Kinetics of Reactions of Amines with Isatoic Anhydride

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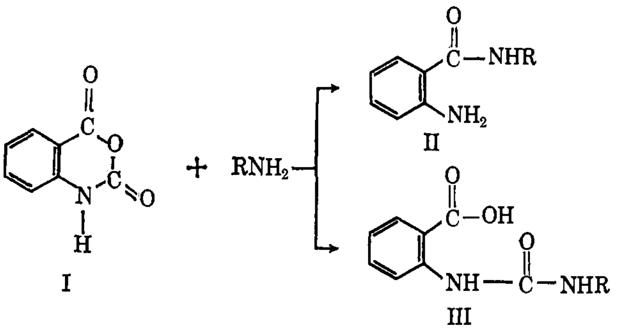
Abstract: The reaction of *n*-butylamine with isatoic anhydride (I) in water gives two products, an anthranilamide (IIa) and an *o*-ureidobenzoic acid (IIIa). The rate law for formation of IIa is zero order in amine and first order in *n*-butylammonium ion. Formation of IIIa is first order in amine and zero order in *n*-butylammonium ion. Under our reaction conditions, *t*-butylamine and I formed only ureidobenzoic acid IIIb and anthranilic acid, a hydrolysis product. IIIb was formed according to the same rate law as IIIa. At pH >10, hydrolysis was mostly first order in hydroxide ion but there was a small pH-independent component. Reaction of I with aniline formed only anthranilamide IIc, and was first order in aniline. These observations are in accord with the scheme of Chart I. The rate laws for formation of IIa and IIc differ because I is mainly present as such in solutions with aniline and as its conjugate base in solutions with *n*-butylamine.

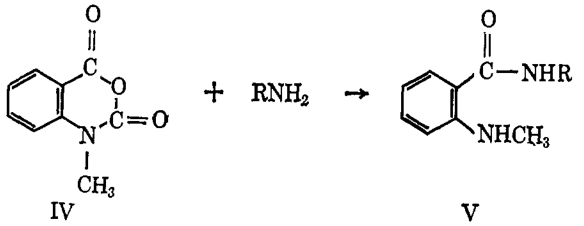
Two types of products are formed in reactions of amines with isatoic anhydride[3] (I).[4-6] Anthranilamides (II) appear to result from nucleophilic attack at C-4 of isatoic anhydride, with subsequent loss of carbon dioxide from a presumed intermediate of the carbamic acid type. *o*-Ureidobenzoic acids (III) are formally the consequence of nucleophilic attack at C-2 of I, but another mechanism for their formation is also conceivable (*vide infra*).



I II III

a, R = n-C_4H_9
b, R = t-C_4H_9
c, R = C_6H_5

Staiger and Wagner[5] showed that formation of ureidobenzoic acids is favored by bulkiness in the amine; for example, *t*-butylamine gave mainly IIIb under most conditions while *n*-butylamine gave mainly IIa. Also, they demonstrated that formation of ureidobenzoic acids was greater at higher concentrations of the amine reactant. Staiger and Miller[6] found that N-methylisatoic anhydride (IV) reacts with amines and other nucleophiles exclusively at C-4, forming (with amines) amides of N-methylanthranilic acid (V).



IV V

The question of what governs the formation of type II *vs.* type III products in reactions with amines is an interesting one. It has been discussed by Staiger and Miller.[6] We felt that a kinetic study would be illuminating and therefore undertook the investigation described below.

Experimental Section

Preparation and Properties of IIa and IIIa. Initially, samples of IIa and IIIa were prepared from I and *n*-butylamine after Staiger and Wagner.[5] A pure sample of IIa was obtained by dissolving 1 g of crude IIa in 50 ml of 1.25 *M* hydrochloric acid, extracting three times with 20-ml portions of ethyl ether, reprecipitating IIa by addition of sodium hydroxide, collecting the precipitate, washing with distilled water, and finally subliming at 100° and 0.1 mm. Pure IIa had mp 88.8–90.2°, λ_{max} 224 mμ (ϵ 10,000), in water solution at pH 1.0.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.38. Found:[7] C, 68.72, 68.49; H, 8.35, 8.26.

