(SO_2ClF) cooled to −78° and with vigorous agitation was slowly added to the acid solution. The acid was always in large excess as indicated by the large acid peak at δ 10.6–10.9.

Registry No.—Methyl *N*,*N*-(diisopropyl)carbamate, 31603-49-3, 31585-09-8 (protonated derivative); ethyl *N*,*N*-(diisopropyl)carbamate, 20652-39-5, 31585-10-1 (protonated derivative).

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

A Kinetic Study of the Nitrogen-15 Exchange of Para-Substituted Benzamides with Ammonia[1a]

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Received January 20, 1971

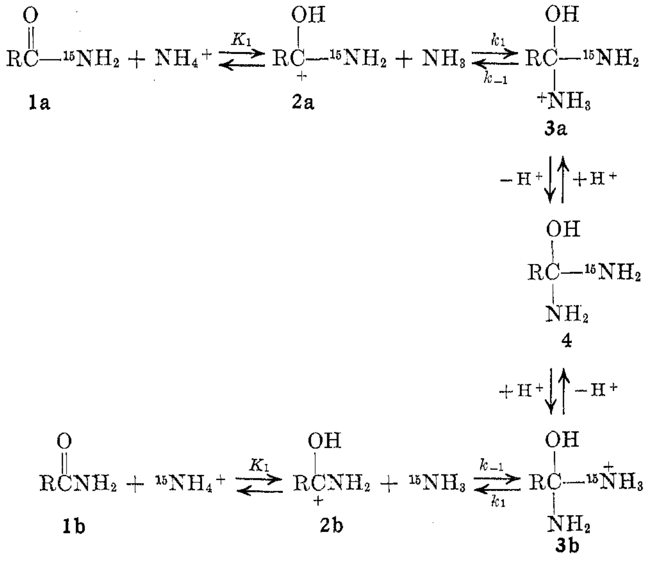
A kinetic study has been carried out on the nitrogen-15 exchange of para-substituted benzamides-^{15}N with liquid ammonia as a function of temperature and catalyst concentration. Neither a neutral nor a base-catalyzed exchange pathway is detectable under the conditions employed. The relative rates for the acid-catalyzed (ammonium chloride catalyzed) exchange of the para-substituted benzamides at 40° in the presence of 3 *M* ammonium chloride are $NO_2:Cl:H:CH_3:CH_3O = 8.78:2.13:1.00:0.55:0.44$. Hammett plots are linear with $\rho = +1.25$. The kinetic data indicate a first-order dependence of the exchange rate on the ammonium ion concentration. All of the reactions exhibit pseudo-first-order kinetics. The trends in the kinetic data are what would be expected for an exchange mechanism involving a rapid preequilibrium protonation of the amide followed by a slow rate-determining addition of ammonia to form a tetrahedral intermediate, which can revert to reactants or decompose to products depending upon which nitrogen is lost.

Nitrogen-15 labeled benzamide and other amides are known[2-4] to undergo isotopic exchange with ammonia in liquid ammonia solution catalyzed by ammonium ion. No exchange is observed in the absence of a catalyst except at very high temperatures.[2,3] At 20° in the presence of 3.33 molar ammonium chloride, Heyns, Brockmann, and Roggenbuck[2] observed that *p*-nitrobenzamide, benzamide, and *p*-methoxybenzamide underwent 29.7 ± 2.0, 4.2 ± 2.0, and 1.8 ± 2.0% exchange, respectively, after 7 days. They determined the rate constant for exchange of *p*-nitrobenzamide at 20° in the presence of 3.33 *M* ammonium chloride as $1.27 \times 10^{-8}\ \text{sec}^{-1}$. In a related study Heyns, Grutzmacher, and Roggenbuck[3] determined the activation energy for the liquid ammonia ammonolysis of *p*-nitrobenzamide to be 17.0 ± 0.5 kcal/mol.[5] They also noted a continual increase in exchange rate with increased ammonium chloride concentration up to about 12 mol/l.

Brodskii and coworkers[4] have also made a study of the nitrogen exchange between ammonia enriched with nitrogen-15 and various compounds dissolved in the ammonia. The exchange proceeds (at 180°)[6] in $-C(=X)-NH_2$ ($X = O, S, NH$), amino acids, and urea. According to these workers, the relative rates of exchange in a series of amides are proportional to the electrophilicites of the carbon atoms to which the nitrogen is attached. Electron donor groups in meta and para positions in aromatic amides hinder the exchange, while electron acceptor groups accelerate it.

