

was observed. At the end of 20 hours total reaction time 4.15 liters of hydrogen was obtained, corresponding to 65 mole % based on limonene charged. Most of the sodium remained unchanged with the exception of a small amount of a powdery dark brown material. The hydrocarbon layer was also colored brown. On filtration over 90% of material boiling within limonene range was recovered. The liquid product consisted according to ultraviolet analysis of 57% *p*-cymene and of about 41% of a menthadiene having a maximum absorption peak at 244 μ in iso-octane solution. The structure of the menthadiene by application of Woodward's rule,³ is thought to be 3-isopropylidene-6-methyl-1-cyclohexene. The absorptivity of 67 l./g. cm. used to calculate the concentration of the menthadiene was derived from an average absorptivity of 9100 l./mole cm. for semicyclic dienes.⁴

It was observed that with a reaction time of seven hours instead of 20 hours, the rate of isomerization to conjugated dienes is much greater than the rate of dehydrogenation to *p*-cymene.

In the absence of *o*-chlorotoluene as a "promoter" marked evolution of hydrogen began only after about 13 hours of refluxing. After 23 hours of total reaction time only 23 mole % of hydrogen was produced and the liquid product was composed of 21% *p*-cymene and 37% of conjugated terpenes.

Sodium hydride acts also as a catalyst for the dehydrogenation and isomerization of *d*-limonene. The liquid product obtained from the reaction, which was carried out for 21 hours at a reflux temperature, consisted of 71% *p*-cymene and 16% of conjugated menthadienes.

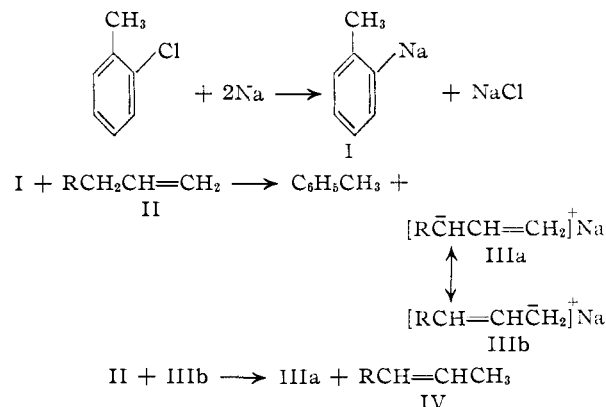
Discussion of Results

It was found that sodium in the presence of compounds such as *o*-chlorotoluene or anthracene acts as an efficient catalyst for the shifting of double bonds in olefinic hydrocarbons. In the case of aliphatic olefins the isomerization seems to proceed without extensive side reactions, which usually

(3) R. B. Woodward, *THIS JOURNAL*, **64**, 72 (1942).

(4) H. Booker, L. Evans and A. Gillam, *J. Chem. Soc.*, 1456 (1940).

occur when acid types of catalysts are used. Although the mechanism of this reaction has not yet been studied systematically, it seems, on the basis of these and unpublished data, that the function of the "promoter" is to form a sodium organic compound which can then metalate the olefin according to the following series of reactions



Compound IV may undergo another metalation which would result in a further shift of the double bond.

The catalytic dehydrogenation of *d*-limonene by means of sodium promoted by *o*-chlorotoluene can also be explained by a series of reactions similar to those outlined above. It is probable that *d*-limonene isomerizes to endocyclic menthadiene prior to undergoing metalation and dehydrogenation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Intermediates in the Reactions of Carboxylic Acid Derivatives. IV. The Hydrolysis of Benzamide¹⁻³

BY MYRON L. BENDER AND ROGER D. GINGER

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Benzamide-O¹⁸ has been prepared. The kinetics of hydrolysis of benzamide under acidic and basic catalysis have been determined in aqueous solution. The oxygen exchange accompanying hydrolysis has been determined. Oxygen exchange was found to occur between benzamide-O¹⁸ and water during the basic hydrolysis of benzamide, but no exchange was observed during its acidic hydrolysis. The fact that $k_{\text{exch}} > k_{\text{hydrolysis}}$ in the basic hydrolysis of benzamide whereas $k_{\text{hydrolysis}} > k_{\text{exch}}$ in the basic hydrolysis of ethyl benzoate may be related to the competitive breakdown of the addition intermediate $\text{RC}(\text{OH})_2\text{X}$. The lack of oxygen exchange in the acidic hydrolysis of benzamide is attributed to the greater basicity of nitrogen relative to oxygen, which may result in a displacement reaction involving the conjugate acid of benzamide and water or in the formation of an addition intermediate from which the products of hydrolysis are formed without any appreciable back (exchange) reaction.

