Procedure A.—Upon removal from the constant temperature bath, the tubes were extracted with three 8-ml. portions of demineralized water. The combined aqueous extracts were acidified with dilute nitric acid, neutralized with 5% sodium bicarbonate solution, and titrated with 0.010 *N* silver nitrate solution, using the Mohr method. A 1.0-ml. aliquot was withdrawn from the dried ($MgSO_4$) organic layer and diluted with cyclohexane for ultraviolet analysis. The remaining organic portion was extracted with three 5-ml. portions of Claisen alkali and two 5-ml. portions of water, concentrated, and examined in the infrared to determine the dienone ether ratio.

Procedure B.—Upon removal from the constant temperature bath, each tube was extracted with three 10-ml. portions of demineralized water. The combined aqueous extracts were neutralized in the manner previously described and titrated with 0.10 *N* silver nitrate solution. The organic layer was extracted with three 10-ml. portions of Claisen alkali and washed with two 10-ml. portions of water. From the dried neutral layer ($MgSO_4$) was withdrawn 1.0 ml. which was diluted with cyclohexane for ultraviolet analysis. An additional 10 ml. was concentrated and used for quantitative infrared analysis.

It was demonstrated that reactions after slowing down at a late stage still contained 4-*t*-butyl-2,6-dimethylphenol, presumably as the sodium salt. The phenol could be determined quantitatively in a synthetic mixture with toluene and benzyl chloride by extraction with Claisen alkali and examination of the ultraviolet absorption at 282 mμ (λ_{max} for the phenol). Using this method with a mixture 8.35 *M* gave a value of 8.56×10^{-4} *M*. Using this method a reaction which had been found by chloride titration to have proceeded 80.7% to completion was shown by extraction and ultraviolet analysis to contain 19% of unreacted phenol, and a reaction which had gone 75.9% to completion contained 18% of starting phenol.

Rate of Alkylation of Sodium 4-*t*-Butyl-2,6-dimethylphenoxide (I) in the Presence of Tetrabutylammonium Bromide.—To 0.7265 g. (3.63×10^{-4} mole) of the sodium salt I and 0.0584 g. (1.81×10^{-4} mole, 5.0% of the stoichiometric amount) of the ammonium salt was added 5.74 ml. of tetrahydrofuran (5.7% of final volume) and 95.5 ml. of toluene (under nitrogen, with stirring), followed by 1.06 g. (8.38×10^{-4} mole, 2.3-fold excess) of benzyl chloride. Five combustion tubes were filled in a dry-box under nitrogen with 15.0-ml. aliquots of this solution (the addition of toluene to the solution of the two salts in tetrahydrofuran caused some cloudiness) and immediately placed in a constant temperature bath at 109.8 ± 0.1°.

Upon removal from the bath, halide ion was removed by extraction, Claisen's alkali was used to remove acidic products, and the neutral fraction was concentrated prior to infrared analysis to determine the dienone:ether ratio. The results are summarized in Table VII.

TABLE VII

RATE OF ALKYLATION OF SODIUM 4-*t*-BUTYL-2,6-DIMETHYLPHENOXIDE IN 5.6% TETRAHYDROFURAN IN TOLUENE IN PRESENCE OF TETRABUTYLAMMONIUM BROMIDE AT 109.8 ± 0.1°

Time, sec. $\times 10^{-4}$	0.100 *N* $AgNO_3$, ml.	% compl.	k,[a] l./mole sec. $\times 10^{+4}$	Dienone ether (i.r.)
0.061	1.49	22.9	53	0.06
.24	1.91	30.8	20	.18
.46	2.05	33.4	11	.23
1.73	2.76	46.7	4.9	.29
4.26	3.57	61.9	3.2	.40

[a] Assuming chloride ion to be formed in a second-order reaction.

Light Scattering by the Reaction Mixtures for the Alkylations in Toluene and Tetrahydrofuran.—The absorbance of each of the reaction mixtures, with varying amounts of tetrahydrofuran in toluene, was measured (at room temperature, prior to reaction) in the visible spectrum from 800 to 600 mμ using toluene or a blank reaction mixture (all of the components except the sodium salt) in the reference cell (the same reading was obtained each way). The reaction mixtures with 5.6 and 16.4% tetrahydrofuran showed absorbances at 750 mμ of only 0.003. That with 1.3% had an absorbance of 0.032 and that with 0.84% tetrahydrofuran 0.076.

[CONTRIBUTION NO. 133 FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

The Solvolysis of 1-Acetylimidazole in Concentrated Acid and Salt Solutions

BY STEPHEN MARBURG AND WILLIAM P. JENCKS

RECEIVED JULY 17, 1961

The rates of solvolysis of 1-acetylimidazole in acid solutions, in which it is completely converted to its conjugate acid, and of 1-acetyl-3-methylimidazolium cation are decreased by added concentrated salts and acids, with the exception of F^- and $SO_4^=$. In the case of $NaClO_4$ the logarithm of the rate is proportional to the salt concentration over a 500-fold range of rate variation. Widely different effects are found with different salts and acids, and the results cannot be correlated with simple functions of a_{H_2O} or C_{H^+} and h_0. The order of rate-decreasing effectiveness is $ClO_4^- > OTs^- > Br^- > Cl^- \sim NO_3^- > SO_4^= > F^-$ and $La^{+++} \sim Mg^{++} \sim Ca^{++} > Li^+ \sim Na^+ \sim K^+ > Cs^+ \sim NH_4^+ \sim (CH_3)_4N^+ \sim$ imidazolium$^+ \sim H^+$. It is concluded that, although the observed rate decreases undoubtedly reflect the decreased availability of water in concentrated electrolyte solutions, large influences of other factors on the substrate and transition state must be considered in any quantitative treatment of such reactions.

The remarkably high protonating ability of moderately concentrated aqueous solutions of strong acids may be in large part accounted for in terms of equilibrium (1) by the decrease in the availability of water in such solutions, without invoking

$$H(H_2O)_4^+ + B \rightleftarrows BH^+ + 4H_2O \qquad (1)$$

major activity coefficient effects.[1] The high protonating ability of acids in certain concentrated salt solutions may be explained in part in a similar manner, since electrolyte hydration will also decrease water availability, and in part by salting out of the free base by concentrated salt.[2,3] If protonation of a substrate, S, shows activity coefficient behavior similar to that of an indicator, B, a reaction of SH^+ that does not involve addition or loss of water in the transition state will generally follow the acidity function, h_0. A reaction that does require water will generally increase in rate less rapidly than h_0 because of the decreased availability of water in concentrated acid solutions.[4] If only one molecule of water is required and if activity coefficient effects are small, such a reaction might be expected to follow $h_0a_{H_2O}$. Surprisingly, a num-

---

(1) K. N. Bascombe and R. P. Bell, *Disc. Faraday Soc.*, **24**, 158 (1957).

