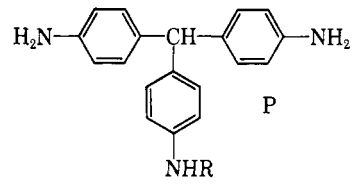
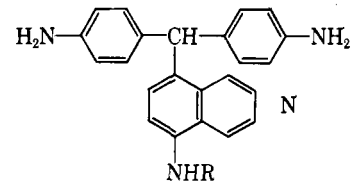
TABLE I
TRISARYLMETHANES




| Compd. no. | Structural type | R | M.p., °C. | Yield purified, % | Purification solvent[a] | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | P | H | 245 dec. | 32 | A | $C_{19}H_{19}N_3 \cdot 3HCl$[b,c] | 57.22 | 57.22 | 5.56 | 5.64 | 10.54 | 10.64 |
| 2 | P | $C_2H_5$ | 233 dec. | 30 | A | $C_{21}H_{23}N_3 \cdot 3HCl \cdot 3H_2O$[d] | 52.45 | 52.32 | 6.71 | 6.64 | 8.74 | 9.12 |
| 3 | N | H | 273–277 | 40 | B | $C_{23}H_{21}N_3$ | 81.38 | 81.20 | 6.24 | 6.34 | 12.38 | 12.52 |
| 4 | P | $(CH_2)_2N(C_2H_5)_2$ | 200 dec. | 49 | C | $C_{26}H_{32}N_4 \cdot 4HCl \cdot 0.75H_2O$[e] | 54.80 | 55.05 | 6.90 | 7.18 | 10.23 | 10.16 |
| 5 | P | $(CH_2)_3N(CH_2)_5$ | 219–229 dec. | 55 | D | $C_{27}H_{34}N_4 \cdot 4HCl \cdot 2H_2O$[f] | 54.36 | 54.55 | 7.10 | 7.17 | 9.39 | 9.45 |
| 6 | N | $(CH_2)_2N(C_2H_5)_2$ | 177–179 | 45 | E | $C_{29}H_{34}N_4$ | 79.41 | 79.14 | 7.81 | 7.90 | 12.78 | 12.75 |

[a] A, dilute hydrochloric acid; B, not recrystallized; C, ethanol–methanol (9:1); D, crude product extracted with warm methanol; E, methanol. [b] E. Fischer and O. Fischer, *Ann.*, **194**, 272 (1878). [c] Contains 7.15% water by Karl Fischer water determination (analytical values reported are corrected for water). Cl: calcd., 26.67; found, 26.63. [d] Water: calcd., 11.24; found, 10.40. Cl: calcd., 22.11; found, 22.32. [e] Water: calcd., 2.47; found, 2.62. [f] Water: calcd., 6.04; found, 5.50. Cl: calcd., 23.78; found, 23.51.

aromatic halogen to hydrogenolysis in the presence of palladium.

The trisarylmethanes II (Table I) were obtained readily by refluxing an ethanol solution of the diarylcarbinol and the aromatic amine in the presence of concentrated hydrochloric acid. Primary or secondary naphthylamines and anilines gave comparable yields.

### Experimental[15]

**4',4'''-(Hydroxymethylene)bisacetanilide (I).**—A solution of 200 g. (0.675 mole) of 4',4'''-carbonylbisacetanilide[10] in 1.5 l. of methanol was hydrogenated over 4.0 g. of 20% palladium-on-charcoal catalyst[16] poisoned with 0.01 g. of nicotinamide at 26° and an initial hydrogen pressure of 50 p.s.i.g. After 1 equivalent of hydrogen had been absorbed, the catalyst was collected by filtration, and the filtrate was evaporated to dryness *in vacuo*. Ultraviolet assay of the crude product (207 g.) indicated the presence of approximately 10% of the starting ketone. The crude hydrol was divided into two equal portions and each was crystallized from 2 l. of acetonitrile yielding a total first crop of 107 g. An additional 20 g. of product separated after the filtrates were allowed to stand at room temperature for 24 hr. The ratio of solvent to crude product (20 ml./g.) is crucial in the purification since the use of a lower ratio leads to coprecipitation of the starting material. The hot crystallization mixture should be allowed to cool slowly to room temperature and filtered promptly; it should not be refrigerated. The total yield of purified material was 63%; it melted at 174.5–176.5°, resolidified at 195°, and remelted at 258–266°.

