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) $= K_{\mathrm{EtSH}}/K_{\mathrm{MeOH}}$, 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 $\Delta \log (k_{\mathrm{O}}/k_{\mathrm{S}})$ 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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[29] M. L. Bender and A. Williams, *J. Am. Chem. Soc.*, **88**, 2502 (1966).

[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 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.

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

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

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

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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[1] R. N. Haszeldine and A. G. Sharpe, *J. Chem. Soc.*, 993 (1952).

[2] A. L. Henne and W. F. Zimmer, *J. Am. Chem. Soc.*, 73, 1362 (1951).

[3] P. B. D. De la Mare, I. C. Hilton, and S. Varma, *J. Chem. Soc.*, 4044 (1960).

[4] P. B. D. De la Mare and J. L. Maxwell, *ibid.*, 4829 (1962).

[5] Y. Hatanaka, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.*, 87, 4280 (1965).

bromite reacts with toluene at a rate too rapid to permit kinetic measurement, while under comparable conditions a rate study of the reaction of the hypoiodite and pentamethylbenzene has easily been conducted.

Experimental Section

Materials. Reagent grade acetic acid and mercuric acetate were further treated and dried before use by the procedures employed in earlier investigations.[5,6] Resublimed reagent grade iodine and Eastman Organic Chemicals pentamethylbenzene were used without further purification.

Determination of the Equilibrium Constant for Acetyl Hypoiodite Formation. Solutions of iodine in acetic acid were prepared, brought to the temperature at which measurements were to be made, and sampled for analysis by iodometric methods. Solutions of mercuric acetate of known concentrations were prepared by dissolving weighed samples of the salt in the requisite amounts of acetic acid at the appropriate temperatures. Aliquots of the iodine and mercuric acetate solutions were mixed and samples were transferred to silica absorption cells of known path length. The cells were stored in a temperature-controlled (±0.1°) housing of a Beckman DU spectrophotometer. After temperature equilibration of the cells and housing, the free iodine concentrations of the solutions were determined through optical density measurements at 475 mμ (the absorption maximum of the halogen) using pure acetic acid as a blank. The extinction coefficients of iodine in acetic acid at various temperatures were established through optical density measurements on iodine solutions which contained no mercuric acetate; at 475 mμ, ϵ_{I_2} values are 750 and 744, respectively, at 25 and 45°.[7] It was assumed in calculating the iodine concentrations of the acetyl hypoiodite solutions that the free halogen was the only component which absorbed at the wavelength used. Equilibrium constants K_{AcOI} were calculated from equilibrium iodine concentrations and known initial reactant concentrations of the solutions contained in absorption cells on the assumption that acetyl hypoiodite was formed as shown in eq 2. Inclusion of small amounts of water in the reaction mixtures ($\sim$0.1 M) resulted in a slight reduction of the apparent value of K_{AcOI}.

Rate Studies of Pentamethylbenzene Iodination in Acetic Acid Solutions of Mercuric Acetate and Iodine. Stock solutions of pentamethylbenzene and mercuric acetate were prepared by dilution of weighed samples of the reactants to known volumes with acetic acid at 25°. Solutions of iodine in acetic acid were brought to 25° and standardized iodometrically. Runs were started by mixing known volumes of the solutions of the three reactants. Usually the pentamethylbenzene solution was added last. Samples of the mixture were transferred to 1-cm, glass-stoppered silica absorption cells. The cells were stored in the temperature-controlled Beckman spectrophotometer housing, and the optical densities of the cell contents at 475 mμ were determined at intervals. The free iodine concentrations of the rate samples at various times, $[I_2]$, were calculated from the optical densities and the known value of the extinction coefficient of the halogen in acetic acid at 475 mμ. In turn the acetyl hypoiodite concentrations of the rate samples during the course of the runs, [AcOI], were calculated from the free iodine concentrations and the initial concentrations of mercuric acetate and iodine (before reaction to form hypoiodite) using a modified form (eq 4) of eq 2.

$$[CH_3COOI] = \frac{K_{AcOI}\{[Hg(OCOCH_3)_2]_i - [I_2]_i + [I_2]\}[I_2]}{[I_2]_i - [I_2]} \qquad (4)$$

The optical densities of samples of reaction mixtures which were exposed to room light between readings were found to change in the same way as those of samples of the same mixtures which were stored in the spectrophotometer cell housing between readings. In general the reactions were followed to high percentages of completion (at least 80%).