Two grams of crude IIIa was dissolved in 200 ml of 5% sodium bicarbonate solution, the solution was twice extracted with 100-ml portions of ethyl ether, and the aqueous layer was carefully acidified by addition of cold 2.5 *M* hydrochloric acid. The precipitate was collected, washed with cold distilled water, and dried 12 hr *in vacuo* over phosphorus pentoxide. Pure IIIa melts at 165–165.5° (somewhat dependent on the rate of heating) (lit.[5] 164°), and in water solution at pH 1.0 had λ_{max} 222 mμ (ϵ 31,200), 250 (10,500), and 313 (3820).

The ratio of IIIa to IIa was found to be increased by having sodium hydroxide present during reaction of I with *n*-butylamine. A solution of 5.05 g of I in 20 ml of dimethylformamide was poured into 125 cc of water at 0°; I was precipitated as a microcrystalline suspension. With efficient stirring, 155 ml of 0.2 *M* sodium hydroxide solution (precooled to 0°) was quickly added. Sixty seconds later, 100 ml of a 1.55 *M* *n*-butylamine solution in water was added with continued efficient stirring. IIa and IIIa were isolated by acid–base extraction and precipitation, as described above. A 56% yield of IIIa was obtained, but only a trace of IIa.

Preparation and Properties of IIc and IIIc. To a suspension of 1.63 g of I in 300 ml of water at 6°, a chilled suspension of 9.31 g of aniline in 100 ml of water was quickly added with vigorous stirring and external cooling by ice. The temperature rose to 10° and then slowly receded, and solid started to precipitate almost immediately. The mixture was allowed to stand in the refrigerator overnight, and IIc and IIIc were isolated by acid–base extraction and precipitation, as above. The yield of IIc was 1.92 g (90.3%); that of IIIc was 0.013 g (0.5%).

In another experiment, to a suspension of 1.63 g of I in 50 ml of water at 9°, 250 ml of a chilled 0.05 *M* aqueous sodium hydroxide solution was quickly added with rapid stirring. Within 75 sec all

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[2] On sabbatical leave from Dickinson College, 1964–1965.

[3] The current official *Chemical Abstracts* name for isatoic anhydride is 2H-3,1-benzoxazine-2,4(1H)-dione.

[4] R. P. Staiger and E. C. Wagner, *J. Org. Chem.*, **13**, 347 (1948).

[5] R. P. Staiger and E. C. Wagner, *ibid.*, **18**, 1427 (1953).

[6] R. P. Staiger and E. B. Miller, *ibid.*, **24**, 1214 (1959).

[7] Analyses by Triangle Chemical Laboratories, Chapel Hill, N. C.

the I had dissolved. Immediately a suspension of 9.31 g of aniline in 100 ml of water was added with vigorous stirring. The mixture was stirred a further 1.5 hr at 9° and allowed to stand in the refrigerator overnight; then IIc and IIIc were isolated. The yield of IIc was 0.59 g (28%); that of IIIc was 1.23 g (48%). In a similar run the aniline was added as a solution in 40% dioxane–60% water, but conditions were otherwise the same; the yields of IIc and IIIc were 38 and 46%, respectively.

IIc was purified as described above for IIa: mp 133–133.5°; λ_{max} 264 mμ (ε 9900) in water at pH 1.

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70. Found:[7] C, 73.20, 73.36; H, 6.12, 6.10.

IIIc was purified as described above for IIc: mp 183–183.4° (lit.[5] 183°); λ_{max} 226 mμ (ε 21,100), 260 (19,400), and 312 (5650) in water at pH 1.

IIb and IIIb were prepared after Staiger and Wagner,[5] and pure samples were prepared as described above for IIa and IIIa. IIb, mp 126–126.8°, had (at pH 1.0 in water) λ_{max} 223 mμ (ε 9530).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.38. Found:[7] C, 68.72, 69.05; H, 8.27, 8.33.

IIIb, mp 169.6–170° (lit.[5] 174–176°), had (at pH 1.0 in water) λ_{max} 224 mμ (ε 31,100), 252 (12,300), and 314 (4160).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83. Found:[7] C, 60.75, 60.70; H, 6.41, 6.68.

Materials for Kinetics. Isatoic anhydride, mp 244.4–245.2° (with gas liberation), and N-methylisatoic anhydride, mp 177.5–179°, were furnished by the Maumee Chemical Co. *n*-Butylamine (Eastman White Label) was twice fractionated through a spinning-band column; a center fraction, bp 76.5°, was used. *t*-Butylamine, bp 44° (755 mm), was a purified and redistilled sample kindly furnished by Mr. John H. Beale. Reagent grade aniline was redistilled from zinc dust through a column packed with stainless steel wool; a center fraction of bp 183–184° was used. Triethylamine (Matheson Coleman and Bell) was distilled from sodium hydroxide pellets; a center fraction of bp 89° was used. A pure sample of *n*-butylamine hydrochloride prepared by Dr. Roger H. Garst was used.