*Anal.* Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.46; H, 6.07; N, 9.44.

**4',4'''-Carbonylbistrifluoroacetanilide.**—To a solution of 226 g. (1.06 moles) of 4,4'-diaminobenzophenone in 800 ml. of dimethylformamide was added gradually a solution of 550 g. (2.62 moles) of trifluoroacetic anhydride in an equal amount of dimethylformamide. The mixture cautiously was heated to its boiling point and then boiled under reflux for 3 hr., cooled, and poured into iced water. The suspension was neutralized with ammonium hydroxide and filtered. Recrystallization of the crude product from 95% ethanol gave 315 g. (73%) of product, m.p. 235–236°.

*Anal.* Calcd. for $C_{17}H_{10}F_6N_2O_3$: C, 50.50; H, 2.49; N, 6.93. Found: C, 50.79; H, 2.70; N, 7.67.

**4',4'''-(Hydroxymethylene)bistrifluoroacetanilide.**—A mixture of 19 g. (0.047 mole) of 4',4'''-carbonylbistrifluoroacetanilide, 300 ml. of ethanol, and 2 drops of N,N-diethylnicotinamide was hydrogenated as described previously over 1.0 g. of 20% palladium on charcoal. The crude product recrystallized from dilute ethanol gave 12 g. (61%) of purified material, m.p. 213–214°.

*Anal.* Calcd. for $C_{17}H_{12}F_6N_2O_3$: C, 50.25; H, 2.98; N, 6.89. Found: C, 49.95; H, 3.18; N, 7.17.

**4,4',4''-Methylidynetrianiline (Compound 1, Table I).**—A solution of 60 g. (0.2 mole) of 4',4'''-(hydroxymethylene)bisacetanilide, 18.6 g. (0.2 mole) of aniline, and 20 ml. of concentrated hydrochloric acid in 600 ml. of 95% ethanol was heated under reflux for 4 hr. Concentrated hydrochloric acid (250 ml.) was added, and the mixture was heated under reflux for an additional 6 hr. Upon cooling, a yellow solid was deposited (32.6 g.). It was purified by dissolving in water, adding concentrated hydrochloric acid until a solid formed, warming to effect solution, and cooling to give 24.4 g. (32%) of the hydrated trihydrochloride salt. Conversion to the free base was effected by addition of ammonium hydroxide to an aqueous solution of the salt. Recrystallization of the base (ethanol) gave 4,4',4''-methylidynetrianiline, m.p. 207–210°.

The other trisarylmethanes (Table I) were prepared similarly. Because they did not precipitate directly from the reaction mixture, the solvent was removed *in vacuo;* compounds 2 and 5 were triturated with 2-propanol and crystallized as indicated, while compounds 3, 4, and 6 were dissolved in water, converted to the bases, and processed.

**4-Methylbenzhydrol.**—A solution of 19.6 g. (0.1 mole) of 4-methylbenzophenone in 150 ml. of methanol was hydrogenated over 0.5 g. 20% palladium on charcoal poisoned with 0.1 g. of nicotinamide. The mixture was filtered from the catalyst, concentrated to dryness, and recrystallized from petroleum ether (b.p. 30–60°) to give 15.7 g. (80%) of product, m.p. 53–55°.

*Anal.* Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.74; H, 7.38.

When only 0.01 g. of nicotinamide was used, the hydrogenation proceeded rapidly to the diphenylmethane.

**Acknowledgment.**—The authors wish to express their appreciation to Mr. Charles E. Childs and associates for the microanalytical data, and to Dr. John M. Vandenbelt and associates for the spectral data.

(15) Melting points (corrected) were taken on a Thomas Hoover capillary melting point apparatus.

(16) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **83**, 4800 (1961).

