attack. 6-APA in frozen solutions undergoes an autocatalytic hydrolysis of the β-lactam, probably owing to availability of the nucleophilic amino group.

That imidazole attack in the frozen state is not limited to a β-lactam structure is demonstrated by experiments with trypsin as substrate. In 42 hours at $-18°$, 80% of the tryptic activity[2] was lost, while at $-7°$ or in the absence of imidazole at $-18°$, no loss occurred.

Penicillin hydrolysis rate and extent were independent of freezing rate. For example, after rapid freezing to $-78°$, systems warmed to and stored at $-18°$ showed 78% penicillin destruction with imidazole and 38% destruction with pH 9.9 borate. Splitting was not influenced by the degree of stirring during freezing or by the container shape and dimensions.

When solid and liquid phases in equilibrium at $-2°$ were separated and assayed, imidazole and control penicillin concentrations changed by less than 10% from their initial concentrations; subsequent storage of the solid at $-2°$ led to as much as 77% hydrolysis while storage of the liquid at both $-2°$ (unfrozen) and $+22°$ gave no hydrolysis. Glycerol, ethanol, and acetone, at 5–10% by volume, all abolished imidazole-catalyzed hydrolysis in the frozen state at temperatures within the optimal range for controls, although these agents gave little or no protection to the β-lactam during lengthy storage at $22°$ in the absence of imidazole. With several substrates and imidazole-β-lactam concentration ratios, hydrolysis in frozen solutions was inhibited by Na^+ in proportion to its concentration (74% inhibition with penicillin G and 0.3 M NaCl), while the K^+ effect was far smaller and more dependent upon the imidazole concentration. This difference may result from the fact that Na^+, surrounded by a larger hydrate envelope than K^+, probably is more capable of disrupting ordered water structures.[3] Further experiments on structure forming and breaking solutes,[4] undertaken because of possible significance of crystal lattice order and dielectric properties of ice, showed inhibition of the hydrolysis by 10% formamide and no influence by NaI, $MgCl_2$, $CaCl_2$, or EDTA at 10^{-3} M, by NaCl, KCl, $NaNO_3$, NaBr, LiBr, or KSCN at 10^{-2} M, or by urea at 8 M.

In attempts to determine whether the effect was from local concentration of the reactants on freezing, we studied the distribution of reactants in several ways, including the sectioning and assaying of solutions frozen from one end of capillaries; no evidence for local concentration was observed. These and a number of the experiments outlined make doubtful, but do not completely exclude, concentration effects as the basis for the hydrolysis observed.

The marked increase in efficiency in going from bimolecular to intramolecular to enzymatic catalysis has stressed the importance of spatial orientation.[5,6] The freezing effect in the present

(2) M. L. Anson, *J. Gen. Physiol.*, **22**, 79 (1938).

(3) H. S. Frank and W. Wen, *Discussions Faraday Soc.*, **24**, 133(1957).

(4) J. D. Bernal and R. H. Fowler, *J. Chem. Phys.*, **1**, 515 (1933).

(5) G. L. Schmir and T. C. Bruice, *J. Am. Chem. Soc.*, **80**, 1173 (1958).

(6) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

experiments suggests the possible imposition of a favorable substrate-catalyst positional constraint. In addition, the exceptionally high proton mobility in ice[7] may facilitate fast proton transfer in either nucleophilic or general base catalysis of β-lactam cleavage. Recent studies have suggested that ice-like water structures containing "cavities" may provide biological systems with fast proton transport mechanisms.[8]

(7) M. Eigen and L. DeMaeyer, *Proc. Roy. Soc. (London)*, **247A**, 505 (1958).

(8) H. Fernandez-Moran, "Abstracts of Lectures on Fast Fundamental Transfer Process," M.I.T., Cambridge, Spring, 1960, pp. 26 and 33.