Introduction

A continuation of studies concerned with the elucidation of intermediates in the reactions of carboxylic acid derivatives has led to the investigation of the hydrolysis of benzamide. Earlier investigations⁴ concerned with the oxygen exchange accompanying the hydrolysis of benzoate esters

(1) Previous paper: M. L. Bender, R. D. Ginger and K. C. Kemp, *THIS JOURNAL*, **76**, 3350 (1954).

(2) Presented at the New York Meeting of the American Chemical Society, September, 1954.

(3) This investigation was supported by a Frederick Gardner Cottrell grant from the Research Corporation.

(4) M. L. Bender, *THIS JOURNAL*, **73**, 1626 (1951).

indicated that in those reactions a symmetrical intermediate was formed by the addition of water to the carbonyl group of the ester. In the present paper oxygen exchange data for the acid and basic hydrolysis of benzamide in aqueous solution are reported.

Kinetic investigations of amide hydrolysis⁵ have indicated that amide hydrolysis is in general similar to ester hydrolysis. The rate of basic hydrolysis is proportional to the concentrations of amide and of

(5) H. V. Euler and A. Ölander, *Z. physik. Chem.*, **131**, 107 (1928). N. V. Peskoff and J. Meyer, *ibid.*, **82**, 129 (1913); V. K. Kriehle and K. A. Holst, *THIS JOURNAL*, **60**, 2976 (1938); B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **B20**, 73 (1942).

hydroxide ion. The rate of acidic hydrolysis is in general proportional to the concentrations of amide and of hydronium ion. The hydrolysis of acetamide in dilute acid solution is proportional not to the concentration of hydronium ion but rather to the concentration of the conjugate acid of acetamide. Further the rate goes through a maximum at higher acid concentrations, a fact which has been interpreted as due to the occurrence of a maximum concentration of the amide cation at a certain acid concentration.

The kinetics of the acid and basic hydrolyses of benzamide and substituted benzamides in a 60-40 alcohol-water mixture have been determined by Meloche and Laidler.⁶ From a study of the substituent effect on the energy of activation, they proposed an activated complex involving (1) the approach of OH⁻ or H₂O to the carbonyl carbon atom, (2) the ionic splitting of the C-N bond and (3) the approach of H₂O or H₃O⁺ to the nitrogen atom. The present investigation leads to a further elaboration of the mechanism of the hydrolysis of benzamide.

Experimental

Materials.—Benzoic acid-O¹⁸ was prepared by the equilibration of benzoic acid (Mallinckrodt, analytical reagent) of normal isotopic composition with H₂O¹⁸ (1.4 atom %, Stuart Oxygen Co., San Francisco, Calif., through the Atomic Energy Commission) made 0.1 *N* in hydrochloric acid.⁴ Treatment of the benzoic acid-O¹⁸ with purified⁷ thionyl chloride yielded benzoyl chloride-O¹⁸ which was dissolved in dry benzene and converted to benzamide-O¹⁸ with anhydrous ammonia. The yield of benzamide-O¹⁸ (m.p. 127.5⁹) was approximately 90% after recrystallization from water.

Kinetics.—The kinetics of hydrolysis of approximately 0.1 *M* benzamide in aqueous solution with equivalent concentrations of hydrochloric acid or sodium hydroxide were measured. The acid-catalyzed reactions were carried out in sealed Pyrex ampoules and the basic hydrolyses were carried out in tubes of Corning brand alkali resistant glass, No. 728, maintained for various lengths of time at 109.0 ± 0.2° in a thermostatically controlled oil-bath. Ampoules were removed after various lengths of time, quenched, and after Nesslerization⁸ the solutions were analyzed spectrophotometrically for ammonia at 390 m μ using a Beckman DU spectrophotometer. The kinetic data are shown in Fig. 1. From the slopes of the lines the second order specific constants for basic and acidic hydrolysis are 26.3 × 10⁻⁴ l./mole sec. and 7.33 × 10⁻⁴ l./mole sec., respectively. These values have been corrected for expansion.