Information about nitrogen exchange reactions of aromatic amides is, at best, qualitative and incomplete. We now wish to present the results of a kinetic study of the effect of para substituents on the rate of the acid- and base-catalyzed isotopic exchange between benzamides-^{15}N and liquid ammonia. If the aminolysis of benzamides with an acid catalyst is analogous to the acidic hydrolysis of amides, as suggested by Heyns and coworkers,[2,3] then a similar mechanism may be postulated involving attack by an ammonia molecule on the conjugate acid of the amide as the rate-determining step, shown in Scheme I. The tetrahedral intermediate

SCHEME I



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[1] (a) Supported by U. S. Atomic Energy Commission Contract AT-(40-1)-3234; from the Ph.D. Dissertation of C. R. E., University of Arkansas, Fayetteville, Ark., 1970; presented in part at the Combined Southeast–Southwest Regional Meeting of the American Chemical Society, New Orleans, La., Dec 1970. (b) NSF Trainee, 1966–1969.

[2] K. Heyns, R. Brockmann, and A. Roggenbuck, *Justus Liebigs Ann. Chem.*, **614**, 97 (1958).

[3] K. Heyns, H. F. Grutzmacher, and A. Roggenbuck, *Chem. Ber.*, **93**, 1488 (1960).

[4] A. I. Brodskii, N. A. Vysotskaya, I. I. Kukhtenko, G. P. Miklukhin, L. L. Strizhak, and L. V. Sulima, *Izotopy Izluch. Khim., Tr. Vses. Nauch. Tekh. Konf. Primen. Radioaktiv. Stabil. Izotop. Izluch. Nar. Khoz. Nauke, 2nd*, 20 (1957); L. L. Gordienko and A. I. Brodskii, *Dokl. Akad. Nauk SSSR*, **134**, 595 (1960); L. L. Strizhak, S. G. Demidenko, and A. I. Brodskii, *ibid.*, **124**, 1089 (1959).

[5] Instead of determining the extents of exchange at a series of times and calculating the rate constants from the best straight lines, they calculated rate constants from the amount of exchange only at 120 hr for each temperature or catalyst concentration studied.

[6] Ammonia has a critical temperature of 132°; hence reactions above 132° are not liquid ammonia ammonolyses but vapor phase reactions.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE AMMONIUM CHLORIDE CATALYZED NITROGEN-15 EXCHANGE OF PARA-SUBSTITUTED BENZAMIDES, p-$XC_6H_4CO^{15}NH_2$, WITH AMMONIA (NH_4Cl) = 3.00 *M*

X	Registry no.	$k_{32} \times 10^7$ sec^{-1} [a]	$k_{36} \times 10^7$ sec^{-1} [a]	$k_{40} \times 10^7$ sec^{-1} [a]	$\Delta H^{\ddagger}$, ±2.0 kcal	$\Delta S^{\ddagger}$, ±6.0 eu	$\Delta G^{\ddagger}$, ±0.1 kcal
NO_2	31656-60-7	11.77	16.41	24.42	16.7	−31.2	26.3
Cl	31656-61-8	2.52	3.51	5.93	16.9	−33.4	27.2
H	31656-62-9	1.37	1.89	2.78	14.0	−44.1	27.6
CH_3	31656-63-0	0.77	1.15	1.52	13.7	−46.0	27.9
CH_3O	31656-64-1	0.53	0.75	1.21	16.4	−38.0	28.1

[a] The rate constants are reproducible to ±4%.

4 can decompose to reactants or products depending upon which amino group is lost.

Results and Discussion

The main findings of this research are summarized in Tables I and II. No exchange is noted in the absence of a catalyst at temperatures as high as 40.0°. In the acid-catalyzed exchange reactions of these para-substituted benzamides, electron-withdrawing groups accelerate the exchange and electron-donating groups retard the exchange relative to the unsubstituted compound. The relative rates of exchange at 40° in the presence of 3 *M* ammonium chloride as a function of the para substituent are $NO_2:Cl:H:CH_3:CH_3O = 8.78:2.13:1.00:0.55:0.44$. The kinetic data (Table II) indicate a first-order dependence of the exchange rate on the ammonium ion concentration. All of the reactions exhibit excellent pseudo-first-order kinetics. Hammett plots of of log k/k_0 *vs* σ for the data at 32, 36, and 40° give good straight lines, with $\rho = +1.25$.

