[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Effect of Solvent on Some Reaction Rates

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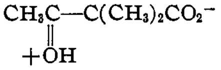
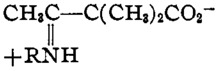
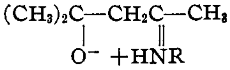
It has been shown recently that the decarboxylation of dimethylacetoacetic acid[1] and the dealdolization of diacetone alcohol[2] are reactions catalyzed specifically by primary and secondary amines. In the absence of general base catalysis it seems logical to assume that the amine is effective because it reacts with the carbonyl group of the keto acid or keto alcohol to form a Schiff base. Pedersen[3] tentatively advanced the ingenious hypothesis that the true intermediate for decarboxylation is the dipolar ion A, and for the amine catalyzed decarboxylation the dipolar ion, B. A similar intermediate (C) is possible for the amine catalyzed dealdolization.[4]



$CH_3C(=\overset{+}{O}H)—C(CH_3)_2CO_2^-$ (A)



$CH_3C(=\overset{+}{R}NH)—C(CH_3)_2CO_2^-$ (B)



$(CH_3)_2C(O^-)—CH_2C(=\overset{+}{H}NR)—CH_3$ (C)

Pedersen's hypothesis appeared attractive since it explained the fact that the primary product of the decarboxylation of dimethylacetoacetic acid is the enol form of methyl isopropyl ketone.

The present paper is concerned with an experimental test of Pedersen's hypothesis. This has been accomplished by measuring the rate of reaction in solvents with various dielectric constants. The work of separating a positive and negative charge to form a dipolar ion should be greater the smaller the dielectric constant of the medium in which the separation takes place. It follows, therefore, that reactions which take place by way of a highly polar activated complex should proceed much more rapidly in solvents of high than of low dielectric constant. Stearn and Eyring,[5] and Scatchard,[6] have verified this conclusion for the preparation of quaternary ammonium salts and for the hydrolysis of tertiary halides. Furthermore, Edsall and Blanchard[7] have measured the equilibria between the amino acid and dipolar ion forms of glycine, β-alanine, ε-aminocaproic acid, etc. An estimate from their data suggests that the ratio of the concentration of dipolar ion to undissociated amino acid would be only a tenth as great in 75% methanol as in water. Furthermore, all these studies were carried out in mixed solvents. While dipolar ions may tend to unmix such solvents, and to surround themselves preferentially with the more polar solvent, it is clear that in no case was the lack of homogeneity sufficient to obscure the effect of changing dielectric constant.

There was no evidence available concerning the effect of solvents on the amine catalyzed reactions, although Wiig[8] had measured the rate of decarboxylation of acetone dicarboxylic acid in various media. Pedersen[1] has pointed out limitations to the quantitative significance of this work. In so far as Wiig's data can be interpreted, they are in agreement with the results reported in this article.

The present work showed that there is no diminution in rate of decarboxylation or amine catalyzed dealdolization in solvents of low dielectric constant. The intermediate in decarboxylation cannot, then, be A, nor can the decomposition of C be the rate determining step in the dealdolization. Other mechanisms, tenable in the light of the new experimental results, are suggested in the discussion.

Experimental

Materials.—Eastman Kodak Co. technical diacetone alcohol was purified by vacuum distillation, and redistilled for each velocity determination. Purified[9] dimethylacetoacetic ester was fractionated through a Podbielniak column, and material boiling from 74.2–74.8° at 10 mm. was employed. Methylamine hydrochloride, prepared from Sharples monomethylamine, was recrystallized twice from butyl alcohol, once from ethyl alcohol, and dried *in vacuo*. Silver nitrate titration showed that the material was 99.8% pure. Eastman *o*-chloroaniline, distilled through a Podbielniak column, melted sharply at −2.0°. *o*-Chloroaniline hydrochloride prepared from the purified amine was recrystallized from 10% hydrochloric acid and was kept under 20 mm. pressure of hydrogen chloride in a vacuum desiccator. Methanol was dried with magnesium and distilled with precautions to exclude carbon dioxide. Dioxane, dried over sodium, melted at 11.72°. Ethanol was dried with barium oxide.

Apparatus.—The decarboxylation was followed by measuring the increase in pressure at constant volume due to

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(1) Pedersen, THIS JOURNAL, **60**, 595 (1938); **51**, 2098 (1929).

(2) Westheimer and Cohen, *ibid.*, **60**, 90 (1938).

(3) Pedersen, *J. Phys. Chem.*, **38**, 559 (1932).

(4) Westheimer, *Ann. N. Y. Acad. Sci.*, **XXXIX**, 401 (1940).

(5) Stearn and Eyring, *J. Chem. Phys.*, **5**, 113 (1937).

(6) Scatchard, *ibid.*, **7**, 657 (1939).