Oxygen Exchange Experiments.—Samples of benzamide-O¹⁸ were partially hydrolyzed in water of constant O¹⁸ content under conditions identical to those used in the determination of the rates of hydrolysis. Ampoules were removed from the bath at desired times (corresponding to 0-85% hydrolysis) and chilled in cold water. The contents were extracted six times with ethyl acetate (Matheson, Coleman and Bell anhydrous) (The acid catalyzed reactions were first neutralized with dilute sodium hydroxide.) The combined extracts were dried over sodium sulfate and concentrated to about 3 ml. The residual solvent was allowed to evaporate to yield colorless benzamide (m.p. 127-127.5°, 80-90% recovery) which was dried in vacuum before analysis for oxygen-18 content.

Oxygen-18 Analysis.—The analysis of benzamide for oxygen-18 content was performed by conversion of the oxygen of benzamide to carbon dioxide in either of two ways,

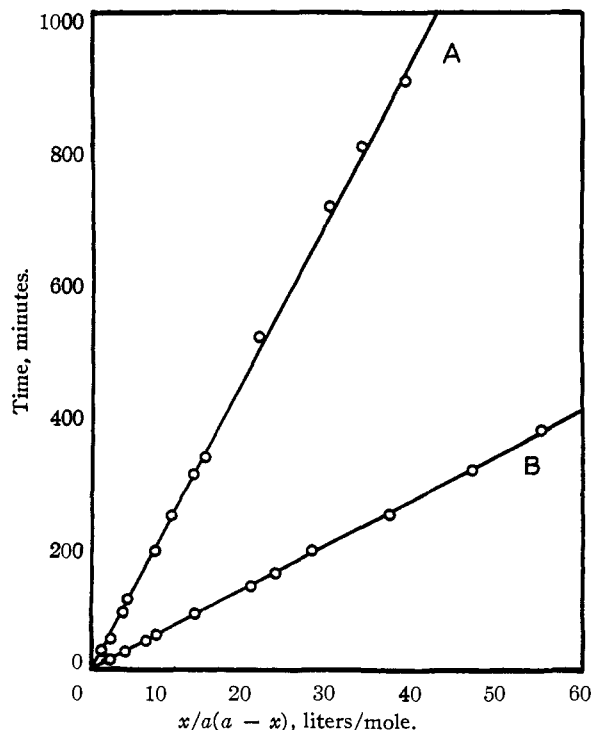


Fig. 1.—Kinetics of hydrolysis of benzamide in aqueous solution at 109.0 ± 0.2°: curve A, HCl catalyzed; curve B, NaOH catalyzed.

followed by analysis of the carbon dioxide samples by means of a Consolidated-Nier model 21-101 isotope ratio mass spectrometer.

The first method for the conversion of benzamide to carbon dioxide consisted of the pyrolytic cleavage of benzamide to benzonitrile and water. Infrared spectrophotometric analysis indicated that the reaction proceeded quantitatively. This method is an adaptation of a reaction reported by Boehner and Ward.¹⁰ Benzamide samples were distilled through a Pyrex tube (50 cm. × 12 mm. o.d.) packed with sand-blast sand at 500 ± 25° employing purified nitrogen at a flow rate of 15 cc./min. as a carrier gas.

The products of the pyrolysis, benzonitrile and water, were collected from the gas stream in a trap which was at boiling nitrogen temperature, protected from the atmosphere by a guard tube, and connected to a high vacuum line by means of a stopcock. The H₂O¹⁸ was fractionated from the benzonitrile into the vacuum line and then equilibrated with a known amount of carbon dioxide of normal isotopic composition.¹¹ The carbon dioxide samples were purified by multiple vacuum distillation and then analyzed for their oxygen-18 content. The equation developed by Dostrovsky and Klein¹² was used to calculate the oxygen-18 content of the original benzamide samples.

The second and more generally useful method employed for the conversion of benzamide to carbon dioxide is one that has been recently reported by Doering and Dorfman.¹³ It involves the pyrolysis of oxygen-containing organic compounds over carbon at 1100° to carbon monoxide followed by oxidation of the carbon monoxide by iodine pentoxide to carbon dioxide. The volume of carbon dioxide produced in each pyrolysis was determined to check for quantitative conversion of the oxygen in the organic compound to carbon dioxide. It was found that identical results were obtained by this method both with and without the use of a trap containing 3% bromine in 1:1 chloroform-carbon tetrachloride described by these authors.

(6) I. Meloche and K. J. Laidler, *THIS JOURNAL*, **73**, 1712 (1951).
 (7) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 381.
 (8) Fisher-Johns block corrected; literature, m.p. 127-127.5°. H. A. Taylor and T. W. Davis, *J. Phys. Chem.*, **32**, 1470 (1928).
 (9) I. Kolthoff and E. Sandell, "Textbook of Quantitative Inorganic Analysis," The Macmillan Co., New York, N. Y., 1948.