TABLE II

RATE CONSTANTS AS A FUNCTION OF ACIDITY (AMMONIUM CHLORIDE CONCENTRATION) AT 36.0°

Benzamide	NH_4Cl, *M*	$k \times 10^7$ sec^{-1} [a]
p-$NO_2C_6H_4CO^{15}NH_2$	0.75	3.58
	1.50	7.30
	3.00	16.41
	4.30	25.03
	5.00	33.39
	6.00	42.75
$C_6H_4CO^{15}NH_2$	0.75	0.35
	1.50	0.83
	3.00	1.89

[a] The rate constants are reproducible to ±4%.

The large errors associated with the enthalpy and entropy of activation shown in Table I arise from the fact that the kinetics were determined at points separated by only 8°. This small temperature range was made necessary by the slowness of the exchange reactions at low temperatures and the high vapor pressure of liquid ammonia at higher temperatures.

Acid-Catalyzed Nitrogen Exchange.—The trends in the kinetic data are what would be expected for an exchange mechanism (Scheme I) involving a rapid preequilibrium protonation of **1a** followed by a slow, rate-determining addition of ammonia to form, after rapid proton transfer, a tetrahedral intermediate **4**. This mechanism is similar to that proposed for the hydrolysis of amides.[7] The proposed mechanism[8] gives rise to the kinetic expression, $k_{\text{obsd}} = {}^1/_2 k_1 K_1 \cdot (NH_4^+)$, if it is assumed that (a) the rate-determining step is the formation of the tetrahedral intermediate, (b) the proton transfer steps are not kinetically significant, and (c) any isotope effects involved are included in the rate and equilibrium constants. This rate expression predicts first-order dependence of the exchange rate on the ammonium ion concentration. It can be seen from the data in Table II that the exchange rate approximately doubles when the NH_4^+ concentration is doubled, indicating a first-order dependence of rate on NH_4^+ ion concentration within the limits to be expected for data taken at such high acid concentrations.

Para substituents on the ring would be expected to have opposing electronic effects on the rate constant and equilibrium constant in the above expression. Electron-withdrawing groups should decrease the basicity of the carbonyl oxygen, decreasing the equilibrium constant K_1. At the same time, electron-withdrawing groups should increase the electrophilicity around the carbonyl carbon, facilitating the formation of the tetrahedral intermediate and increasing the rate constant k_1. The reverse would be expected for electron-donating groups.

In the case of the analogous acidic hydrolysis of aromatic amides in dilute acid solution, these ambiguous polar requirements have been cited[9] as the cause of the almost complete insensitivity to polar effects which that reaction demonstrates. This same behavior was noted by Menon[10] for the acid-catalyzed oxygen exchange between para-substituted benzophenones and water. He found the rate constants for exchange to vary by only a factor of two in the series p-methoxy to p-nitro. In the present study the rate of isotopic exchange in the presence of 3.00 *M* ammonium chloride at 36.0° varies by a factor of 22 as one proceeds from the strongly electron-donating p-methoxy substituent to the strongly electron-withdrawing p-nitro substituent. This is not a particularly large variation and could easily arise from a combination of opposing electrical factors on K_1 and k_1 with those on k_1 predominating. If the isotopic exchange reaction were to be studied at higher ammonium ion concentrations where all of the para-substituted benzamides would be converted substantially completely to their conjugate acids, a somewhat larger vari-

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

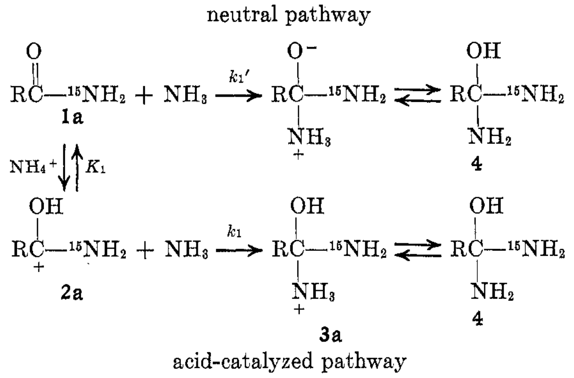
[8] C. R. Everly, Ph.D. Dissertation, The University of Arkansas, Fayetteville, Ark., 1970.

[9] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 786.

[10] B. C. Menon, Ph.D. Dissertation, University of Arkansas, Fayetteville, Ark., 1964.

ation of rate with substituent would be expected. This type of behavior was observed by Leisten[11] in his study of the effects of substituents as a function of acid concentration in the hydrolysis of benzamides in perchloric acid at 95°.