(2) M. A. Paul, *J. Am. Chem. Soc.*, **76**, 3236 (1954).

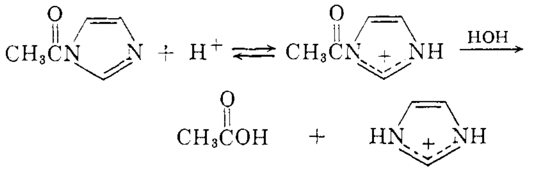
(3) F. A. Long and D. McIntyre, *ibid.*, **76**, 3243 (1954).

ber of such reactions follow the concentration of solvated protons, C_{H^+}, rather than $h_0 a_{H_2O}$, over a considerable concentration range and thus follow the Zucker–Hammett hypothesis.[4,5] Such behavior may be explained in terms of either (i) a cancelling of certain activity coefficient terms in the Brönsted rate equation[5,6] or (ii) a cancelling of most of the increase in h_0 by a decrease in $a_{H_2O}{}^u$, corresponding to a requirement for several (u) more molecules of water in the transition state than are bound to the substrate.[7–10] The rate of a reaction of this type, which follows C_{H^+} when only a small fraction of the substrate is protonated, must decrease with increasing acidity according to eq. 2 when the substrate is completely protonated, since

$$\text{rate} = kC_S C_{H^+} = kKC_{SH^+}C_{H^+}/h_0 \qquad (2)$$

h_0 increases faster than C_{H^+} in concentrated acid solutions. This apparently surprising result follows directly from the statement that the reaction follows C_{H^+} (with only a small fraction of the substate protonated) and the relation $h_0 = KC_{SH^+}/C_S$, without any further assumptions regarding activity coefficients. There are several examples of reactions, such as the hydrolysis of fully-protonated amides, which decrease in rate in concentrated acid solution and follow this relationship more or less closely.[11–16]

The experiments reported here were carried out in an attempt to determine the extent to which the rate of a reaction of this type in concentrated acid and salt solutions can be accounted for by changes in the activity of water or the acidity function. The reaction studied was the acid-catalyzed hydrolysis of the heterocyclic amide, acetylimidazole (eq. 3). Since the conjugate acid of this compound, acetylimidazolium cation ($AcImH^+$), has a pK_a of 3.6, the substrate was completely protonated under the conditions of the experiments so that the degree of substrate protonation is not a variable. It has been shown previously that the rate of hydrolysis of $AcImH^+$ is markedly decreased by salts and that concentrated $NaClO_4$ has a greater rate-decreasing effect than $HClO_4$.[17] Although experiments carried out under conditions of complete substrate protonation have the advantage that the degree of protonation and activity coefficient changes of the free substrate are eliminated as variables, it should be borne in mind that the observed activity coefficient effects will be different from those observed when only a small fraction of the substrate is protonated. Nevertheless, we suggest that the results and conclusions reported here will apply with some generality to a number of reactions involving the addition of water to the carbonyl group and/or proton transfer in the transition state.



(3)

Experimental

Reagent grade inorganic salts and acids were used without further purification. Reagent grade sodium toluenesulfonate was dried to constant weight before use. Solutions of halides and acids were standardized by titration with $AgNO_3$ and base, respectively. Acetonitrile was distilled from P_2O_5 before use. Acetylimidazole was prepared by the method of Boyer.[18] 1-Acetyl-3-methylimidazolium chloride was prepared from acetyl chloride and N-methylimidazole.[19] Benzoylimidazole and *p*-methoxybenzoylimidazole were kindly supplied by Michael Caplow. D_2O, 99.9%, was obtained from Bio-Rad Laboratories, Richmond, Calif. $Li_2SO_4.H_2O$ was dissolved in D_2O, evaporated to dryness and redissolved in D_2O prior to the appropriate experiments. Water and D_2O were glass-distilled before use.

The hydrolysis of acetylimidazole at 25 ± 0.05° was followed spectrophotometrically by measurement of the change in absorption at 245 mμ with a Zeiss PMQ II spectrophotometer equipped with a thermostated cell compartment. The salt or acid solution was brought to temperature equilibrium and a freshly prepared solution of acetylimidazole (0.05 ml , 0.02 *M*) was introduced with a micropipet. Adequate mixing was obtained by blowing air through the solution for 5 seconds. Reactions in concentrated acid solution were carried out in cuvettes snugly fitted into a hollow brass block, through which water at 25° was circulated. A transient rise in temperature (about 1°) occurred on addition of substrate to the more concentrated sulfuric and perchloric acid solutions, but rate constants were calculated from readings obtained as the temperature returned to 25° and it was estimated that the possible error due to temperature changes in these experiments is less than 3%.

Reactions in which ultraviolet absorption of the salt interfered with the above procedure were followed by determination of unreacted acetylimidazole by the method of Lipmann and Tuttle.[17] The reaction was initiated by pipetting a freshly prepared solution of acetylimidazole (0.20 ml., 1.0 *M*) into a thermally pre-equilibrated salt or acid solution (5.80 ml.) and mixing as above. Samples (0.2 ml.) were taken at 5- second intervals with a 1-cc. syringe and quenched by immersing the tip of the needle under the surface of the hydroxylamine solution contained in a 10-ml. beaker. The needle was wiped with a tissue before and after quenching. Rate constants obtained by this method were shown to be

---

[4] F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1957).

[5] L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).

[6] (a) N. C. Deno and C. Perizzolo, *ibid.*, **79**, 1345 (1957). (b) N. C. Deno, H. E. Berkheimer, W. L. Evans and H. J. Peterson, *ibid.* **81**, 2344 (1959).

[7] J. F. Bunnett, *ibid.*, **82**, 499 (1960).

[8] J. A. Leisten, *Chemistry & Industry*, 397 (1959); *cf.* also L. Melander and P. C. Myhre, *Arkiv. Kemi*, **13**, 507 (1959).

[9] K. J. Pedersen, *Acta Chem. Scand.*, **14**, 1448 (1960).

[10] Zucker and Hammett[5] suggested that for a reaction to follow C_{H^+} it is necessary for the ratio $f_S f_{H_3O^+}/f^{\ddagger}$ to remain constant, and that this may be approximately true if the solvated proton and the transition state each contain one molecule of water and are thus similar in structure and activity coefficient behavior. This condition might be restated today in terms of a solvated proton and transition state that each contain several (*e.g.*, 4) molecules of water; the resulting activity coefficient term ($f_S f_{H^+\text{solv}} a^u_{H_2O}/f^{\pm} a^n_{H_2O}$, where $f_{H^+\text{solv}}$ refers to the solvated proton according to eq. 1), may remain constant when the numbers u and n are approximately the same for the proton and the transition state. We prefer the noncommittal notation H^+ or H^+solv for the solvated proton, since H_3O^+ is probably not the predominant species in dilute and moderately concentrated acid solutions, and the use of H_3O^+ may be misleading if structural significance is attached to the formula.