Kinetic Procedure. Reactions of I with *n*-Butylamine. Reactions were performed in the cell of a Cary 14 spectrophotometer, the cell compartment of which had been cooled to 1.3 ± 0.2° by circulation of water from an ice-water bath with external insulation by means of foam plastic blocks. A cuvette containing 2 ml of an aqueous solution of all reactants except isatoic anhydride was placed in the cell compartment and allowed to come to thermal equilibrium. The cell compartment was continuously flushed with nitrogen gas. A small diameter glass tube, through which a current of nitrogen gas was passing, was inserted into the solution in the cuvette, and then 25 μl of *ca.* 2×10^{-3} *M* isatoic anhydride in water was injected from a syringe. Shortly before injection, the chart motor was started. A few seconds after injection, the glass tube passing nitrogen (the function of which was to stir the solution) was withdrawn and the instrument was then able to draw a continuous record of absorbance as a function of time. The apparatus was arranged so that the operations of injection and insertion and withdrawal of the glass tube could be performed without lifting the lid of the cell compartment. Measurements were made at 222 mμ, with slit width *ca.* 0.15 mm. From the record of absorbance *vs.* time, pseudo-first-order rate coefficients (k_ψ) were reckoned by the Guggenheim method.[8]

In the kinetic runs, the initial concentration of I was not precisely known; therefore, the infinity absorbances from kinetic runs could not be used for dissection of k_ψ into the pseudo-first-order coefficients for formation of IIa and IIIa (symbolized k_A' and k_U', respectively). The yields of IIa and IIIa were determined in separate experiments in which, in an erlenmeyer flask jacketed with crushed ice, measured volumes of ice-cold standard solutions of I in water and of the amine and (sometimes) the amine hydrochloride and/or sodium chloride in water were combined so as to give reaction solutions having the same concentrations of the amine, amine hydrochloride, and NaCl as in the corresponding kinetic runs. After more than 10 half-lives at 0°, a measured volume of cold 1.3 *M* hydrochloric acid solution was added to each reaction solution, bringing it to pH 1, and the spectrum of the acidified infinity solution was measured at 222 mμ. From the absorbance at 222 mμ and the known extinction coefficients of IIa and IIIa at 222 mμ at pH 1 (*vide supra*), the yields of IIa and IIIa were reckoned. These were multiplied by k_ψ to furnish k_A' and k_U', respectively. Infinity spectra gave no indication of the formation of products other than IIa and IIIa.

It was shown that IIa and IIIa were stable, both under reaction conditions and at pH 1, for the periods of time involved in our experiments.

Reactions of I with NaOH. The procedure was the same as above, measurements being made again at 222 mμ. The measured pseudo-first-order rate coefficients pertain entirely to the formation of anthranilic acid. Runs were made at several temperatures, as indicated in Table IV.

Reactions of IV with *n*-Butylamine. The method was substantially the same as for reactions of I with this amine. The chief difference was that solutions of *n*-butylamine hydrochloride (0.02 *M*) in borate buffers were used to provide *n*-butylamine. Ionic strength was maintained constant at 0.2 by compensation with KCl. All measurements were made at 222 mμ. *n*-Butylamine concentrations were reckoned on the basis of $pK_a = 11.52$ at 1.3°; this value was extrapolated from measurements of Evans and Hamann[9] and agrees with a rough determination by Pearson and Williams.[10]

Reactions of I with *t*-Butylamine. The method was substantially the same as for reactions of I with *n*-butylamine. Measurements were made at 230 mμ. Separate runs to determine the spectra of infinity solutions were performed, and the k_ψ's were dissected (see text).