Neutral Nitrogen Exchange.—The existence of an equilibrium between the benzamide and its conjugate acid (**1a** and **2a**) shown in Scheme I infers that the exchange might proceed partly through a neutral pathway. This would involve a nucleophilic attack by ammonia on the benzamide leading to the tetrahedral intermediate **4**. If a neutral exchange were occurring, it should be possible to increase the proportion of molecules undergoing exchange by this pathway by lowering the acid concentration, since this would shift the equilibrium in favor of the amide. The neutral exchange pathway would be expected to be facilitated by electron-withdrawing groups. Hence the ratio of the rate constant for exchange of benzamide to that for *p*-nitrobenzamide should decrease as the acid catalyst concentration is lowered (k_{NO_2} should decrease more slowly than k_H) if any exchange is taking place by the neutral mechanism. The nitrogen exchange of benzamide and *p*-nitrobenzamide was studied at 36.0° in the presence of decreasing amounts of ammonium chloride. The ratio k_H/k_{NO_2} is 0.11, 0.11, and 0.10 at 3.00, 1.50, and 0.75 *M* ammonium chloride concentration, respectively (see Table II). The constancy of this ratio, within experimental error, shows that para-substituted benzamides undergo exchange only by an acid-catalyzed mechanism even at the lowest acid concentration employed. Experiments at lower acid concentrations were not attempted because of the slow rate of exchange. It might be possible to demonstrate the existence of a neutral exchange employing lower acid concentrations at higher temperatures.



Base-Catalyzed Nitrogen Exchange.—A base-catalyzed pathway of exchange employing added amide ion was not detectable. Sodium and potassium amide concentrations ranging from 5 × 10^{-5} to 5.0 *M* with an organic amide concentration of 0.1 *M* were employed at 32.00° for as long as 18 days. In every case the recovered amide showed the same nitrogen-15 enrichment as did the starting material. Only in the cases of the most dilute base concentrations were the reaction solutions homogeneous, the precipitates probably being the metal salts of the benzamides, $RCONH^-M^+$. Even for that portion of the salt which is in solution, the exchange reaction would be expected to be very slow, since nucleophilic attack on an anion would be involved.

Other Possible Mechanisms.—Other mechanisms which have been discussed for the nitrogen exchange of amides with ammonia or for the acid-catalyzed hydrolysis of amides which might be extended to the present research can be ruled out on the basis of the present evidence. If the rate-determining step in the nitrogen exchange reaction were the protonation of benzamide,[12] the effect of an electron-withdrawing para substituent in the benzamide surely would be to decrease the rate by decreasing the stability of the carbonium ion formed. The opposite is observed to be true in the present research.

A mechanism involving a preequilibrium protonation[12] of the benzamide followed by a unimolecular rate-determining decomposition step to an ammonia molecule and an acyl carbonium ion can be eliminated for the present case by an analogous argument to that given in the last paragraph. Furthermore, the proposal by Long, Pritchard, and Stafford[13] that the entropy of activation be used as a criterion of the mechanism of acid-catalyzed hydrolysis reactions can be applied directly in the present case. These hydrolysis reactions are usually classified as involving a unimolecular rate-determining decomposition step or a bimolecular rate-determining step. It seems quite reasonable that the loss of translational and rotational freedom of a water molecule associated with the formation of a tetrahedral intermediate in the acid-catalyzed bimolecular process should lead to a lower entropy of activation than the unimolecular loss of water from one positive ion to form another positive ion case. This prediction is borne out by entropies of activation for acid-catalyzed hydrolyses, typical values of $\Delta S^{\ddagger}$ being 0 to 10 eu for unimolecular and −15 to −30 eu for bimolecular reactions.[14] The isotopic exchange reaction being studied here shows a large negative entropy of activation, indicating by this criterion[13,15] that the rate-determining step is bimolecular rather than being a unique molecular decomposition. It is interesting to note that the acid-catalyzed oxygen exchange in water of benzoic acids exhibits an entropy of activation of −30 eu.[16]

Other mechanisms involving variations in the timing of the protonation (and possibly even its position), nucleophilic attack, and leaving group release cannot be excluded on the basis of the present data. For instance, the present data are also consistent with concerted rate-determining protonation and nucleophilic attack to form a tetrahedral intermediate. Furthermore, the assumptions of rapid proton transfers among tetrahedral intermediates such as those proposed here may not be so reliable as they once seemed,[17] although, as pointed out above, the positive ρ value observed makes it clear that nucleophilic attack is the predominant factor in controlling the rate. Although it does not seem likely in view of the greater basicity of amide oxygen than nitrogen, the present data do not exclude mechanisms involving protonation on nitrogen, either

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

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

[13] F. A. Long, J. G. Pritchard, and F. E. Stafford, *ibid.*, **79**, 2362 (1957).