The Product of Reaction of Pentamethylbenzene and Acetyl Hypoiodite. To a solution of 2.55 g (0.010 mole) of iodine and 3.20 g (0.010 mole) of mercuric acetate in 300 ml of acetic acid was added 0.83 g (0.0056 mole) of pentamethylbenzene. The resulting solution was stirred for 12 hr at room temperature and then diluted with a large volume of water containing sufficient sodium thiosulfate to destroy excess iodine. The mixture was then extracted several times with ether. The combined extracts were washed with sodium hydroxide solution and water and dried over anhydrous magnesium sulfate. The crude crystalline product obtained after evaporation of the ether melted at 102–105°. It was recrystallized twice from ethanol to provide 0.90 g (58% yield) of 6-iodo-1,2,3,4,5-pentamethylbenzene, mp 135–136°; with an authentic sample,[8] mmp 135–138°.

Results

Acetyl Hypoiodite Formation. As has been reported earlier[5] for bromine solutions, the addition of mercuric acetate to solutions of iodine in acetic acid results in a drop in intensity of the halogen color. The oxidizing power of the solution is not affected. As described in detail in the Experimental Section, spectrophotometric methods have been applied quantitatively in a study of this color change, which is ascribed to the establishment of an equilibrium (eq 1) with respect to the formation of acetyl hypoiodite. Equilibrium constants K_{AcOI} (eq 2) which are reported in Table I were calculated from equilibrium optical densities at 475 mμ of a series of solutions of varying initial concentrations of iodine and mercuric acetate. Equilibrium constants K' (eq 5) were calculated on the assumption that the reactions summarized in Table I proceeded according to eq 6. These were found to vary widely, as was also true of the corresponding constants calculated in connection with the previous work on acetyl hypobromite. If the reaction actually were leading to the formation of mercuric iodide (eq 6) rather than acetoxymercuric iodide (eq 1), the solubility

$$K' = [HgI_2][CH_3COOI]^2/[Hg(OCOCH_3)_2][I_2]^2 \qquad (5)$$

$$Hg(OCOCH_3)_2 + 2I_2 \rightleftharpoons HgI_2 + 2CH_3COOI \qquad (6)$$

of mercuric iodide[9] should have been exceeded in at least one of the solutions of Table I (see the last entry at 25°).

Table I. Equilibrium Constants for Acetyl Hypoiodite Formation in Acetic Acid[a]

$10^4[I_2]_i$, mole/l.	$10^4[Hg(OCOCH_3)_2]_i$, mole/l.	d_{475}[b]	$10^4[I_2]$, mole/l.	K_{AcOI}
		At 25.0°		
3.19	7.40	0.043	0.57	2.52
6.38	7.40	0.165	2.20	2.46
12.76	7.40	0.537	5.60	2.43
19.14	7.40	0.970	12.93	2.50
19.86	13.04	0.788	10.51	2.25
25.9	26.07	0.755	10.07	2.41
35.4	52.14	0.750	10.0	2.42
49.9	104.3	0.758	10.11	2.43
			Av 2.43 ± 0.05	
		At 45.0°		
12.7	39.3	0.152	2.04	1.93
25.4	59.1	0.387	5.20	2.00
38.2	59.1	0.822	11.07	2.05
			Av 1.99 ± 0.04	

[a] The subscripts on the columns labeled $[Hg(OCOCH_3)_2]_i$ and $[I_2]_i$ indicate that the concentrations in question are those of materials prior to the establishment of equilibrium. The equilibrium iodine concentrations are listed in the fourth column. [b] Equilibrium optical densities of the solutions at 475 mμ.

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(6) K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, 983 (1927).

(7) R. E. Buckles and J. F. Mills, *J. Am. Chem. Soc.*, **75**, 552 (1953), report λ_{max} 478 with an extinction coefficient of 775 for iodine in acetic acid at room temperature.

(8) R. M. Keefer and L. J. Andrews, *ibid.*, **78**, 5623 (1956).

(9) A. W. Davidson and W. Chappell, *J. Am. Chem. Soc.*, **60**, 2043 (1938).

The observed value of K_{AcOI} at 25° (2.43) is over ten times as large as that (0.198) found[5] for K_{AcOBr} at the same temperature. The value of K_{AcOI} drops to 1.99 at 45.0°. The enthalpy of the reaction to form acetylhypoiodite is approximately -1.9 kcal/mole. The $\Delta H°$ value for the corresponding reaction to form acetyl hypobromite is of the order of $+300$ cal/mole.