Reactions of I with Aniline. Reactions were performed in volumetric flasks in a thermostat at 29.7°. Measured volumes of thermostated aqueous standard solutions of I and of aniline were thoroughly mixed to start a run. The concentration of I in the reaction solutions was *ca.* 4×10^{-4} *M*. Aliquots (2 ml) were withdrawn at measured times and quenched in 25 ml of 0.122 *M* hydrochloric acid solution. Absorbances were read at 222 mμ by means of a Cary 14 or Hitachi–Perkin-Elmer 139 spectrophotometer. Spectra of infinity solutions from the kinetic runs were found to match those of IIc under the same conditions (of aniline concentration and pH) within experimental error. It was concluded that IIIc was not formed, and that IIc was the sole product.

pK_a of Isatoic Anhydride. To a solution of 0.146 g of I in 100 ml of 60% methanol–40% water, at 0°, increments of 0.1 *M* sodium hydroxide solution were added rapidly with stirring, and the pH was read (glass electrode) after each addition. The pH at successive (total) volumes of NaOH was as follows: 2.55 ml, 8.14; 3.50 ml, 8.30; 4.5 ml, 8.40; 5.5 ml, 8.50; 6.5 ml, 8.60. The pK_a reckoned from these data by the expression, $pK_a = \text{pH} + \log$ [(initial moles of I less moles of NaOH added)/(moles of NaOH added)], decreases with increasing volume of NaOH. This is attributed to hydrolysis of I which forms isatoic acid and/or anthranilic acid and carbonic acid, all of which are stronger acids than I. Accordingly, the more reliable values for the pK_a are those at lower volumes of titrant. From these data, we estimate the pK_a of isatoic anhydride to be 8.6 ± 0.1.

Results

Reaction of Isatoic Anhydride (I) with *n*-Butylamine. This reaction was studied in water solution. Isatoic anhydride is soluble in water to a small extent which is adequate for the purposes of a photometric kinetic study.[11] Its reaction with *n*-butylamine is quite rapid; at 1.3°, half-lives ranged from 25 to 316 sec under the conditions we employed.

When solutions of I and *n*-butylamine were combined, the absorbance at 222 mμ was at first much higher than if the amine were not present. If the mixture was quenched with hydrochloric acid soon after mixing, the spectrum of the resulting solution (at pH *ca.* 1) indicated very little consumption of isatoic anhydride. The initial rapid rise in absorbance is attributed to salt formation, which is to be expected on combination of an acid of $pK_a = 8.6$ and an amine of $pK_a = 11.5$.

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[8] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p 49.

[9] A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, 47, 34 (1951).

[10] R. G. Pearson and F. V. Williams, *J. Am. Chem. Soc.*, 76, 258 (1954).

[11] The solubility of I in water is 0.032 g/100 ml at 25°; information supplied by Maumee Chemical Co., Toledo, Ohio.

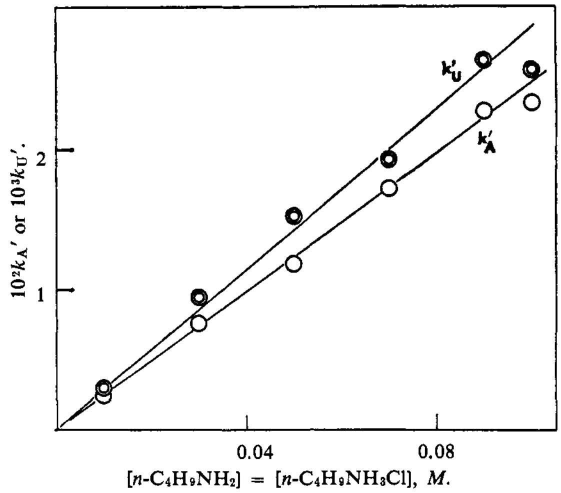

Figure 1. Reaction of isatoic acid with 1:1 n-butylamine–n-butylammonium buffers. Dependence of k_A' and k_U' on buffer concentration (data of Table I, series A).

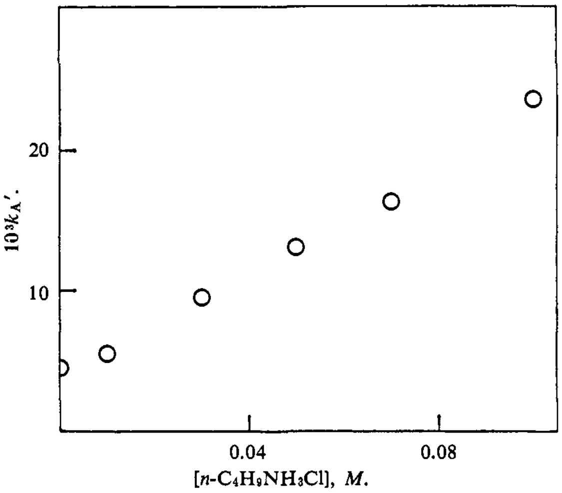

Figure 2. Dependence of k_A' on n-butylammonium chloride concentration, with butylamine constantly 0.2 M (data of Table I, series B).