[14] L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 24 (1963).

[15] R. Taft, *J. Amer. Chem. Soc.*, **74**, 5372 (1952).

[16] C. A. Bunton, D. James, and J. Senior, *J. Chem. Soc.*, 3364 (1960).

[17] For instance, see D. G. Oakenfull and W. P. Jencks, *J. Amer. Chem. Soc.*, **93**, 178 (1971), and earlier papers cited therein.

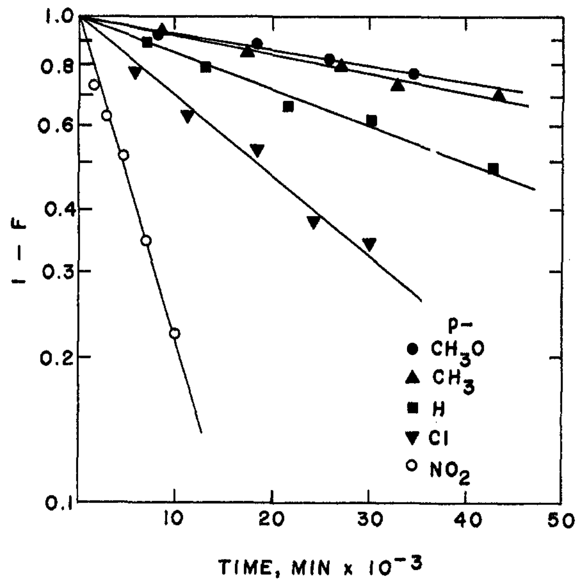

Figure 1.—The kinetics of the ammonium chloride catalyzed nitrogen-15 exchange of nitrogen-15 enriched para-substituted benzamides with liquid ammonia at 40.0° (NH_4Cl = 3.00 *M*).

concerted with or followed by nucleophilic attack on carbon and release of the leaving group.

Experimental Section

Preparation of Labeled Compounds.—For the preparation of the labeled amides, ammonia-^{15}N was generated from an aqueous solution of commercial ammonium-^{15}N nitrate or chloride by the dropwise addition of 40% sodium hydroxide. The ammonia-^{15}N was carried on a stream of dry nitrogen through a sodium hydroxide drying tube and bubbled through a solution of the appropriate para-substituted benzoyl chloride in dry benzene. The unreacted ammonia was trapped in two hydrochloric acid traps. As the ammonia–nitrogen mixture bubbled through the benzene solution, the forming amide precipitated. The precipitate was filtered, washed with benzene to remove excess acid chloride, washed with water to remove ammonium chloride, and then crystallized from water or methanol. In all cases the physical constants of the labeled benzamides agree with the literature values for the unlabeled compounds. In general, the amides were prepared with a nitrogen-15 content of approximately 6%, and they were then diluted with unlabeled material to the desired enrichment of about 1.5% excess nitrogen-15. Yields typically ranged from 62 to 88%.

Kinetics of Acid-Catalyzed Exchange.—The acid-catalyzed exchange reactions were carried out using 5-ml samples of liquid ammonia which were 0.1 *M* in para-substituted benzamide and which contained various concentrations of ammonium chloride. For one run usually six samples were prepared. Exchange flasks were made from 15-cm-long sections of 19-mm Pyrex tubing with smaller neck sections 10 cm long of 9-mm Pyrex tubing; the smaller neck made sealing easier when the tube was evacuated. After weighing appropriate quantities of the benzamides and ammonium chloride into the sample flasks, 5 ml of liquid ammonia was distilled into each flask with a system patterned after that of Blair.[18] The ammonia solution was frozen with a liquid air bath, the exchange tube was evacuated, and the reaction tube was sealed off. The exchange flasks were placed in steel bombs, which were then placed in an oil bath at 32, 36, or 40° ± 0.01°. When the contents of the flasks had reached temperature equilibrium, usually after 1 hr, the zero-time sample was removed. The remaining samples were taken out at convenient intervals. The exchange flasks were removed from the steel bombs and placed in an alcohol–Dry Ice bath to stop the reaction. The flasks were then opened and the ammonia was allowed to evaporate. The amide was crystallized from water and dried thoroughly in a vacuum desiccator overnight, and the melting point was taken. In every case the melting point was identical with that of the starting amide. The nitrogen-15 content of each sample was then determined. It should be pointed out that the nitrogen-15 enrichment of the zero-time samples agreed within experimental error with the determined enrichments of the starting materials. This showed that the ammonium chloride had been removed during the work-up.