## General Base Catalysis for Imidazole-Catalyzed Hydration of *sym*-Dichloroacetone[1]

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Evidence implicating the imidazole side chain of a histidine residue as a constituent of the active site of several enzymes including trypsin, chymotrypsin, and

ribonuclease,[2] has focused considerable attention on the mechanism of catalysis of nonenzymatic reactions by imidazole. Imidazole is known to function, in a variety of reactions, as both a nucleophilic and general base catalyst.[2,3] This molecule possesses several structural features which make it a particularly suitable catalyst.[3b] In particular, imidazole is unusual in that the attack of one nitrogen atom may be aided by proton removal from the other nitrogen atom by a second base molecule.[2c,3b] Bruice and co-workers have demonstrated catalysis of *p*-nitrophenyl acetate hydrolysis by the anion of imidazole substituted with electron-withdrawing groups,[4] but have suggested that the corresponding reaction path is probably not important for imidazole itself owing to the weakly acidic character of this molecule.[5] However, Kirsch and Jencks have demonstrated hydroxide ion catalysis for the imidazole-catalyzed hydrolysis of several esters.[6] In addition, Jencks and co-workers have established general base catalysis, by a second imidazole molecule, for the imidazole-catalyzed hydrolysis of phenyl benzoates and certain phenyl acetates.[6,7] In these reactions, imidazole functions as a nucleophilic catalyst involving the intermediate formation of acyl imidazoles. Evidence presented below strongly suggests that catalysis by imidazole, acting as a general base, rather than nucleophilic, catalyst, is also subject to catalysis by a second imidazole molecule.

In Fig. 1, first-order rate constants for the hydration of *sym*-dichloroacetone[8] at 25° are shown as a function of the concentration of imidazole and N-methylimidazole in 95% dioxane–5% water and 95% dioxane–5% deuterium oxide. In the case of the imidazole-catalyzed reactions, the rate constants increase more rapidly than the concentration of catalyst. Plots (not shown) of $k_{obs}/[Im]$ against [Im] yield good straight lines for the data in both water and deuterium oxide, strongly suggesting the presence of a term in the rate law for this reaction proportional to the first power of imidazole concentration (intercept) and a term proportional to the second power of imidazole concentration (slope). From these plots came the following rate laws.

$$k_{obs}^{H_2O}\ (\text{min.}^{-1}) = 2.36[Im] + 3.55[Im]^2 \quad (1)$$

$$k_{obs}^{D_2O}\ (\text{min.}^{-1}) = 0.84[Im] + 1.40[Im]^2 \quad (2)$$

Curves for imidazole catalysis shown in Fig. 1 are calculated lines based on these rate expressions. In contrast, the rate law for catalysis of *sym*-dichloroacetone hydration by N-methylimidazole, a molecule of basicity similar to that of imidazole, but for which a general base-catalyzed reaction is excluded, shows only a first-order term in catalyst concentration.

$$k_{obs}^{H_2O}\ (\text{min.}^{-1}) = 1.54[Im] \text{ and } k_{obs}^{D_2O}\ (\text{min.}^{-1}) = 0.45[Im]$$

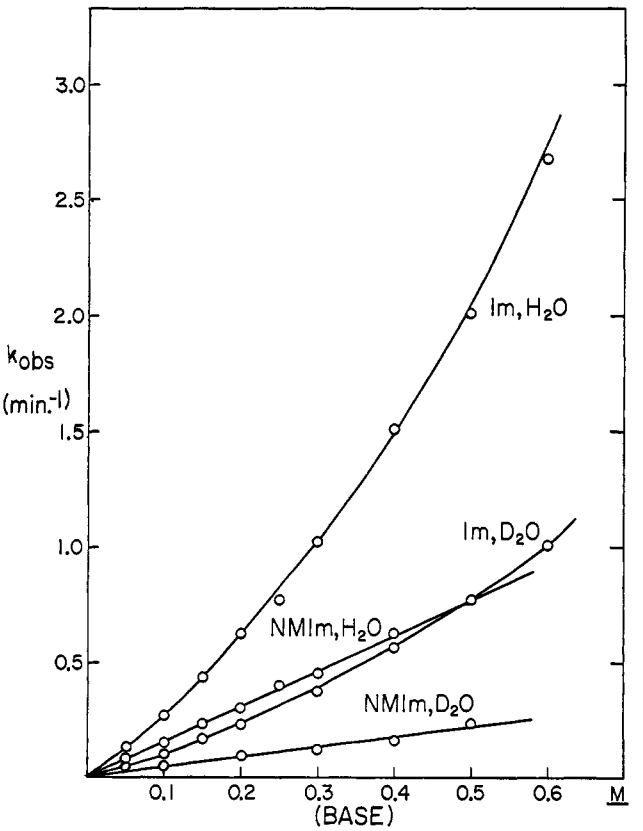
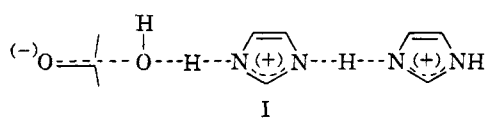



Fig. 1.—First-order rate constants for the hydration of *sym*-dichloroacetone in 95% dioxane–5% water and 95% dioxane–5% deuterium oxide as a function of the concentration of imidazole and N-methylimidazole at 25°. Points are experimental; lines are calculated (see text). Reactions followed spectrophotometrically at 290 mμ; 0.03 *M* *sym*-dichloroacetone.

