0185	9.88
	0.0100	0.0212	8.95
	0.0100	0.0239	8.38
5.5	0.0100	0.0185	15.2
	0.0100	0.0212	13.9
	0.0100	0.0239	13.1
9.5	0.0100	0.0185	19.8
	0.0100	0.0212	18.3
	0.0100	0.0239	17.4

[a] Concentrations as if no reaction of $NaOCH_3$ with C_2H_5SH had occurred. [b] Each entry is average of two runs.

was clearly better than treatment according to eq 4. Nevertheless about three iterations were necessary before slopes ($1/K_1$) were not changed by further iteration. The resulting k_S and K_1 values[16] are listed in Table VI.

Table VI. Calculated Rate and Equilibrium Constants from Isomerization of Cholest-5-en-3-one in Methanolic Solutions of Sodium Thioethoxide[a]

Temp, °C	$10^2 k_S$, l. mole^{-1} sec^{-1}	K_1,[b] l. mole^{-1}
−5.3	2.4	320
−0.5	4.2	340
5.5	7.4	360
9.5	11.1	410

[a] Calculation according to eq 5. [b] K_1 is defined by eq 3.

The K_1 values estimated from the cholestenone isomerization kinetics (Table VI) are about double those estimated from the menthone studies (Table IV). The considerable agreement of these estimates is regarded as more significant than their difference. It is to be noted that these estimates are based on measurements with different substrates at different ranges of excess ethanethiol concentration and utilizing different analytical methods. The differences can perhaps be attributed to differences in temperature. However, the K_1 estimates within the two series do not extrapolate to a common K_1 value at an intermediate temperature.

Activation parameters calculated by standard expressions[17] from data in Tables I, II, IV, and VI are presented in Table VII.

Table VII. Activation Parameters

Substrate	Catalyst	$\Delta H^{\pm}$, kcal/mole	$\Delta S^{\pm}$, cal. deg^{-1} mole^{-1}
(−)-Menthone	CH_3O^-	14.5[a]	−20[a]
	$C_2H_5S^-$	16[a]	−20[a]
Cholest-5-en-3-one	CH_3O^-	8.8	−28
	$C_2H_5S^-$	15	−10

[a] Composite value, based on rate coefficients which are the sum of forward and reverse coefficients.

Conceivable Alternative Rate Laws. We have shown that our data are compatible with the assumption (eq 2) of a rate law involving both methoxide and thioethoxide terms. Let us now consider four other conceivable interpretations of catalysis by sodium thioethoxide solutions. The first is that catalysis was due entirely to methoxide ion generated by equilibrium 1. If such were true, plots of our data according to eq 4 or 5 should have zero intercepts. The fact that intercepts are substantial shows that more than just methoxide catalysis is involved.

The second possibility is that all the catalysis was due to ethanethiol. This is refuted by the fact that the rate is depressed by increase in ethanethiol concentration.

(15) J. Read, G. J. Robertson, and A. M. R. Cook, *J. Chem. Soc.*, 1276 (1927).

(16) The estimates of K_1 in Tables IV and VI are 1.4- to 3.7-fold greater than a crude early estimate by Tubandt,[5b] which was also based on rate measurements.

(17) J. F. Bunnett in "Investigation of Rates and Mechanisms of Reactions," S. L. Friess, E. S. Lewis, and A. Weissberger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1961, p 199.

A third possibility is that the reactions are wholly catalyzed by thioethoxide ion. This is also negated by the decelerating effect of increasing ethanethiol concentration. Some catalysis by methoxide ion must be admitted.

A fourth alternative is that a term first order in thioethoxide and also first order in ethanethiol must be included in the rate law. If such a term were of major importance, an increase in rate with increase in ethanethiol concentration would have been observed, especially at high thiol concentrations (Table III). It therefore cannot be a major term, but our data do not allow its complete exclusion.

Discussion

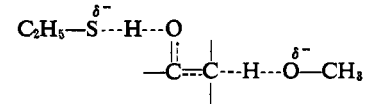
From data in Tables I and IV, methoxide ion is 15 times more effective than thioethoxide ion in effecting isomerization of (−)-menthone (at 30.4°). From data in Tables II and VI, the alkoxide ion is five times as effective as the mercaptide ion in catalyzing the isomerization of cholest-5-en-3-one (at 9.5°).

Naively, one might have taken all these isomerization reactions to involve proton abstraction from an α-carbon atom, to form an enolate ion, as a common rate-limiting step. If so, the rate coefficients we have measured could have been taken as indicative of the relative nucleophilic reactivities of the two bases *vs.* hydrogen in the two ketones. The results could then have been used to test the hypothesis of Bunnett and Baciocchi[18] that the relative nucleophilic reactivity of alkoxide and mercaptide ions *vs.* hydrogen varies with the degree of bonding of base to hydrogen in the transition state.