Kinetics of Base-Catalyzed Exchange.—The attempted nitrogen exchange using commercial sodium amide as the catalyst followed the procedure described previously for the acid-catalyzed exchange except that sodium amide was used in place of ammonium chloride.

The nitrogen exchange reaction was also attempted using potassium amide as the catalyst. The potassium amide was generated by dissolving an appropriate amount of potassium metal in liquid ammonia along with approximately 25 mg of ferric nitrate hydrate to catalyze the formation of the potassium amide.[19] The solution was allowed to sit for 30 min to ensure complete formation of the potassium amide. During this time ammonia was added as necessary to maintain the desired volume.

The potassium amide–liquid ammonia solution was added to an exchange tube containing the organic amide by means of a pipette which had been cooled to liquid air temperature. The remainder of the kinetic run was then carried out as described in the acid-catalyzed section.

Isotopic Analysis.—The nitrogen in the organic samples was converted to nitrogen gas for isotopic analysis by the pyrolysis method of Rolle.[20] For each isotopic analysis a sample of the nitrogen-15 enriched compound of a size sufficient to produce approximately 2 ml of nitrogen upon complete pyrolysis was used. The sample, together with about 500 mg of copper oxide, about 200 mg of calcium oxide, and several small lengths of copper wire, was placed in a tube equipped with a break off seal. The tube was evacuated and sealed. The sample was then pyrolyzed at 500° for 8 hr. The purification of the nitrogen produced in the pyrolysis was carried out on a vacuum line by circulating the pyrolysis gases for 30 min over copper–copper oxide contained in a Vycor tube heated to approximately 700° by means of an automatic Toepler pump. During the circulation any carbon dioxide and water which had formed were condensed in a liquid air cold trap. The nitrogen was then pumped into a sample bulb for mass spectrometric analysis.

The 29/28 *m/e* ratios for the samples were determined with an isotope ratio mass spectrometer. In order to correct for any day-to-day instrumental variations, an analysis of standard nitrogen taken from a lecture bottle was made after each series of three analyses. The factor necessary to correct the standard to an arbitrary nitrogen-15 value, taken as the normal abundance figure of 0.359%, was determined, and all the analytical results taken for a given series were multiplied by this factor. Periodically, a background spectrum was determined. It was never necessary to make a background correction.

Calculations.—The nitrogen-15 content of the nitrogen gas was calculated from the mass spectra by standard means.[8]

An example of the kinetics obtained is shown in Figure 1, a semilogarithmic plot of $(1 - F)$, where F is the fraction of reaction, *vs.* time for the ammonium chloride catalyzed nitrogen-15 exchange of nitrogen-15 enriched para-substituted benzamides with liquid ammonia at 40°. Figure 1, as well as all of the others obtained, clearly shows a first-order dependence of the exchange rate with time. The rate constants shown in Tables I and II were calculated from the slopes of these lines using a least-squares program on an IBM 7040 computer. Several of the fastest exchange reactions have been followed for several half-lives and have proved to be first order over the entire range. Many of the reactions could not be followed through even 1 half-life due to the excessive time requirements.

In calculating the fraction of reaction from the analyzed nitrogen-15 content, the value of the nitrogen-15 content at infinite time was taken as 0.359%, the natural abundance, since ammonia is present in large excess compared to the amide. The ammonia used as the solvent for these exchange reactions gave this natural abundance figure within experimental error when analyzed for nitrogen-15.

Registry No.—Ammonia, 7664-41-7.

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[18] J. S. Blair, *J. Amer. Chem. Soc.*, **48**, 91 (1926).

[19] L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 907.

[20] W. Rolle, *Abh. Deut. Akad. Wiss. Berlin, Kl. Chem., Geol., Biol.*, 395 (1964) (published 1965); W. Rolle, Ph.D. Dissertation, University of Leipzig, Leipzig, Germany, 1966; W. Rolle, *Kernenergie*, **5**, 403 (1962).