The term in the rate law for the hydration of *sym*-dichloroacetone which is second order in imidazole concentration may be most simply accounted for in terms of either general base catalysis for general base catalysis of *sym*-dichloroacetone hydration (I) or general base catalysis of water attack on a pre-equilibrium tetrahedral intermediate formed from the imidazole anion



I

and substrate.[9] The second alternative seems unreasonable on chemical grounds since the intermediate should be less reactive than the starting material.[3b] Furthermore, there is no change in the absorption spectrum of *sym*-dichloroacetone on the addition of 1 *M* imidazole to this substrate indicating that, under these conditions, detectable amounts of this intermediate are not formed. In addition, the rate laws for catalysis of this reaction by several other secondary and tertiary amines exhibit only first-order terms in catalyst concentration.[8] The decreased rates of catalysis in deuterium oxide compared to water, $k_H/k_D = 2.8$ for the first-order term and 2.5 for the second-order term, are consistent with transition state I, although it might have been expected that the solvent deuterium isotope effect for the latter term would have been the larger of the two. The solvent deuterium isotope effect for the second-order

(1) Supported by a grant (GB-431) from the National Science Foundation. Contribution No. 1176 from Department of Chemistry, Indiana University.

(2) (a) F. H. Westheimer, *Adv. Enzymology*, **24**, 441 (1962); (b) D. E. Koshland, Jr., *ibid.*, **22**, 45 (1960); (c) E. A. Barnard and W. D. Stein, *ibid.*, **20**, 51 (1958); (d) M. Bender, *Chem. Rev.*, **60**, 53 (1960).

(3) (a) R. Breslow and M. Bender, "Comprehensive Biochemistry," Vol. 2, M. Florkin and E. Stotz, Ed., Elsevier Press, New York, N. Y., 1962, p. 1; (b) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1280 (1959); (c) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961).

(4) T. C. Bruice and G. L. Schmir, *ibid.*, **80**, 148 (1958).

(5) T. C. Bruice and J. J. Bruno, *ibid.*, **84**, 2128 (1962).

(6) J. F. Kirsch and W. P. Jencks, *ibid.*, in press.

(7) M. Caplow and W. P. Jencks, *Biochemistry*, **1**, 883 (1962).

(8) R. P. Bell and M. B. Jensen, *Proc. Roy. Soc.* (London), **A261**, 38 (1961).

(9) A. W. D. Avison, *J. Chem. Soc.*, 732 (1955).

term may be accounted for in terms of transition state I provided one assumes either that, in the transition state, the proton transferred between the imidazole molecules is quite asymmetrically placed[10] or that the position of the proton transferred from water to imidazole in the transition state is altered by the presence of the second imidazole molecule. The strongest evidence in favor of transition state I is the failure to observe a second-order term in the rate law for catalysis by N-methylimidazole. N-Methylimidazole is similar to imidazole in terms of structure and base strength but cannot lose a proton from one nitrogen atom concurrent with the attack of the other. Although other kinetically indistinguishable mechanisms for the reaction involving two imidazole molecules cannot be rigorously excluded, the present evidence strongly suggests that transition state I is correct for this reaction. The imidazole-catalyzed hydration of *sym*-dichloroacetone appears to be the only known case of general base catalysis for general base catalysis.