The hydrogen at C-4 of III is doubtless more acidic than the tertiary α-hydrogen of I. It is therefore probable that the transition state for enolate ion formation from III has less bonding of base to hydrogen than in the corresponding reaction of I.[8c] According to the hypothesis of Bunnett and Baciocchi, the alkoxide/mercaptide ratio of nucleophilic reactivity toward hydrogen increases as the degree of bonding of base to hydrogen in the transition state is greater. If enolate ion formation were the rate-limiting step in all four of the reactions we studied, our results would indeed support that hypothesis. However, the situation is too complex to warrant such straightforward conclusions.

First, there is a strong possibility that the methoxide- and thioethoxide-catalyzed isomerizations occur by different mechanisms. The methoxide-catalyzed reactions probably do occur *via* enolate ions. This mechanism is also possible for the thioethoxide-catalyzed isomerizations, but reaction *via* enol intermediates seems more probable.

An enol may be formed in a termolecular step involving ketone, methoxide ion, and ethanethiol. Such a mechanism calls for the same rate law as the enolate ion mechanism, because the product of methoxide ion and enthanethiol concentrations is proportional to thioethoxide ion concentration (eq 3). In the enol-forming step, the methoxide ion takes a proton from the α-carbon as the thiol donates a proton to the carbonyl oxygen. The transition state may be represented as



The feasibility of such mechanisms has been discussed by Swain,[19] Bell and Jones,[20] and Bell,[21] and experiments which call for such a mechanism for the acetate ion catalyzed hydrogen isotope exchange of 2-butanone in deuterium oxide have been described by Warkentin and Tee.[22]

An attractive postulate is that whether isomerization occurs *via* the enolate ion or the enol is determined by the relative stability of the alternative intermediate pairs (enol plus base *vs.* enolate ion plus conjugate acid of base). Applying this criterion to the methoxide ion catalyzed isomerization of menthone, one takes account of the greater pK_a of methanol in methanol (18.1)[23] than of cyclohexanone enol in methanol (16.3)[25] and judges the enolate ion to be the intermediate. With respect to the same reaction catalyzed by thioethoxide ion, one notes that the pK_a of ethanethiol in water (10.5)[28] is less than that of cyclohexanone enol (11.3)[26] and that the alkyl substituents of menthone would somewhat increase the latter value; he judges that reaction *in water* would occur largely *via* the enol. If the pK_a's of ethanethiol and the enol increase by equal increments on going to methanol, the enol intermediate should also prevail for isomerization in that solvent.

Because of greater electron delocalization in the enolate ion, cholesta-3,5-dien-3-ol is doubtless a stronger acid than cyclohexanone enol. By the criterion of intermediate stability, it is therefore all the more probable that the methoxide-catalyzed isomerization goes *via* the enolate ion. However, it is now difficult to judge whether enolate ion plus ethanethiol or enol plus thioethoxide ion would be the less energetic pair.

Neither the criterion of intermediate stability nor our application of it to specific reactions merits acceptance without reservation. However, they are sufficiently strong to warrant the tentative conclusion that all these reactions do not follow the same mechanistic pathway.

If the methoxide-catalyzed isomerization of cholest-5-en-3-one goes *via* the enolate ion and the thioethoxide-catalyzed isomerization *via* the enol, further nonparallelism would result from the involvement of different carbon atoms in rate-limiting proton-transfer steps. Malhotra and Ringold[8b] have shown that protonation of the enol of this ketone occurs preferentially at C-6. Accordingly the rate-limiting step in

(18) J. F. Bunnett and E. Baciocchi, *Proc. Chem. Soc.*, 238 (1963).

(19) C. G. Swain, *J. Am. Chem. Soc.*, 72, 4578 (1950).

(20) R. P. Bell and P. Jones, *J. Chem. Soc.*, 88 (1953).

(21) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 149, 172.

(22) J. Warkentin and O. S. Tee, *Chem. Commun.*, 190 (1966).

(23) 18.1 is the sum of the autoprotolysis constant for methanol (16.7)[24] and the logarithm of the molar concentration of methanol in methanol.

(24) K. Bowden, *Chem. Rev.*, 66, 124 (1966).

(25) To the pK_a for cyclohex-1-en-1-ol in water (11.3)[26] a generous rule-of-thumb increment of 5.0 is added to correct for the change to methanol solvent.[27]

(26) R. P. Bell and P. W. Smith, *J. Chem. Soc., Sect. B*, 241 (1966).

(27) *Cf.* B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Am. Chem. Soc.*, 88, 1911 (1966).