[11] V. K. Krieble and K. A. Holst, *J. Am. Chem. Soc.*, **60**, 2976 (1938).

[12] J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000, 2009 (1957).

[13] D. Rosenthal and T. I. Taylor, *J. Am. Chem. Soc.*, **79**, 2684 (1957).

[14] J. A. Leisten, *J. Chem. Soc.*, 765 (1959).

[15] R. H. DeWolfe, *J. Am. Chem. Soc.*, **82**, 1585 (1960).

[16] H. Burkett, W. M. Schubert, F. Schultz, R. B. Murphy and R. Talbott, *ibid.*, **81**, 3923 (1959).

[17] W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272 (1959).

[18] J. H. Boyer, in "Biochemical Preparations," Vol. 4, W. W. Westerfield, editor, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 54.

[19] R. Wolfenden and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4390 (1961).

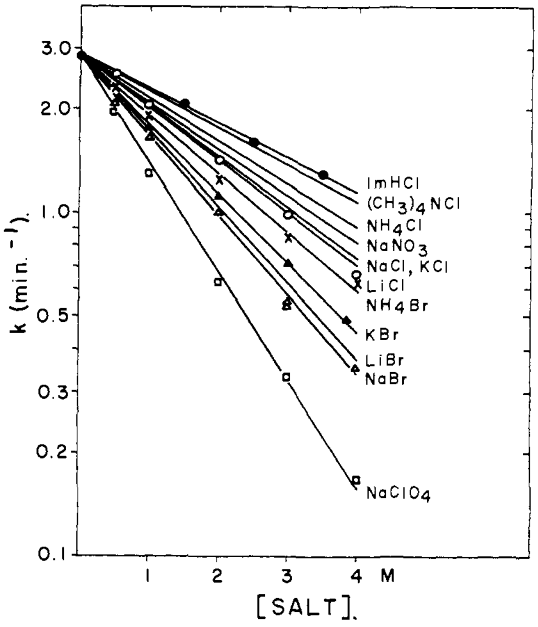


Fig. 1.—Plots of log *k* for the hydrolysis of acetylimidazole in solutions of salts at 25.0°. All solutions contained 0.1 *M* HCl.

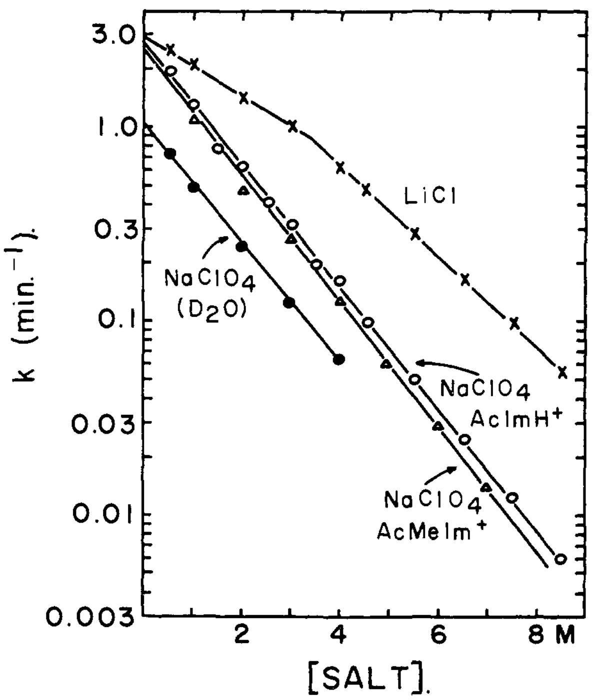


Fig. 2.—Plots of log *k* for the hydrolysis of acetylimidazole (in 0.1 *M* HCl) and 1-acetyl-3-methylimidazolium chloride in solutions of salts up to 8.5 *M* and in D_2O, at 25.0°.

identical to those obtained by the spectrophotometric method for a series of runs in NaCl solutions. In the case of acid solutions, enough NaOH was added to the quench solution to neutralize any excess acid. The hydrolysis of 1-acetyl-3-methylimidazolium chloride was initiated by adding about 1 mg. of the solid material to a solution of salt or acid in a cuvette in the spectrophotometer compartment. Mixing was accomplished by stirring with a plastic rod and the decrease in absorption at 245 mμ was observed as a function of time.

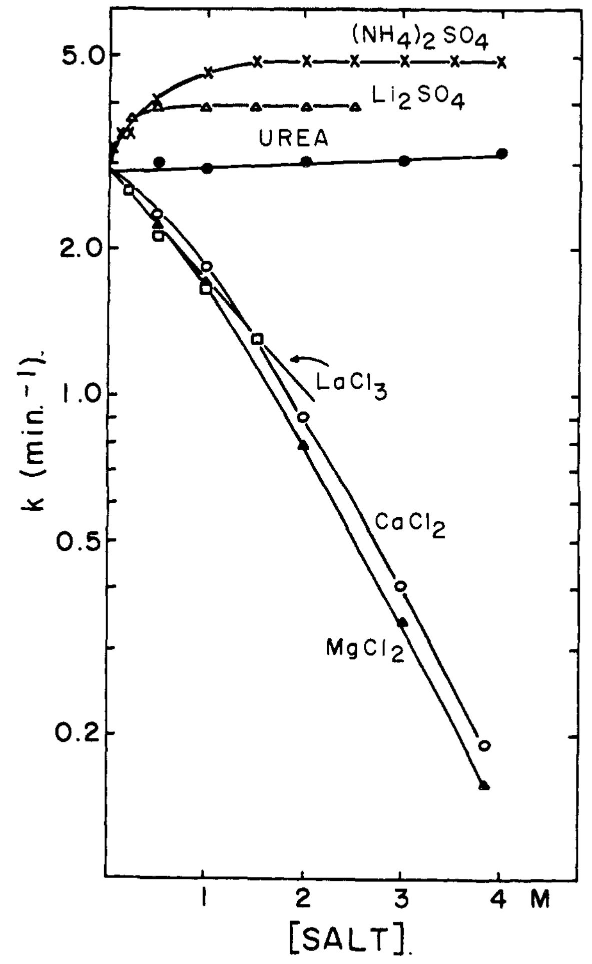


Fig. 3.—Plots of log *k* for the hydrolysis of acetylimidazole at 25.0° in solutions of polyvalent ions and urea in 0.1 *M* HCl. The data for Li_2SO_4 and $(NH_4)_2SO_4$ refer to the solvolysis of 1-acetyl-3-methylimidazolium chloride.