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ORGANOMERCURIALS. VIII. MERCURY AS THE LEAVING GROUP IN SOLVOLYSIS REACTIONS[1]

Sir:

In our studies of the stereochemistry of the electrophilic cleavage of organomercurials by acids, it was noted that the alkylmercuric salts produced in the reaction undergo decomposition in a solvolytic type reaction.[2] This decomposition reaction has been described by Winstein and Traylor[3] as "oxidation of the solvent," by Robson and Wright[4] to be "classed as auto oxidation of an alkylmercuric salt" since it doesn't require inorganic salt, and by Ichikawa and Ouchi[5] to occur by direct attack of the nucleophile on the ionized alkylmercuric salt. Robson and Wright[4] reported that the alkyl group is converted only to olefin and that the reaction is "not entirely a general one...as we have been unable yet to oxidize a primary alkylmercuric salt." The present communication reports the stoichiometry and the mechanism of the reaction.

The reaction has been found to be general for all alkyl groups thus far studied. In each instance, the only products are those expected for a solvolytic reaction.

$$RHgY + HS \longrightarrow HY + Hg + RS + olefin$$
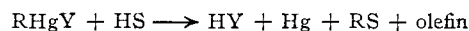
Cyclohexylmercuric acetate in acetic acid reacts slowly by first order kinetics to give only olefin, alkyl acetate and mercury. If a catalytic amount of perchloric acid is added, a fast pseudo zero order reaction occurs whose rate constants are proportional to the concentration of acid added. When an equimolar amount of perchloric acid is added, a fast first order reaction results whose rate constant is equal to the first order rate constant obtained by dividing the zero order rate constant by the concentration of acid in those cases where a catalytic

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.
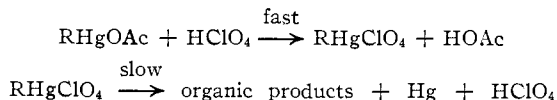
(2) L. H. Gale, F. R. Jensen and J. A. Landgrebe, *Chem. and Ind.* (London), 118 (1960).

(3) S. Winstein and T. G. Traylor, *J. Am. Chem. Soc.*, **77**, 3748 (1955).

(4) J. H. Robson and G. F. Wright, *Can. J. Chem.*, **38**, 21 (1960). These workers have also classed the reaction as possibly being a free radical or solvolysis reaction.

(5) K. Ichikawa and H. Ouchi, *J. Am. Chem. Soc.*, **82**, 3876 (1960).

quantity of acid had been added. Indicator studies have shown that when perchloric acid is added to cyclohexylmercuric acetate in acetic acid an instantaneous reaction occurs which eliminates the free acid. The only scheme that can accommodate these facts is

$$RHgOAc + HClO_4 \xrightarrow{\text{fast}} RHgClO_4 + HOAc$$

$$RHgClO_4 \xrightarrow{\text{slow}} \text{organic products} + Hg + HClO_4$$

The fact that at the completion of the reaction all the acid had been regenerated is considered conclusive evidence for the scheme.

This method allows the conversion of alkylmercuric acetates to other more ionic salts in solution. The high reactivity of these salts and the influence of the solvent on their stability by coördination, which will be discussed in later papers, does not readily permit their isolation except in the case of primary alkyl mercuric salts.

The effect of the anion on the rate of solvolysis indicates that the rate parallels the expected ionization of the salt (Table I). The free energy of

TABLE I

REACTION PARAMETERS FOR THE SOLVOLYSIS OF CYCLO-HEXYLMERCURIC SALTS IN ACETIC ACID SOLUTION AT 25°

Anion	ΔH^*, kcal./mole	ΔS^*, e.u.	ΔF^*, kcal./ mole	k_{rel}.
ClO_4^-	25.3 ± 0.4	10.9 ± 0.9	22.1	1
BF_4^-	$24.5 \pm .2$	$5.0 \pm .5$	23.0	0.193
OTs^-	$25.1 \pm .1$	$3.7 \pm .3$	24.0	0.037
OAc^-	$27.8 \pm .3$	-3.2 ± 1.0	28.8	1.44×10^{-5}
Br^-	Rate too slow to measure.			

activation for the oxygen-containing compounds parallels the ionization of the corresponding acids in acetic acid.[6] The products of the reaction, $89.5 \pm 1.3\%$ cyclohexene and $10.5 \pm 1.3\%$ alkyl acetate, are independent of the nature of the anion.