(28) G. B. Barlin and D. D. Perrin, *Quart. Rev.* (London), 20, 75 (1966).

isomerization of III to IV *via* enol is proton removal from C-4 (concerted in the present case with proton donation to carbonyl carbon). However, the same workers have shown that the enolate ions derived from steroidal Δ^4-3-ketones are preferentially protonated at C-4. It follows that the rate-limiting step in isomerization of III to IV *via* enolate ion must be proton donation to C-6.

pK_a for Ethanethiol in Methanol. It is easily shown that K_1 (eq 3) = K_{EtSH}/K_{MeOH}, the ratio of the acid dissociation constant of ethanethiol and the ionic product for methanol. Taking K_1 as 180 (Table IV), one reckons pK_a for ethanethiol in methanol as 14.4. This is 3.9 units greater than in water. For comparison, Parker, *et al.*,[27] list pK_a for thiophenol in methanol 4.4 units greater than in water.

Comparison of Catalyst Reactivity. The 5- to 15-fold superiority of methoxide over thioethoxide ion as an isomerization catalyst represents a difference of 0.7 to 1.2 common logarithm units. The difference in pK_a of the two bases is 2.3 if the autoprotolysis constant is used without further correction or 3.7 if it is corrected (rather arbitrarily) by adding the logarithm of the molar concentration of methanol in methanol. Depending on which $\Delta \log (k_O/k_S)$ value and which ΔpK_a value are used, the Brønsted β value is reckoned to lie between the extremes of 0.19 and 0.52. For comparison, the Brønsted β values for amine and carboxylate ion catalyzed halogenation of acetone are about 0.8 or higher.[21,29]

It is thus evident that thioethoxide ion is more effective in catalyzing formation of enol or enolate ion from ketones than one would have anticipated from its basicity.

The relatively high catalytic activity of the mercaptide ion is of possible biological significance. Inasmuch as many enzymes contain thiol groups in their active centers,[30] these groups (or their anions) require consideration as possible proton donor or acceptor sites in the functioning of enzymes.

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(30) F. Sanger, *Proc. Chem. Soc.*, 76 (1963).

Acetyl Hypoiodite as an Aromatic Iodinating Agent

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Abstract: In acetic acid solution the reaction of mercuric acetate and iodine to form acetyl hypoiodite and acetoxymercuric iodide reaches equilibrium. The equilibrium constant has been evaluated spectrophotometrically. It is much larger than that for the corresponding reaction to form acetyl hypobromite Evidence is presented, which is based on a study of the kinetics of ring iodination of pentamethylbenzene in acetic acid solutions of iodine and mercuric acetate, that acetyl hypoiodite is a much weaker electrophile than acetyl hypobromite.

Acyl hypohalites generated by mixing halogens and the silver salts of carboxylic acids are reported to be relatively powerful aromatic halogenating agents.[1,2] Kinetic evidence has been presented that acetyl hypochlorite is substantially more reactive than molecular chlorine as a chlorinating agent for alkylbenzenes in aqueous acetic acid.[3] Similar though less convincing evidence concerning the relative reactivities of acetyl hypobromite and bromine has been obtained in a study of aromatic bromination by hypobromous acid in aqueous acetic acid.[4]

Recently a method has been devised for generating acetyl hypobromite by the reaction of mercuric acetate with bromine in acetic acid.[5] The reaction which takes place reaches equilibrium as shown in eq 1 (in which X_2 is the molecular halogen). The constant K_{AcOX} has been evaluated by spectrophotometric methods (eq 1 and 2). On the basis of the results of a detailed study

$$Hg(OCOCH_3)_2 + X_2 \rightleftharpoons Hg(OCOCH_3)X + CH_3COOX \quad (1)$$

$$K_{AcOX} = [Hg(OCOCH_3)X][CH_3COOX]/[Hg(OCOCH_3)_2][X_2] \quad (2)$$

of the bromination of toluene and benzene in such mixtures, it has been concluded that the slow step (eq 3) is one involving the hydrocarbon and acetyl hypobromite and that the reaction is polar in character.

$$CH_3COOX + ArH \longrightarrow ArX + CH_3COOH \quad (3)$$

Good evidence has been obtained that in acetic acid acetyl hypobromite is considerably more electrophilic in character than bromine itself.

On the grounds that the halogen atom of an acyl hypohalite is positively polarized it can be predicted that acetyl hypoiodite should be more stable than acetyl hypobromite. This prediction is borne out by the results of the present study of the effectiveness of acetyl hypoiodite as an aromatic iodinating agent. The hypoiodite has been generated in acetic acid by a procedure analogous to that used in the earlier study[5] of acetyl hypobromite. The equilibrium constant, K_{AcOI}, for formation of the hypoiodite (eq 2) is substantially larger than K_{AcOBr}. At 25° in acetic acid the hypo-

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