The rates of hydrolysis of benzoylimidazole and *p*-methoxybenzoylimidazole were determined after the addition of 0.01 ml. of an acetonitrile solution of acylimidazole (9 mg./ml. and 2.5 mg./ml., respectively) to HCl (3.5 ml.) by following the decrease in absorption at 250 mμ, for benzoylimidazole, and at 284 mμ, for *p*-methoxybenzoylimidazole.

Rate constants were obtained by plotting the absorption due to remaining acylimidazole, $A_t - A_\infty$, against time on semi-logarithmic graph paper. First-order rate constants were calculated from the equation $k = 0.693/t_{1/2}$. Values of a_{H_2O} were obtained from Robinson and Stokes or calculated from the osmotic coefficients given by the same authors.[20] Values of H_0 were taken from Paul and Long[21] and values of C_{H^+} for H_2SO_4 solutions from the data of Young, Maranville and Smith.[22]

Imidazole was shown to be the product of the solvolysis of acetylimidazole in 8 *M* HCl by quantitative analysis of the reaction mixture after ten half-times by the diazo-coupling procedure of Macpherson.[23] The expected yield of imidazole was obtained from each of four different concentrations of acetylimidazole. To rule out a conversion of acetylimidazole in concentrated acid to some other product, which might undergo a change in absorption at 245 mμ at a rate different from that of acetylimidazole, a solution of acetylimidazole

---

[20] R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworths Scientific Publications, London, 1955.

[21] M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957).

[22] T. F. Young, L. F. Maranville and H. M. Smith, in "The Structure of Electrolyte Solutions," W. J. Hamer, editor, John Wiley and Sons, Inc., New York, N. Y., 1959, p. 51.

[23] H. J. Macpherson, *Biochem. J.*, **36**, 59 (1942).

was allowed to stand in 12 M $HClO_4$ for 32 minutes, then diluted with cold water to give a 4.67 M acid solution and brought to 25°. Acetylimidazole subjected to this treatment disappeared at the same rate as a control which was not treated with concentrated acid.

Results

The effects of increasing concentrations of salts and acids on the rates of solvolysis of acetylimidazolium ($AcImH^+$) and of 1-acetyl-3-methylimidazolium ($AcMeIm^+$) cations are shown in Figs. 1–4. The effects of salts on acetylimidazole solvolysis were studied in the presence of 0.1 M HCl, in which this compound is completely converted to its conjugate acid.[17] Representative experimental points are given for some of the curves in Fig. 1; in other cases the complete data are reported. The slopes, A, of plots of the logarithm of the rate constants against electrolyte concentration, are summarized

$$\log k = A[\text{electrolyte}] + C$$

in Tables I and II. For singly charged electrolytes, such plots are linear, within experimental error, up to a concentration of 4 M. For doubly charged salts the plots are curved, and for acids they exhibit one or more changes in slope in concentrated solutions; in these cases the initial slopes are given. Urea has almost no effect on the rate of acetylimidazolium solvolysis (Fig. 3).

TABLE I

EFFECT OF CONCENTRATED SALTS ON THE RATE OF HYDROLYSIS OF ACETYLIMIDAZOLE IN 0.1 M HCl AT 25.0°

Salt	$-A^a$	Number of points	Max. concn., M
LiCl	0.156[b]	5	8.5
NaCl	.150	5	3.84
KCl	.150	5	3.84
$(CH_3)_4NCl$	.105	5	4.0
CsCl	.110	3	1.85
NH_4Cl	.124	5	4.0
$CaCl_2$	.20[b]	5	3.84
$MgCl_2$	.23[b]	5	3.84
ImHCl[c]	.097	4	3.50
LiBr	.227	5	4.0
NaBr	.235	5	4.0
KBr	.196	5	3.84
NH_4Br	.176	5	4.0
$NaClO_4$	.301	8	8.5
$NaNO_3$[d]	.141	5	4.0
NaOTs[d,e]	.240	9	2.0
$LaCl_3$	.237	4	1.5

[a] $\log k = A[\text{salt}] + C$. [b] Initial slopes. [c] Imidazole HCl. [d] Followed by the hydroxamic acid method. [e] Sodium toluenesulfonate.

TABLE II

EFFECT OF CONCENTRATED ACIDS ON THE RATE OF HYDROLYSIS OF ACETYLIMIDAZOLE AT 25.0°

Acid	$-A^a$	Number of points	Max. concn., M
HBr	0.210	10	7.30
HCl	.090	13	11.85
H_2SO_4	.107	14	12.75
$HClO_4$	.353	19	11.17
CH_3SO_3H	.100	10	10.02
TsOH[b]	.205	9	4.00

[a] Initial slope. [b] Toluene sulfonic acid; followed by the hydroxamic acid method.

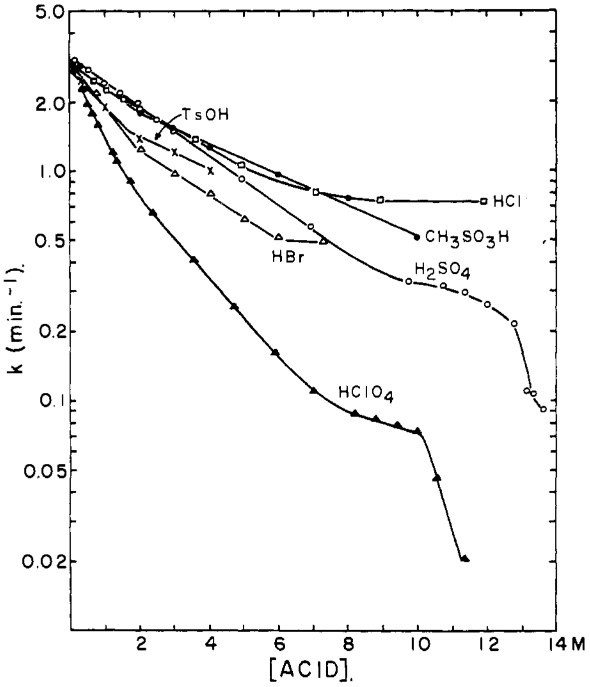


Fig. 4.—Plots of log k for the hydrolysis of acetylimidazole in solutions of various acids at 25.0°.

The effect of $NaClO_4$ on the rate of hydrolysis of $AcMeIm^+$, a model for the conjugate acid of imidazole ($AcImH^+$),[19] is almost identical to that for $AcImH^+$ (Fig. 2). Similar results were obtained for NaCl, up to 4 M, and $HClO_4$, up to 9 M.