(10) R. S. Boehner and A. L. Ward, *THIS JOURNAL*, **38**, 2506 (1916); compare K. B. Wiberg, *ibid.*, **75**, 3961 (1953).
 (11) M. Cohn and H. C. Urey, *ibid.*, **60**, 879 (1938).
 (12) I. Dostrovsky and F. Klein, *Anal. Chem.*, **24**, 414 (1952).
 (13) W. E. Doering and E. Dorfman, *THIS JOURNAL*, **75**, 5595 (1953).

Results

The results of the experiments designed to determine the oxygen exchange accompanying the hydrolyses of benzamide are shown in Table I. These data were plotted according to the method developed previously,⁴ as shown in Fig. 2. The data indicate that extensive oxygen exchange accompanies the basic hydrolysis of benzamide, but that no observable oxygen exchange occurs during the acidic hydrolysis of benzamide.

TABLE I
OXYGEN EXCHANGE DURING THE HYDROLYSIS OF BENZAMIDE

Basic hydrolysis ^a		Basic hydrolysis ^b		Acidic hydrolysis ^a	
Hydrolysis, %	Atom % O ¹⁸	Hydrolysis, %	Atom % O ¹⁸	Hydrolysis, %	Atom % O ¹⁸
0	0.578	0	0.877	0	0.578
21.0	.331	38.2	.290	19.9	.586
25.2	.293	52.2	.230	48.5	.584
28.2	.277	61.0	.218	59.4	.574
37.1	.238	81.2	.206	69.6	.583
42.6	.235			84.5	.579
55.0	.211				
75.0	.203				

^a Pyrolysis to carbon dioxide, average deviation of 0.8% for O¹⁸ analyses. ^b Pyrolysis to benzonitrile and water, average deviation of 3% for O¹⁸ analyses.

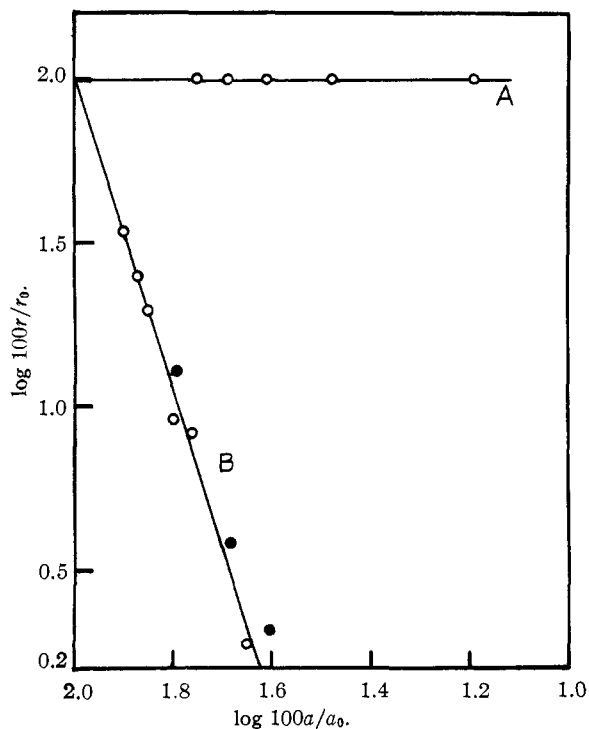


Fig. 2.—Oxygen exchange vs. hydrolysis; r represents the excess atom fraction O¹⁸ and is the measured atom fraction O¹⁸ minus 0.00204, a represents the amide concentration; curve A, HCl catalyzed; curve B, NaOH catalyzed; open circles, pyrolysis to carbon dioxide; filled circles, pyrolysis to benzonitrile and water.