(7) Edsall and Blanchard, THIS JOURNAL, **55**, 2337 (1933).

(8) Wiig, *J. Phys. Chem.*, **32**, 961 (1928).

(9) Michael, *Ber.*, **38**, 2083 (1905).

TABLE I

METHYLAMINE CATALYZED DEALDOLIZATION OF DIACETONE ALCOHOL IN WATER–ALCOHOL MIXTURES AT 25°

	Concentration in m./l.[a]						
	Diacetone alcohol	CH_3NH_2 (B)	CH_3NH_3Cl (A)	Buffer ratio, B/A	$k_{obs} \times 10^3$ min.$^{-1}$[b]	$k \times 10^3$ calcd.	$k_{RNH_2} \times 10^3$ min.$^{-1}$(m./l.)$^{-1}$
Water							20.2[c]
50% Ethanol	0.0805	0.060	0.020	3	1.250	1.201	
	.0805	.090	.030	3	1.675	1.702	16.7
	.0805	.150	.050	3	2.685	2.705	
50% Methanol	.0546	.060	.020	3	1.370	1.395	
	.0546	.120	.040	3	2.680	2.672	21.3
	.0580	.150	.050	3	3.240	3.310	
75% Methanol	.0450	.045	.135	$^1/_3$	1.083		24.0
	.0450	.040	.080	$^1/_2$	0.935	0.955	23.4
	.0386	.045	.090	$^1/_2$	1.063	1.077	
	.0450	.060	.120	$^1/_2$	1.400	1.434	
	.0450	.075	.150	$^1/_2$	1.710	1.790	
	.0386	.045	.015	3	1.020	1.011	20.9
	.0386	.060	.020	3	1.370	1.323	
	.0386	.090	.030	3	1.920	1.950	
	.0450	.120	.040	3	2.632	2.578	
	.0450	.150	.050	3	3.130	3.205	
	.0450	.090	.018	5	1.880	1.878	20.3
	.0450	.150	.030	5	3.045	3.093	
	.0450	.050	In 0.050 m NaOH		2.627		20.0[d]

[a] The ionic strength was 0.150 throughout. [b] Decadic logarithms rather than natural logarithms were used throughout in order to be consistent with the previous workers. [c] From Miller and Kilpatrick, THIS JOURNAL, **53**, 3217 (1931). [d] Calculated using k_{OH^-} = 32.5 min.$^{-1}$ (m./l.)$^{-1}$.

the carbon dioxide evolved. The apparatus was essentially that of Brönsted and King,[10] with the improvements suggested by Marlies and LaMer.[11] The whole apparatus was immersed in a thermostat and the manometer was read through the glass thermostat wall. The flask containing the solution was shaken about 180 times a minute through an arc of about 15 mm.[1]. The thermostat was maintained at 25.0° with a maximum variation of 0.01°.

The dealdolization reaction was followed dilatometrically.[2] During individual experiments, the temperature was maintained at 25.0°, with a variation of not more than ±0.001°.

Procedure.—Alcohol–water and dioxane–water mixtures were made up to the stated per cent. by volume at 20°. Solutions of the reactants were prepared directly in the solvent mixture.

For decarboxylation experiments, the sodium salt of dimethylacetoacetic acid was prepared by saponifying a weighed sample of ester with a known quantity of alkali in the desired solvent. The time required for complete reaction was calculated from approximate saponification constants. A solution of dimethylacetoacetic acid was obtained by adding sufficient hydrochloric acid to react with all the sodium hydroxide, plus an additional amount of acid which remained in excess. In the experiments involving *o*-chloroaniline, the excess acid was, of course, converted into *o*-chloroaniline hydrochloride. Experiments in which *o*-chloroaniline and hydrochloric acid were employed checked within the experimental error with those in which *o*-chloroaniline and *o*-chloroaniline hydrochloride were used. The ionic strength was maintained with Merck Analytical Grade sodium chloride. Part of the solution of dimethylacetoacetic acid was used to wash out the decarboxylation apparatus, and then 100 cc. was transferred to the apparatus for the experiment.

The reactions studied are both first order, and the velocity constants were usually computed graphically by the method of Guggenheim.[12] The method of least squares and the computation based on a final pressure reading did not give significantly different results. The reproducibility was about 2 per cent.

Results

The data for the methylamine catalyzed dealdolization are given in Table I. The reaction is strictly first order, and follows the equation $-d(D)/dt = k_{obs}(D)$ where (D) is the concentration of diacetone alcohol. For water it has been found that $k_{obs} = k_{OH^-}(OH^-) + k_{RNH_2}(RNH_2)$ where k_{OH^-} and k_{RNH_2} are specific rate constants for catalysis by hydroxide ion and amine. For alcohol–water solvents, it is expected that the concentration of hydroxide ion will be considerably less than in water.[13] When the observed rate constant is plotted against buffer concentration at constant buffer ratio, a straight line is

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[10] Brönsted and King, THIS JOURNAL, **47**, 2523 (1925).