The fact that reported kinetic runs were carried out in unbuffered solutions raises the possibility of a contribution to the observed rates from a reaction involving hydroxide ion or the imidazole anion, particularly at high imidazole concentrations. The imidazole catalysis data cannot be explained on the basis of concurrent reactions of imidazole and hydroxide ion since no hydroxide ion reaction was observed in the presence of N-methylimidazole, an equally strong base. General base catalysis of imidazole catalysis by either hydroxide ion or the imidazole anion cannot be rigorously excluded although such reactions, in the absence of detectable direct attack of hydroxide ion on the substrate, seem quire unlikely. Furthermore, such reactions should not depend on the square of the imidazole concentration since the concentration of hydroxide ion or the imidazole anion depends, approximately, on the square root of imidazole concentration. Thus the rate law would have contained terms proportional to the first and to the three-halves powers of imidazole concentration. At any event, such reactions would be mechanistically similar to that proposed in I. A second-order term in imidazole concentration is observed in buffered reaction mixtures containing 90% of the imidazole as the free base and 10% as the hydrochloride. This second-order term may, of course, be due to a reaction involving an imidazole–imidazolium ion or its kinetic equivalent. Many such reactions have been observed for the hydration of *sym*-dichloroacetone catalyzed by a variety of acid–base pairs.

Imidazole, in contrast to N-substituted imidazoles, is known to be associated, presumably through hydrogen-bonded structures, in nonpolar media such as benzene, naphthalene, and carbon tetrachloride.[11] This observation raises a question as to the extent of imidazole self-association in 95% aqueous dioxane. Although experimental data concerning this point are not available, the observed rate laws suggest that imidazole is probably not largely associated in this solvent, since, if dimer formation were to approach completion, one would obtain only first-order rate dependence on imidazole concentration. Regardless of the extent of imidazole association, the observation that the first-order rate constants increase more rapidly than imidazole concentration indicates that the imidazole dimer is a more effective catalyst than the monomeric species for this reaction.

(10) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

(11) (a) K. Hofmann, "Imidazole and its Derivatives," part 1, Interscience Publishers, New York, N. Y., 1953, p. 24; (b) D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, *J. Chem. Soc.*, 2165 (1961).

### Experimental

**Materials.**—Imidazole was recrystallized twice from benzene, and N-methylimidazole and *sym*-dichloroacetone were redistilled before use. Dioxane was purified according to the method given by Wiberg.[12] Distilled water was employed throughout. "95% aqueous dioxane solutions" were prepared by diluting 5 volumes of water to 100 volumes with dioxane.

**Kinetic measurements** were carried out spectrophotometrically with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell compartment as previously described.[13] All reactions were carried out at 25°. Rate laws for reactions exhibiting both first- and second-order terms in catalyst concentration were derived from plots of $k_{obs}$/[catalyst] against [catalyst]. The rate coefficient for the first-order term was evaluated from the intercept of such plots at zero catalyst concentration, and the second-order rate coefficients were evaluated from the slopes of these plots.

**Acknowledgment.**—We are indebted to Dr. William P. Jencks, Brandeis University, for communicating his findings concerning base catalysis for imidazole-catalyzed reactions prior to publication.

(12) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Co., New York, N. Y., 1960.

(13) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).

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## The Mechanism of Acid-Catalyzed Methyl Orthobenzoate Hydrolysis[1,2]

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Results of determinations of entropies of activation, volumes of activation, Bunnett's $w$ values, and correlation of hydrolysis rates with the Hammett $H_0$ acidity function, strongly suggest that the acid-catalyzed hydrolysis of formals,[3-6] acetals,[3-7] ketals,[4] and ethyl orthoformate[4,5] does not involve solvent as a nucleophilic reagent in the transition state (A-1). In contrast, Kwart and Price have suggested, principally on the basis of correlation of the rate of hydrolysis of methyl ortho-*p*-nitrobenzoate with a solvent composition–acidity function,[8] that the acid-catalyzed hydrolysis of methyl orthobenzoates, a reaction related to those indicated above, does involve solvent as a nucelophilic reagent in the transition state (A-2).[9] More re-

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(2) Presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963, Abstracts, p. 18Q.

(3) J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).

(4) E. Whalley, *Trans. Faraday Soc.*, **55**, 798, 809 (1959).

(5) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).

(6) M. Kreevoy and R. Taft, Jr., *ibid.*, **77**, 3146 (1955).

(7) D. McIntyre and F. A. Long, *ibid.*, **76**, 3240 (1954).

(8) (a) H. Kwart and L. B. Weisfeld, *ibid.*, **80**, 4670 (1958); (b) H. Kwart and A. Goodman, *ibid.*, **82**, 1947 (1960).

(9) H. Kwart and M. Price, *ibid.*, **82**, 5123 (1960).