In Table II the ratios of k_{hydrol} to k_{exch} calculated from the slopes of the line in Fig. 2, are compared with the corresponding ratios obtained in the hydrolyses of ethyl benzoate.⁴

TABLE II

Compound	RATIOS OF k_{hydrol} TO k_{exch}	
	Basic Hydrolysis	Acidic Hydrolysis
Benzamide ¹⁴	0.21	$\infty (>374)$
Ethyl benzoate	4.8	5.2

Discussion

The fact that oxygen exchange accompanies the basic hydrolysis of benzamide indicates that in this hydrolytic reaction, as in the previous ester hydrolyses, a symmetrical intermediate capable of exchange occurs. This intermediate most probably has the structure of the addition compound $\text{RC}(\text{OH})_2\text{NH}_2$. Under the basic reaction conditions this neutral intermediate is undoubtedly in equilibrium with the ion formed by the removal of a proton from one of the oxygens. In fact, this ion is probably formed first by the addition of hydroxide ion to the carbonyl carbon atom of the amide. However, for exchange to occur, a compound symmetrical with respect to both oxygens must exist, a condition which can be satisfied most easily by the neutral addition compound mentioned above.¹⁵

Table II indicates that $k_{\text{ex}} > k_{\text{h}}$ in the basic amide hydrolysis, but $k_{\text{h}} > k_{\text{ex}}$ in the ester hydrolysis. These orders may be related to the competitive breakdown of the addition intermediate, $\text{RC}(\text{OH})_2\text{-X}$. The ease of removal of groups is presumably in the order: $\text{OH}^- > \text{NH}_2^-$ from the amide intermediate and $\text{OR}^- > \text{OH}^-$ from the ester intermediate. In the amide case the order is in accord with the relative anionic stabilities of the groups, but not in the ester case, in which the large steric requirement of the OR^- group may be important. This hypothesis is currently being tested. A possible complication to this hypothesis is that the amide ion (or alkoxide ion) upon expulsion from the addition compound is simultaneously protonated by the aqueous solvent. This suggestion would mean that the amide ion does not exist as a discrete entity.

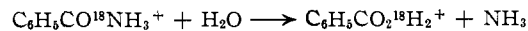
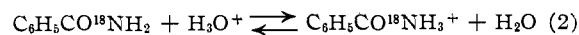
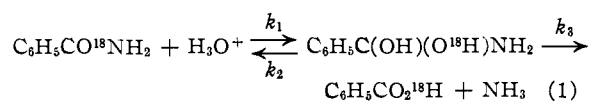
No oxygen exchange occurred during the acidic hydrolysis of benzamide. This is the first instance in which oxygen exchange with the aqueous solvent did not accompany the hydrolytic reaction of a carboxylic acid derivative. Unlike the ester hydrolyses, where acidic and basic hydrolyses produced similar results with respect to oxygen exchange, the amide hydrolyses have produced entirely different oxygen exchange results. The lack of oxygen exchange during the acidic hydrolysis of benzamide may be attributed to the greater basicity of nitrogen relative to oxygen. This phenomenon may manifest itself in two possible mechanisms.

The two alternatives to be considered are (1) the reaction proceeds through an addition intermediate but the carbon-nitrogen bond is broken as the intermediate is formed, (2) the reaction consists of two steps; a fast equilibrium involving the protonation of benzamide to form the conjugate acid, RCONH_3^+ , followed by the direct displacement of

(14) The authors gratefully acknowledge a personal communication from Dr. C. A. Bunton, University College, London, which qualitatively confirms these oxygen exchange results with benzamide.

(15) Another structure symmetrical with respect to the oxygens is $\text{RC}(\text{O}^-)\text{NH}_3^+$. Because of its unlikely charge distribution, it is probably not an important intermediate.

an ammonia molecule by a water molecule without the formation of an addition intermediate.¹⁶



These mechanisms are, in fact, experimentally indistinguishable at this time. If an addition intermediate is formed (reaction 1), a lower limit for the ratio k_3/k_2 can be determined from the relationship $k_h/k_{ex} = 2k_3/k_2$ which follows from the stationary state theory. Using the experimental error of 0.5% (average deviation of five analyses) in the oxygen-18 analysis as a possible oxygen exchange at 85% hydrolysis, it may be calculated that the ratio of $k_h/k_{ex} \geq 374$ and therefore $k_3/k_2 \geq 187$.

This means that if reaction 1 were operative, the ratio of the frequency of the rupture of the carbon-nitrogen bond to that of the carbon-oxygen bond in the intermediate would be greater than 187. Prior to the formation of the hypothetical addition intermediate, the conjugate acid of the amide would be formed.^{16,17} This ion would then be attacked by a water molecule producing the conjugate acid of the addition compound which could assume several forms dependent on the position of the proton. Evidence that proton transfers in the amide system are extremely fast has been furnished by Brodskii,¹⁸ who found that acetamide exchanges two hydrogen atoms (those bound to nitrogen) with deuterium oxide presumably at room temperature and in the absence of any catalyst. This facile proton transfer indicates that it is not necessary or proper to designate the exact structure of the conjugate acids of the amide or of the addition intermediate. The conjugate acid of the addition intermediate would, of course, be in equilibrium with the neutral, symmetrical intermediate, as in the corresponding basic hydrolysis.