The rate of disappearance of $AcMeIm^+$ is increased by potassium fluoride, ammonium sulfate and lithium sulfate (Fig. 3 and Table III). The increase observed with ammonium sulfate is not due to a reaction with ammonia, since at a 2 M concentration of salt, a change in pH from 2.8 to 3.9, which causes more than a tenfold increase in the concentration of free ammonia, was found to cause less than a 10% increase in rate. The experiments with potassium fluoride were carried out with solutions which had been 10% neutralized with HCl; an increase in the percentage of neutraliza-

TABLE III

SOLVENT DEUTERIUM ISOTOPE EFFECTS ON $AcImH^+$ AND $AcMeIm^+$ SOLVOLYSIS AT 25.0°

		k_{H_2O}, min.⁻¹	k_{D_2O}, min.⁻¹	k_{H_2O}/k_{D_2O}
Control[a] ($AcImH^+$)		2.88	1.21	2.5
Control[a,b] ($AcMeIm^+$)		2.80	1.08	2.6
$NaClO_4$[a]	1.0 M($AcImH^+$)	1.30	0.480	2.7
	2.0 M	0.62	0.244	2.6
	3.0 M	0.33	.122	2.7
NaCl[a]	1.0 M ($AcImH^+$)	2.08	.86	2.4
	2.0 M	1.46	.58	2.5
Li_2SO_4	0.1 M($AcMeIm^+$)	3.51	1.43	2.5
	0.5 M	3.96	1.81	2.2
	1.5 M	3.96	1.97	2.0
	2.5 M	3.96	1.92	2.1
KF[c]	0.1 M($AcMeIm^+$)	5.75	2.77	2.1
	0.2 M	8.05	4.55	1.8

[a] In 0.1 M HCl (or DCl). [b] Ref. 19. [c] 10% neutralized with HCl (or DCl).

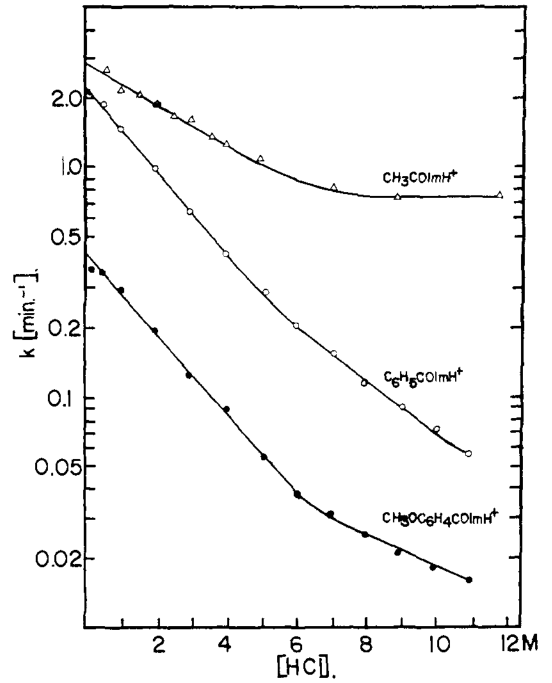


Fig. 5.—Plots of log k for the hydrolysis of various acylimidazoles in HCl at 25.0°. The benzoylimidazole experiments were carried out in solutions containing 0.3% acetonitrile.

tion from 10 to 20% resulted in a decrease in the observed rate from 5.8 to 5.3 min.$^{-1}$.

In concentrated HCl solutions the rate of acetylimidazole disappearance is independent of the concentration of HCl (Fig. 4). Addition of 2 M LiCl to 9 M HCl was found to cause a relatively small further decrease in rate constant, from 0.82 to 0.67 min.$^{-1}$; this is a much smaller decrease than is observed on the addition of LiCl to dilute HCl solutions (Fig. 1).

The effects of increasing concentrations of HCl on the rates of hydrolysis of benzoylimidazole, p-methoxybenzoylimidazole and acetylimidazole are compared in Fig. 5. The rate-decreasing effect is larger for the benzoylimidazoles (A = −0.174 for the two former compounds, compared to −0.090 for AcImH$^+$) and the leveling off at high acid concentrations is less marked, although the breaks in the curves occur at approximately the same acid concentration, 6.4 M.

The solvent deuterium isotope effects on the rates of AcImH$^+$ and AcMeIm$^+$ solvolysis in the presence of NaClO$_4$, NaCl, Li$_2$SO$_4$ and KF are reported in Table III.

Imidazole is a product of the solvolysis of AcImH$^+$ in 8 M HCl and brief treatment with 12 M HClO$_4$ does not convert AcImH$^+$ to a slower-reacting compound (see Experimental). The ultraviolet spectrum of AcImH$^+$ has an absorption maximum at 237 mμ in 11.2 and 14.5 M H$_2$SO$_4$, acid concentrations which are on both sides of the abrupt break in the rate profile (Fig. 4).

The rates of hydrolysis of AcImH$^+$ and AcIm in less acidic solutions have been reported previously.[17] First-order kinetics were followed in all experiments, indicating that the rate constants are independent of AcImH$^+$ concentration in the concentration range investigated. The effect of added imidazolium chloride in 0.1 M HCl is shown in Fig. 1. The rate of hydrolysis of AcImH$^+$ in 10.55 M HClO$_4$ was found to be 0.043 min.$^{-1}$; addition of 0.05 M imidazole, 0.05 M acetic acid, and 0.05 M imidazole plus 0.05 M acetic acid resulted in rate constants of 0.035, 0.036 and 0.037 min.$^{-1}$, respectively.

Discussion

Although we are not able, and shall not attempt, to provide a quantitative explanation of the complex effects of concentrated salts and acids on this or other reactions, the following conclusions may be drawn from the results of these experiments: (1) AcImH$^+$ and 1-acetyl-3-methylimidazolium (AcMeIm$^+$) show very similar or identical behavior in respect to the effects of NaClO$_4$, NaCl, HClO$_4$, D$_2$O and dioxane on their rates of hydrolysis and in respect to their rates of reaction with a series of nucleophilic reagents.[19] It therefore appears justifiable to use AcMeIm$^+$ as a model for reactions of AcImH$^+$ in the pH region of 2 to 4, in which the study of reactions of AcImH$^+$ would be complicated by partial dissociation to free acetylimidazole.

(2) Except for SO$_4^=$ and F$^-$, all salts and acids examined cause large decreases in the rate of AcImH$^+$ (or AcMeIm$^+$) hydrolysis. In the case of NaClO$_4$, the decrease in the logarithm of the rate constant is proportional to the concentration of NaClO$_4$ up to a concentration of over 8 M, corresponding to a 500-fold decrease in rate.