[11] Marlies and LaMer, *ibid.*, **57**, 1812 (1935).

[12] Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

[13] The fact that the basic ionization constant of ammonia is much smaller in alcohols than in water can be inferred from the work of Goldschmidt and Mathiesen, *Z. physik. Chem.*, **119**, 439 (1926).

obtained, but as anticipated the intercept on the rate axis is negligible. Under these circumstances a small error in the experimental points makes a large percentage error in the intercept, and therefore no estimate of the ionization constant of methylamine is justified.

Some typical results for the decarboxylation of dimethylacetoacetic acid are collected in Table II. The rate at which dimethylacetoacetic acid loses carbon dioxide is given by the equation

$$d(CO_2)/dt = k_{ion}(A^-) + k_{acid}(HA)$$

where (HA) is the concentration of the undissociated acid and (A^-) is the concentration of the corresponding anion. Since the specific rate constant for the decomposition of the acid, k_{acid}, is more than a hundred times as great as the constant, k_{ion}, for the decomposition of the ion, the term k_{ion} (A^-) can be neglected for work in acid solution.

TABLE II

THE RATE OF DECARBOXYLATION OF DIMETHYLACETOACETIC ACID AT 25°

Solvent	Concentration in moles/liter Ester	HCl	Fraction ionized[a]	k_{obs} × 10^3[b]	k_{acid} × 10^3[b]
Water		0.1772	0.003	1.810[c]	
		.1772	.003	1.840	
		.0562		1.806[c]	1.826
		.0272	.015	1.790[c]	(av.)
		.0104		1.743[c]	
		.0049	.094	1.680[c]	
25%	0.020	.1772	.001	1.900	1.90
Methanol	.035	.0100	.020	1.843	1.88
	.030	.0050	.038	1.810	1.88
50%	.020	.075	.001	1.880	1.88
Methanol	.040	.010	.009	1.885	1.90
	.035	.005	.018	1.825	1.86
	.040	.003	.028	1.840	1.89
75%	.040	.050	.001	1.730	1.73
Methanol	.060	.010	.003	1.690	1.67
	.060	.003	.011	1.707	1.73
	.040	.001	.033	1.683	1.74
50%	.040	.010	.004	2.090	2.10
Dioxane	.060	.005	.008	2.090	2.11
	.040	.003	.013	2.080	2.11

[a] Ionization constant of dimethylacetoacetic acid in water is 5.11×10^{-4} [Pedersen, THIS JOURNAL, 58, 240 (1936)]. Estimated values 2.0×10^{-4} in 25% methanol, 8.7×10^{-5} in 50% methanol, 3.3×10^{-5} in 75% methanol, 4.3×10^{-5} in 50% dioxane. [b] Decadic logarithms. [c] From Pedersen, ref. 1, ref. *a*.

At low *p*H, the concentration of acid (HA) is almost but not quite equal to the concentration of the acid plus the concentration of the anion. Since the difference is small, it was considered unnecessary to measure the ionization constant of dimethylacetoacetic acid in the solvents used; instead it was assumed that the ionization constant of dimethylacetoacetic acid varies with change in dielectric constant in the same manner as does that of acetic acid.[14] In the presence of excess hydrochloric acid, the degree of ionization should not vary appreciably during an experiment, and (except in aqueous solution) is always less than four per cent.

It should be mentioned at this point, however, that the decarboxylation reaction does not give a quantitative yield of carbon dioxide. The theoretical yield of carbon dioxide for a particular solvent was determined by measuring the pressure generated in the decarboxylation apparatus on acidifying a weighed sample of bicarbonate. The yield of carbon dioxide fell below the theoretical by more than 3% in pure water, by 5% in 50% methanol and by almost 20% in 75% methanol. The decarboxylation reaction, nevertheless, was reproducible, and strictly first order. Titration showed that there was neither decarboxylation nor cleavage during the saponification of the ester and there was probably no esterification of the free acid in aqueous alcohol. In any case, the reverse reaction, in the presence of aqueous acid in 50% methanol, did not appear to take place at all, and usually the rates of esterification and acid hydrolysis are comparable.