Prior to the break of either bond in the hypothetical neutral intermediate, the protonation of one of the electronegative atoms probably would occur. If the basicity of the nitrogen is much greater than

that of oxygen, it is possible that the concentration of $\text{RC}(\text{OH})_2\text{NH}_3^+$ would be much greater than that of the corresponding protonated oxygen compound. This would lead to the production of a neutral ammonia molecule with extreme ease compared with possible exchange reaction resulting from the break of a carbon-oxygen bond and the formation of a water molecule.

Recent experiments have indicated that the previous report¹ of oxygen exchange (with the aqueous solvent) during the acidic hydrolysis of *p*-benzotoluide- O^{18} is erroneous. Analysis of *p*-benzotoluide- O^{18} (0.576 atom %) isolated from runs including 43, 46, 50, 53, 60, 63 and 68% hydrolysis yielded values of 0.582, 0.575, 0.585, 0.586, 0.589, 0.589 and 0.555 atom % O^{18} , respectively. These values have been corrected for a small pyrolysis blank of ordinary isotopic composition which arose during the course of these investigations (*cf.* W. Kirsten, *Anal. Chem.*, 25, 74 (1953)). These results indicate that in two cases there is no observable oxygen exchange during the acidic hydrolysis of amides. Therefore the hypothesis regarding the influence of the relative basicity of the nitrogen atom on the course of these hydrolytic reactions must be qualified.

An intermediate such as described above may be considered, but a direct displacement reaction would suffice as well to account for the experimental results. It is highly probable that, in either case, the conjugate acid of the amide is formed first in a fast reversible step and that this species then undergoes reaction with a water molecule. Evidence for the formation of the conjugate acid of the amide is given not only by the kinetic results mentioned previously,⁵ but also by the work of Rietz¹⁹ who found that the rate constant for the hydrolysis of acetamide in dilute acid solution was 1.5 times as great in deuterium oxide as in water. This fact has been interpreted as indicative of formation of such a conjugate acid.^{19,20} Since all hydrolytic reactions studied to this time, with the exception of the acidic hydrolysis of benzamide, have shown evidence for intermediate formation, it may be profitable to consider the present case as an extreme example of intermediate formation rather than a different type of reaction.

With respect to the mechanism of amide hydrolysis proposed by Meloche and Laidler,⁶ these results are in substantial agreement. However, at least in the basic hydrolysis of benzamide, these results indicate that the best description of the intermediate state of the reaction is a symmetrical addition compound capable of exchange and not an activated complex.

Acknowledgment.—The authors wish to express their appreciation to Dr. H. Taube of the University of Chicago through whose courtesy the mass spectrometer under AEC Contract At(11-1)-92 was made available and to Dr. Jack Hine for valuable discussions of the problem.

CHICAGO, ILLINOIS

(19) O. Rietz, *Z. Elektrochem.*, 44, 694 (1938); *Z. physik. Chem.*, A183, 371 (1939).

(20) J. E. Leffler and E. Grunwald in "Technique of Organic Chemistry," Vol. VIII, Interscience Publishers, Inc., New York, N. Y., 1953, p. 320.

(16) The structure of the conjugate acid of an amide has never been unequivocally established. Nor for that matter has the structure of an amide. Two possibilities exist for the amide (RCONH_2 and $\text{RC}(\text{OH})=\text{NH}$) and two for the conjugate acid of the amide (RCO-NH_3^+ and $\text{RC}(\text{OH})(\text{NH}_3^+)$). The spectroscopic evidence of A. Hantzsch, *Ber.*, 64, 661 (1931), and of R. E. Richards and H. W. Thompson, *J. Chem. Soc.*, 1248 (1947), are in direct conflict with respect to the identity of the amide. Hantzsch claims that the structure of the conjugate acid is best represented by $\text{RC}(\text{OH})(\text{NH}_3^+)$, but this can hardly be accepted as conclusive in the light of Thompson's disagreement with Hantzsch's previous results. The structure RCONH_3^+ is used here because of the straightforward process it involves.

(17) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 786.

(18) A. E. Brodskii, *Trans. Faraday Soc.*, 33, 1180 (1937).