(3) The available data do not permit a definite decision as to whether the marked rate increase observed with F$^-$ represents a nucleophilic reaction, general base catalysis of hydrolysis, or a salt effect. A nucleophilic reaction is not unlikely in this case, since (a) the calculated second-order rate constant of 30 l. mole^{-1} min.$^{-1}$ for such a reaction (after subtracting the rate of hydrolysis in the absence of F$^-$ and assuming no salt effects) is not unreasonable for a compound with the basicity of F$^-$,[24] (b) F$^-$ is known to react with p-nitrophenyl acetate,[24] and (c) the solvent deuterium isotope effect on the over-all rate of AcMeIm$^+$ disappearance is smaller than in the case of other salts. If the reaction is treated as a second-order reaction, the rate constant in D$_2$O is 19 l. mole^{-1} min.$^{-1}$ and the k_{H_2O}/k_{D_2O} ratio is 1.6; this value is neither small enough to favor strongly a nucleophilic reaction nor large enough to suggest strongly general base catalysis.[25] The product of such a nucleophilic reaction, acetyl fluoride, would be expected to undergo rapid hydrolysis, so that the observed reaction would represent nucleophilic catalysis of AcMeIm$^+$ hydrolysis by F$^-$.

The reaction with SO$_4^=$ may also be a nucleophilic reaction, although in this case it is necessary to invoke some such phenomenon as ion-pairing to explain the leveling off of the rate with increasing SO$_4^=$ concentration. It appears less likely that nucleophilic reactions are important with other salts, because (a) the solvent deuterium isotope effects (k_{H_2O}/k_{D_2O} = 2.5–2.7) are the same in the

---

[24] W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960).

[25] W. P. Jencks and J. Carriuolo, *ibid.*, **83**, 1743 (1961), and references therein.

presence and absence of concentrated NaCl and $NaClO_4$, while a nucleophilic reaction would be expected to show a k_{H_2O}/k_{D_2O} ratio near 1 and thus cause a decrease in the over-all isotope effect if a significant part of the observed reaction were a nucleophilic reaction with the anion; (b) the rate constants required to account for the differences between the various salt and acid effects on the basis of nucleophilic reactions are larger, by many orders of magnitude, than would be predicted from an extrapolation of basicity *vs.* reactivity plots[24] to the very low basicity of these anions; and (c) it is difficult to account for the leveling off of the rate at high acid concentrations, the further decrease at very high acid concentrations and the absence of a rate increase upon the addition of LiCl to HCl in terms of nucleophilic reactions.[26]

(4) Although the relationship of acid concentration to the logarithm of the rate does not display the linearity found with many salts, this is at least partly due to the fact that it was possible to examine acids at higher concentrations than most of the salts. In general, the rate decreases in the presence of increasing concentrations of acids are similar to those found with salts, and the large differences in the effects of different acids are similar to the large differences observed with different salts. There do not appear to be any grounds, therefore, for supposing that in this reaction acids and salts are exerting their effects through different mechanisms.

(5) The order of rate-decreasing effectiveness (excluding F^-) is $ClO_4^- > OTs^- > Br^- > Cl^- \sim NO_3^- > SO_4^{=}$ and $La^{+++} \sim Mg^{++} \sim Ca^{++} > Li^+ \sim Na^+ \sim K^+ > Cs^+ \sim NH_4^+ \sim (CH_3)_4N^+ \sim$ imidazolium$^+ \sim H^+$. The differences among anions are much greater than among cations and the large effects of polyvalent cations, on a molar basis, may largely be accounted for by the effect of the high concentrations of accompanying anions. The large differences between the effects of different salts and acids observed in plots of rate constants against molarity are not significantly less in plots against molality.

In the series of monovalent anions, the order generally parallels the more or less related properties of (unhydrated) ionic size, unitary partial ionic entropy, viscosity coefficient, "structure-breaking" effect and affinity for anion exchange resins.[27] However, the facts that NO_3^- falls out of order and that cations, which generally have as large or larger differences in these properties, show a smaller or reverse effect, renders any significant correlation with these parameters unlikely. It is of interest that H^+ is among the least effective of the cations examined.

(6) In addition to the fact that different salts and acids exhibit different effects with the same substrate, different substrates exhibit different effects with the same acid (Fig. 5). The fact that the rate for benzoylimidazolium hydrolysis is only slightly less than that for acetylimidazolium suggests that in the former case there is steric inhibition of resonance, due to the bulky aromatic groups; this is supported by examination of molecular models. The possibility of a competing acid-catalyzed reaction to give an acylium ion, which might account for the leveling off of the rate observed at high concentrations of several acids, is effectively ruled out by the more rapid solvolysis of benzoylimidazolium than of *p*-methoxybenzoylimidazolium, as well as by the further rate decreases observed with $AcImH^+$ at still higher acid concentrations.

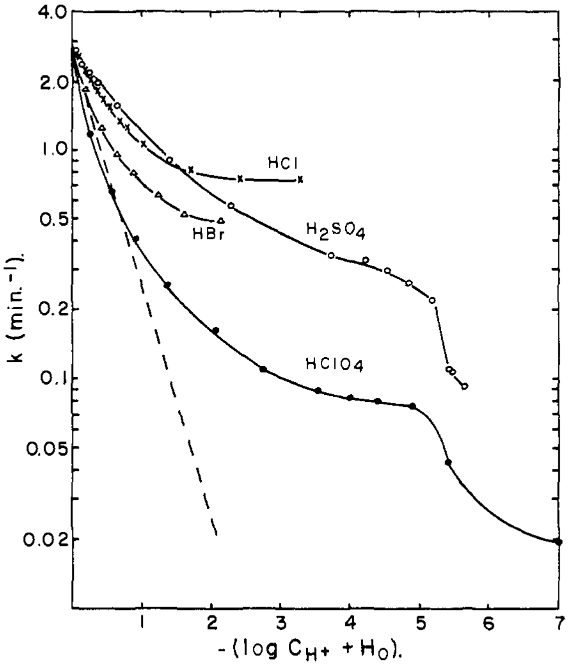


Fig. 6.—Plots of log k *vs.* log $C_{H^+} + H_0$ for the hydrolysis of acetylimidazole in various acids. The theoretical curve is shown as a dashed line.

(7) A reaction which follows $C_{H_3O^+}$ when the substrate is only slightly protonated should show a rate decrease with increasing acid concentration that follows C_{H+}/h_0 when the substrate is completely protonated, as discussed in the Introduction. A logarithmic plot of the experimental results with $AcImH^+$ against this function is shown in Fig. 6, with the theoretical line shown as a dashed line. The theoretical relationship is not followed by any of the acids examined and, furthermore, the relationship is widely different for different acids. Both the failure of the relationship and the large differences observed with different acids imply that no simple function of C_{H+} and h_0 can account for the effects of acid concentration on the rates of $AcImH^+$ hydrolysis. A number of other examples of failure to obtain satisfactory quantitative agreement with these parameters in reactions that appear to involve water have recently been reported,[14,28] and a

---

[26] The leveling off of the rate cannot readily be explained by the canceling out of a decrease in hydrolysis rate, due to a salt effect, by an increase in rate due to a nucleophilic reaction, since such a rate increase should become manifest as a net increase in rate as the hydrolysis rate approaches zero.