Many experiments were conducted using *o*-chloroaniline and *o*-chloroanilinium chloride buffers.[15] The reaction proved as complicated in alcoholic as in aqueous solution. Pedersen found that for *o*-chloroaniline catalyzed decarboxylation in aqueous solution, the data could best be represented by the equation

$$d(CO_2)/dt = k_{acid}(\text{acid}) + k_B(B)(\text{acid}) + k_{BH^+}(BH^+)(\text{acid})$$

where k_{acid} is the rate constant for the decomposition of the acid in the absence of the amine, k_B the rate constant for catalysis by the amine, B, and k_{BH^+} the rate constant for catalysis by the conjugate acid, BH^+. Since the equation is of different form than the one which proved necessary to account for aniline catalysis, and since the equation does not hold for solutions containing excess hydrochloric acid, it is quite possible that the agreement with experiment is fortuitous. At least the significance of the equa-

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(14) Harned, *J. Phys. Chem.*, 43, 275 (1939).

(15) William Archibald Jones, Dissertation, University of Chicago, Chicago, 1941.

tion must await further elucidation of the mechanism.

Our experiments showed that the amine catalysis does not vanish in solutions of low dielectric constant. The results could be fitted more or less well to several equations, and the experimental data hardly warranted a real choice. Tentatively, however, the data have been fitted to Pedersen's equation by the least squares method with a maximum deviation of 4 per cent. The values for the constants k_B and k_{BH^+} are recorded in Table III.

In order to determine these constants, it was necessary to know the concentration of amine, amine salt, hydrogen ion and dimethylacetoacetic acid present in any particular solution. Only as a first approximation are the concentrations of the reagents equal to the concentrations initially added. This is because of the large value for the dissociation constant, K_{BH^+}, of the *o*-chloroanilinium ion. The values of K_{BH^+} recorded in Table III were obtained, using methyl orange and methyl yellow as indicators, by a colorimetric method similar to that of Kolthoff and Guss.[16] Interestingly enough, the ionization constant is higher in the mixed solvent than in either methanol or water.[1,17] A similar increase in K_{BH^+} has been observed for indicator constants involving the ionization of an anilinium ion. The large values of K_{BH^+} make the corrections moderately important.

TABLE III

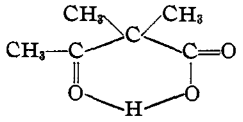
o-CHLOROANILINE CATALYSIS OF THE DECARBOXYLATION OF DIMETHYLACETOACETIC ACID

Solvent	K_{BH^+}	$k_B \times 10^{-3}$	$k_{BH^+} \times 10^{-3}$
Water	2.02×10^{-3}	32.44	3.16
50% Methanol	6.0×10^{-3}	7.78	15.85
75% Methanol	1.2×10^{-2}	2.99	19.03

Discussion of Results

Inspection of Table II shows that the rate of decarboxylation of dimethylacetoacetic acid is independent of solvent. It has already been pointed out that, if the reaction took place by way of a dipolar ion, the rate would decrease sharply as the dielectric constant of the medium was lowered. It is unlikely that there are compensating factors of sufficient magnitude to obscure this effect. It can therefore be concluded that the dipolar ion, A, is not involved in this decarboxylation.

A mechanism, however, must be chosen which will be in agreement with Pedersen's convincing demonstration that the product of the decarboxylation is the enol form of methylisopropyl ketone. A chelate ring as intermediate is consistent with all the facts known at present.



The data in Table I show that the rate constant for the amine catalyzed dealdolization of diacetone alcohol is also independent of solvent. This is the more remarkable because the rate constant for the reaction catalyzed by hydroxide ion is 189 min.$^{-1}$ (m./l.)$^{-1}$ in water, and only 32 and 75% methanol. (The value interpolated from Åkerlöf's data[18] is 30.9.) Since the rate constant for the amine catalysis not decreased in solvents of low dielectric constant, it follows that the reaction cannot be one in which the rate determining step is the decomposition of the dipolar ion, B. The general idea behind the mechanism previously suggested[4] may be correct; the rate determining step can be either the formation of a Schiff base, or the decomposition of a chelate ring structure formed from the ketimine.

Further investigation of the amine catalyzed decarboxylation is necessary before the mechanism can be established.

Summary

The rate of amine catalyzed dealdolization of diacetone alcohol, the rates of uncatalyzed and of amine catalyzed decarboxylation of dimethylacetoacetic acid, have been measured in solvents consisting of water–alcohol and water–dioxane mixtures.

The rates of the amine catalyzed dealdolization and of the uncatalyzed decarboxylation are independent of the medium. It therefore follows that the rate determining step for these reactions cannot be the decomposition of a dipolar ion, or other highly polar intermediate. Alternative mechanisms are proposed.

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[16] Kolthoff and Guss, THIS JOURNAL, **60**, 2516 (1938).

[17] Kuhn and Wassermann, *Helv. chim. acta*, **11**, 3 (1928); Goldschmidt and Mathiesen, *Z. physik. Chem.*, **119**, 439 (1926); Baggesgoard-Rasmussen and Reimer, *Dansk. Tids. Farm.*, **7**, 225 (1933).

[18] Åkerlöf, THIS JOURNAL, **50**, 1272 (1928).