Kinetics of Iodination of Pentamethylbenzene by Acetyl Hypoiodite. Iodine in the presence of mercuric acetate reacts with pentamethylbenzene in acetic acid to give ring-iodinated product by a process which is presumed to be polar in character. In the mixtures prepared for rate study of this reaction, the initial concentration of the halogen was in general substantially less than that of the aromatic hydrocarbon and less than or comparable to that of the mercuric acetate. A summary of the results of the various runs which were made is included in Table II. Rate constants, *k*, which are reported are calculated on the assumption that reaction proceeds according to the rate law

Table II. Rate Constants for Pentamethylbenzene Iodination (Eq 7)[a]

10^3[Hg-(OCOCH$_3$)$_2$]$_i$, mole/l.	$10^3[I_2]_i$, mole/l.	10^3[PMB]$_i$, mole/l.	*k*, l./mole sec
	At 25.0°		
6.77	1.69	71.4	0.081
6.77	3.72	71.4	0.076
6.77	5.59	71.4	0.079
10.15	5.59	71.4	0.082
13.54	5.59	71.4	0.077
20.31	5.59	71.4	0.079
3.90	2.27	75.4	0.073
3.90	2.27	50.3	0.080
3.90	2.27	27.8	0.076
3.90	2.27	16.4	0.082
2.09	2.24	39.4	0.076
			Av 0.078 ± 0.003
	At 45°		
5.19	2.24	24.1	0.298
3.46	2.24	24.1	0.300
			Av 0.299

[a] From the values of *k* at 25° and 45°, one can estimate $\Delta H^{\ddagger} = 12$ kcal and $\Delta S^{\ddagger} = -23$ eu.

$$d[\mathrm{ArI}]/dt = -d[\mathrm{I_2}]_T/dt = k[\mathrm{ArH}][\mathrm{CH_3COOI}] \quad (7)$$

The term $[\mathrm{I_2}]_T$ is defined in eq 8 as the sum of acetyl hypoiodite and free iodine concentrations of the media.

$$[\mathrm{I_2}]_T = [\mathrm{I_2}] + [\mathrm{CH_3COOI}] \quad (8)$$

During the course of the runs values of $[\mathrm{I_2}]$ were determined spectrophotometrically, and the corresponding $[\mathrm{CH_3COOI}]$ values were calculated using eq 4, as described in the Experimental Section. Plots of $[\mathrm{I_2}]_T$ *vs.* time were constructed for each run and slopes of the resultant curves $(-d[\mathrm{I_2}]_T/dt)$ were taken at appropriate intervals. The *k* values were calculated by dividing these slopes by the corresponding values of $[\mathrm{ArH}]\cdot[\mathrm{CH_3COOI}]$. The resulting values of *k* reported in Table II are the average values of constants calculated at five to ten stages of each rate run. The reported constants are essentially invariant over wide ranges of initial reactant concentrations.

To check the accuracy of the spectrophotometric method of evaluating $[\mathrm{I_2}]_T$ during the course of reaction, one run was duplicated with the exception that analysis to determine $[\mathrm{I_2}] + [\mathrm{CH_3COOI}]$ was accomplished both iodometrically and spectrophotometrically. The two sets of values of $[\mathrm{I_2}]_T$ as determined during the course of the run were in agreement within a few per cent.

The average of the rate constants, *k*, obtained for the reaction of pentamethylbenzene and acetyl hypoiodite in acetic acid at 25° (0.078 l./mole sec) is intermediate in value between those obtained[5] for the comparable reactions of acetyl hypobromite with benzene (2.5×10^{-3} l./mole sec) and toluene (1.2 l./mole sec). Apparently acetyl hypoiodite is a much weaker electrophile than acetyl hypobromite. An approximate value of 17 l./mole min (0.28 l./mole sec) has been reported[3,10] for the reaction of toluene with acetyl hypochlorite in acetic acid at 25°. This would place the acetyl hypohalites in the order BrOAc > ClOAc > IOAc for their reactivity with toluene in acetic acid. However it should be noted that the reported reaction of ClOAc with toluene and most likely the BrOAc and IOAc reactions may be subject to catalysis by acids and salts so that a direct comparison of the results is subject to considerable uncertainty.

Acknowledgment. The authors are indebted to the National Science Foundation and to the Petroleum Research Fund of the American Chemical Society for grants in support of this research.

[10] P. B. D. De la Mare, I. C. Hilton, and C. A. Vernon, *J. Chem. Soc.*, 4039 (1960).