[27] (a) R. W. Gurney, "Ionic Processes in Solution," McGraw-Hill Book Co., Inc., New York, N. Y., 1953; (b) H. S. Frank and W. Wen, *Disc. Faraday Soc.*, **24**, 133 (1957); (c) E. R. Nightingale, Jr., *J. Phys. Chem.*, **63**, 1381 (1959); (d) S. Peterson, *Ann. N. Y. Acad. Sci.*, **57**, 144 (1954).

[28] (a) R. P. Bell and B. Lukianenko, *J. Chem. Soc.*, 1686 (1957); (b) R. W. Taft, Jr., N. C. Deno and P. S. Skell, *Ann. Rev. Phys. Chem.*, **9**, 303 (1958); (c) C. A. Bunton, P. B. D. de la Mare and J. G. Tillett, *J. Chem. Soc.*, 1766 (1959); C. A. Bunton and S. G. Perry, *ibid.*, 3070 (1960); (d) J. Koskikallio and E. Whalley, *Trans. Faraday Soc.*, **55**,

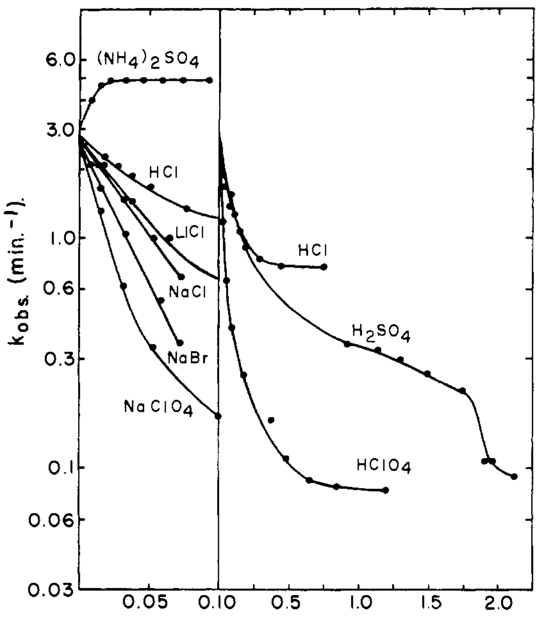


Fig. 7.—Plots of log k vs. $-\log a_{H_2O}$ for the hydrolysis of acetylimidazole. The plot for $(NH_4)_2SO_4$ refers to 1-acetyl-3-methylimidazolium chloride.

marked difference in the effects of different acids may even be a distinguishing characteristic of this type of reaction.[29]

(8) The activity of water is decreased in concentrated salt and acid solutions because of ion hydration, and attempts have been made to explain both the high acidity of strong acids and the effects of strong acids on reaction rates in terms of this decrease, without invoking major activity coefficient effects. If activity coefficient effects are neglected, the difference between the number of water molecules involved in the starting materials and the transition state may be estimated by plotting the appropriate logarithmic function of the rate and h_0 against the logarithm of the activity of water; the slope of the resulting line may be an index of this difference.[7] Such plots for $AcImH^+$ and $AcMeIm^+$ hydrolysis are shown in Fig. 7. A linear relationship is found only for those salts that exhibit a linear concentration effect on the logarithm of the rate and a linear relationship between salt concentration and a_{H_2O}. Furthermore, there are large differences in the relationship for different salts and acids, which are not appreciably less than the differences observed in plots against salt or acid concentration. The initial slopes of such plots ("w") vary from 3.2 for H_2SO_4 through 7.2 for LiCl and 12.3 for LiBr to 19.6 for $HClO_4$ and $NaClO_4$. Similar, but smaller, variations in w have been reported for other reactions.[30] At a constant activity of water, there is a several-fold variation in the rate of $AcImH^+$ solvolysis in the presence of different salts and acids (Table IV).

TABLE IV

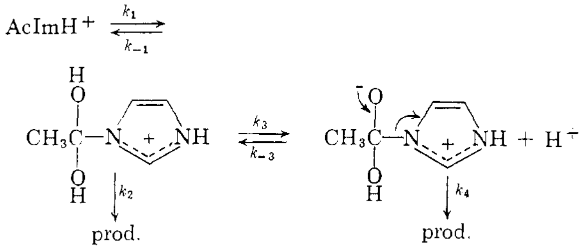
RATES OF $AcIinH^+$ SOLVOLYSIS AT LOG $a_{H_2O} = -0.06$[a]

Salt or acid	k, min.$^{-1}$	Concn., M	Salt or acid	k, min.$^{-1}$	Concn., M
LiCl	1.03	2.84	NaBr	0.50	3.05
$NaNO_3$	0.76[b]	4.25[b]	$(NH_4)_2SO_4$[c]	4.88	3.00
$CaCl_2$	1.05	1.80	HCl	1.55	2.75
NaCl	0.87	3.28	H_2SO_4	1.85	2.8
KCl	.76	3.58	$HClO_4$	0.66	2.4
$NaClO_4$	.29	3.20			

[a] Experimental conditions as in Tables I–III. [b] Extrapolated. [c] $AcMeIm.^+$

The estimation of ionic hydration numbers by different methods gives different results, but there is general agreement that the order of increasing hydration number is $NH_4^+ < K^+ < Na^+ < Li^+ < H^+$ and that anions are considerably less hydrated than cations.[20,31] It is clear that there is no correlation of increasing hydration number with increasing rate-decreasing effectiveness for $AcImH^+$ solvolysis. Although there is independent evidence for the involvement of several water molecules in the hydrolysis of $AcImH^+$ and related acyl compounds,[19,25] and there can be little doubt but that the rate-decreasing tendency of salts and acids is largely due to a decrease in the availability of water to satisfy this requirement, it is apparent that no general quantitative relationship between rate and a_{H_2O} exists and that major activity coefficient effects must be invoked to describe, if not to explain, these reactions.

(9) No entirely satisfactory chemical explanation is available for the differences in slope and shape of the curves for different salts and acids. The observed rate decreases could be accounted for by a change in rate-limiting step



in acid solution from k_1 to k_4, such that the activated complex has no net charge. A slower decomposition by k_2 might account for the slow, concentration-independent reaction observed with some acids. An analogous situation exists in the hydrolysis of oximes and Δ^2-thiazolines.[32] This scheme does not account for the different effects observed with different acids and salts, however, nor does it account for the rate decreases observed in the pH-independent solvolyses of esters[25] and $AcMeIm^+$ with increasing salt concentration.