Although these results prompted the consideration of a number of possible mechanisms, the simplest involves ionization of salt followed by the cation losing mercury to form a carbonium ion.

$$RHgY \rightleftarrows RHg^+ + Y^-$$

$$RHg^+ \longrightarrow R^+ + Hg^0$$

$$R^+ + HS \longrightarrow RS + \text{olefin} + H^+$$
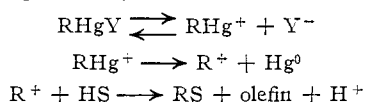
To test this carbonium ion mechanism, studies in water were carried out. The acetates are partially ionized in aqueous solution according to the equation

$$RHgOAc \underset{}{\overset{K}{\rightleftarrows}} RHg^+ + OAc^-$$
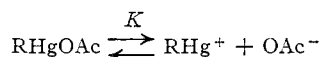
The solvolysis of cyclohexylmercuric acetate follows the expression

$$\text{d product}/\text{d}t = k[RHg^+]$$

The rate data were treated by a complete analytical expression and exhibited the expected dependence on concentration. With added acetate ion, the rate expression becomes

$$\frac{\text{d product}}{\text{d}t} = k[RHg^+] = kK \frac{[RHgOAc]}{[^-OAc]}$$

(6) S. Bruckenstein and I. M. Kolthoff, *J. Am. Chem. Soc.*, **78**, 2974 (1956).

The value for the equilibrium constant for cyclohexylmercuric acetate agrees within a factor of two with that obtained by calculation of an equilibrium constant from conductivity data for methylmercuric acetate.[7] Since the alkylmercuric perchlorates are almost completely ionized in water solution, their solvolysis follows the expression

$$\text{d product}/\text{d}t = k[RHg^+] \text{ and } [RHg^+] = [RHgClO_4]$$

In water solution, the solvolysis of cyclohexylmercuric tosylate gives the same kinetics and rate constant as the perchlorate. Of the mechanisms considered, these results are consistent only with the reaction scheme proposed above. Also, over a range of conditions no evidence was found that RHgY directly undergoes reaction.

Extension of this work to a large variety of solvents and alkyl groups has shown this reaction to be entirely general.

Experimental.—The reactions were carried out in most instances at concentrations of 0.02 M. The alkyl mercuric perchlorates, tosylates and tetrafluoroborates usually were prepared by adding a stoichiometric amount of the corresponding acid to the alkylmercuric acetate and therefore some of the reactions contained about 0.04 M water. Excess acid and water in small amounts had no effect on the rate of reaction.

The reactions were followed by three methods. The alkylmercuric acetates were in some instances treated with bromine ion and the resulting acetate ion titrated with acid. Other alkylmercuric salts were followed by determining the amount of acid generated if the reaction was carried out in a solvent where a convenient indicator system could be devised. The concentration of alkylmercuric salt in some instances was followed by titration with thiocyanate ion by conventional means. The various methods gave identical results. In the case of extremely fast rates, the reaction was quenched with thiocyanate ion and the excess back-titrated with silver ion.

(7) J. L. Maynard and H. C. Howard, *J. Chem. Soc.*, **123**, 960 (1922).

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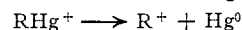BERKELEY 4, CALIFORNIA   ROBERT J. OUELLETTE
         RECEIVED SEPTEMBER 20, 1961

ORGANOMERCURIALS. IX. THE NATURE OF THE CARBONIUM IONS FORMED IN THE SOLVOLYSIS OF ORGANOMERCURIALS[1]

Sir:

In a previous paper,[2] it was demonstrated that alkylmercuric ions undergo solvolysis reactions in which mercury serves as the leaving group.

$$RHg^+ \longrightarrow R^+ + Hg^0$$

This reaction provides a valuable new system for studying solvolytic reactions. Evidence is given in the present paper which indicates that this reaction is less susceptible to nucleophilic attack on carbon than any reaction previously investi-

(2) F. R. Jensen and R. J. Ouellette, *J. Am. Chem. Soc.*, **83**, 4477 (1961).