---

815 (1959); J. Koskikallio and E. Whalley, *Can. J. Chem.*, **37**, 788 (1959); J. Koskikallio, D. Pouli and E. Whalley, *ibid.*, **37**, 1360 (1959); (e) J. G. Tillett, *J. Chem. Soc.*, 5138 (1960); (f) R. H. Boyd, R. W. Taft, Jr., A. P. Wolf and D. R. Christman, *J. Am. Chem. Soc.*, **82**, 4729 (1960); (g) A. J. Kresge and Y. Chiang, *Proc. Chem. Soc.*, 81 (1961). See also the discussion of C. G. Swain and A. S. Rosenberg, *J. Am. Chem. Soc.*, **83**, 2154 1961.

(29) D. S. Noyce, W. A. Pryor and P. A. King, *J. Am. Chem. Soc.* **81**, 5423 (1959).

(30) J. F. Bunnett and E. Buncel, *ibid.*, **83**, 1117 (1961).

(31) (a) E. Glueckauf, *Trans. Faraday Soc.*, **51**, 1235 (1955); *Proc. Royal Soc. (London)*, **228A**, 322 (1955); (b) R. P. Bell, *Endeavour*, **17**, 31 (1958); (c) D. G. Miller, *J. Phys. Chem.*, **60**, 1296 (1956); (d) J. B. Hasted and G. W. Roderick, *J. Chem. Phys.*, **29**, 17 (1958).

(32) (a) R. B. Martin, S. Lowey, E. L. Elson and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959); (b) W. P. Jencks, *ibid.*, **81**, 475 (1959).,

It has been proposed that certain salt effects may be accounted for in terms of complex formation between SH^+ and anions.[33] If an anion replaced a molecule of water in the solvent shell around Ac-ImH^+, to form an ion pair, it would be expected that this complex would undergo hydrolysis at a reduced rate. When the ion concentration becomes sufficiently high that all of the substrate is converted to this species, the rate should level off at a value corresponding to the rate of solvolysis of the ion pair. The further decrease in concentrated acid solutions, which occurs at an H_2O/H^+ ratio of less than 4, may reflect a further replacement of water in the hydration shell, as well as a marked decrease in the availability of water for nucleophilic attack and proton transfer. In these concentrated electrolyte solutions a large fraction of substrate molecules would be expected to be adjacent to anions purely on a statistical basis, as the concentration of anions becomes comparable to the concentration of free water molecules, and even weak electrostatic attractive forces should increase this fraction considerably. The faster rates observed with more basic anions are consistent with the expected greater ability of such ions to aid proton transfer in the transition state by general base catalysis.

Acknowledgments.—We are grateful to the National Cancer Institute of the National Institutes of Health (Grant C-3975) and to the National Science Foundation for financial support. This investigation was carried out by S. M. during the tenure of a Postdoctoral Fellowship from the Division of General Medical Sciences, United States Public Health Service.

---

[33] (a) A. R. Olson and T. R. Simonson, *J. Chem. Phys.*, **17**, 1167 (1949); (b) N. N. Lichtin and K. N. Rao, *J. Am. Chem. Soc.*, **83**, 2417 (1961).

[CONTRIBUTION FROM THE DEPARTMENT OF SYNTHETIC ORGANIC CHEMISTRY, MEAD JOHNSON RESEARCH CENTER, MEAD JOHNSON AND CO., EVANSVILLE 21, IND.]

Absolute Configuration of Cycloheximide from Thermal Degradation[1]

BY BERNARD C. LAWES

RECEIVED JULY 5, 1961

Thermal degradation of cycloheximide afforded, in high optical purity, (+)-2,4-dimethylcyclohexanone, different from but epimeric with (−)-2,4-dimethylcyclohexanone from alkaline degradation of cycloheximide. As a consequence, cycloheximide was shown to possess a *trans*-2,4-dimethyl system of the same absolute configuration as the less stable epimeric ketone from thermal degradation. The above, and other reported data permitted a tentative assignment of the glutarimide-containing group at C-6 as being *trans* with respect to the methyl group at C-2. Thermal degradation of cycloheximide also afforded some glutarimide-β-acetaldehyde, and, as an example of a thermally induced reverse aldol reaction, may proceed *via* a cyclic transition state.

Cycloheximide, an antibiotic from streptomycin-producing strains of *Streptomyces griseus*, was first reported[2] as a crystalline solid in 1947. The antibiotic is best known for its action against a variety of yeasts and molds, and as a result has many applications as an agricultural chemical.[3] The degradation work of Kornfeld, Jones and Parke[4] has shown the structure of cycloheximide to be β-[2-(3,5-dimethyl-2-oxocyclohexyl)-2-hydroxyethyl]-glutarimide (I), and although this structure has not been confirmed by total synthesis, the simple dehydration product has recently been synthesized in these laboratories.[5]

Although the structure is well established, the stereochemistry of cycloheximide has remained elusive, and difficulties, no doubt, arise from the lack of conformational rigidity of a simple cyclohexyl ring, and from the chemical lability of the molecule, both to degradation and possible epimerization. It has been shown that cycloheximide is degraded by alkali, presumably through a reverse aldol reaction, to yield an optically active ketone, 2,4-dimethylcyclohexanone.[4] Recently the absolute configuration of the asymmetric center at C-4 of this ketone has been related to D-glyceraldehyde.[6] Since the degradation should not have affected the configuration of this center, it is expected that the absolute configuration of the C-4 center in cycloheximide itself would also be related to D-glyceraldehyde.[6] The foregoing would say nothing of the relative stereochemistry of the other asymmetric centers in cycloheximide, since the 2,4-dimethylcyclohexanone formed in hot alkali[4] contains a potentially labile α-methyl group.

It has now been demonstrated in these laboratories that cycloheximide can undergo, in addition to an alkaline degradation, a thermal degradation to break the β-ketol structure in the molecule. At a temperature of 200°, and above, a volatile liquid was smoothly distilled from cycloheximide, and this liquid *was different* from that obtained by alkaline degradation. This thermal product, obtained in greater than 50% yield, was shown to be a ketone closely related to the alkaline degradation ketone because of the virtual identity of infrared absorption below 7.0 μ, the similarity of the ketone-type ultraviolet absorption and the closeness of the boiling points, but the differences in optical rotations,

---

[1] Presented in part at the 139th Meeting of the American Chemical Society, St. Louis, Mo., March 30, 1961.

[2] B. E. Leach, J. H. Ford and A. J. Whiffen, *J. Am. Chem. Soc.*, **69**, 474 (1947); referred to as actidione by these authors.

[3] W. Klomparens, J. H. Ford, C. L. Hamner and G. A. Boyack, Abstracts of Papers, 132nd Meeting, American Chemical Society, New York, N. Y., Sept., 1957, p. 24-A.

[4] E. C. Kornfeld, R. G. Jones and T. V. Parke, *J. Am. Chem. Soc.*, **71**, 150 (1949).

[5] B. C. Lawes, *ibid.*, **82**, 6413 (1960).

[6] E. J. Eisenbraun, J. Osiecki and C. Djerassi, *ibid.*, **80**, 1261 (1958).