After the initial rise, absorbance decayed rapidly according to a first-order kinetic law, and pseudo-first-order rate coefficients (k_ψ) were thereby determined. The ultraviolet spectra of infinity solutions, examined at pH 1, indicated that only IIa and IIIa were formed. Multiplication of the k_ψ by the photometric fractional yields of IIa and IIIa gave k_A' and k_U', respectively.[12]

In one series of runs (Table I, series A), I was allowed to react with a set of n-butylamine–n-butylammonium chloride buffers, of constant buffer ratio but varying absolute buffer concentration, at ionic strength 0.1. Both k_A' and k_U' increased linearly with buffer concentration (Figure 1).

In another series (Table I, series B), the amine concentration was held constant at 0.2 M but the amine hydrochloride concentration was varied. k_U' did not vary significantly within this series, but k_A' increased in a nearly linear fashion with n-butylammonium chloride concentration (Figure 2). However, the line of experimental points did not extrapolate to zero rate at zero amine hydrochloride concentration.

In a third series (Table I, series C), the butylammonium chloride concentration was held constant but the amine concentration was varied. Now k_A' was essentially invariant, but k_U' increased linearly with n-butylamine concentration (Figure 3).

In a fourth series (Table I, series D), no amine hydrochloride was present and the amine concentration was varied. k_U' increased nearly linearly with amine concentration (Figure 4). A plot (not shown) of k_A' against amine concentration was curved (concave downward), but k_A' was found to be linearly related to the square root of amine concentration (Figure 5).

Reaction of N-Methylisatoic Anhydride (IV) with n-Butylamine. Because of the great reactivity of IV, it was not feasible to determine reaction rates by our techniques using solutions of n-butylamine in water. At the high dilution of the amine which would be necessary, traces of carbon dioxide and other adventitious impurities might seriously disturb the amine concentration. Dilute solutions of n-butylammonium chloride in borate buffers provided amine concentrations on the order of 10^{-5} M; with such solutions IV reacted at a convenient rate, by a first-order law. IV is known to form only products of type V with amines.[6] In Table II, the measured pseudo-first-order rate coefficients and the derived second-order coefficients are recorded. The second-order rate coefficient (last column) at three

Table I. Reactions of Isatoic Anhydride with n-Butylamine in Water at 1.3°[a]

[n-C_4H_9-NH_2], M	[n-C_4H_9-NH_3Cl], M	[NaCl], M	10^3k_ψ, sec^{-1}	IIIa, %	$10^3k_U'$, sec^{-1}	IIa, %	$10^3k_A'$, sec^{-1}
			Series A				
0.01	0.01	0.09	2.7	11.0	0.30	89.0	2.40
0.03	0.03	0.07	8.6	11.0	0.95	89.0	7.65
0.05	0.05	0.05	13.4	11.4	1.53	88.6	11.9
0.07	0.07	0.03	19.2	10.1	1.94	89.9	17.3
0.09	0.09	0.01	25.3	10.4	2.63	89.6	22.7
0.10	0.10	...	25.9	9.9	2.56	90.1	23.3
			Series B				
0.20	0.01	0.09	9.7	43.0	4.17	57.0	5.53
0.20	0.03	0.07	13.9	31.6	4.39	68.4	9.51
0.20	0.05	0.05	17.2	23.8	4.09	76.2	13.1
0.20	0.07	0.03	20.9	18.9	3.95	81.1	16.9
0.20	0.10	...	27.3	14.0	3.82	86.0	23.5
			Series C				
0.01	0.10	0.10	20.9	0.5	0.10	99.5	20.8
0.03	0.10	0.10	21.8	3.0	0.65	97.0	21.1
0.05	0.10	0.10	20.1	4.6	0.92	95.4	19.2
0.07	0.10	0.10	23.8	6.3	1.50	93.7	22.3
0.09	0.10	0.10	22.8	7.7	1.76	92.3	21.0
0.10	0.10	0.10	25.9	8.5	2.20	91.5	23.7
			Series D				
0.01[b]			1.67	19	0.32	81	1.35
0.02			2.19	24.7	0.54	75.3	1.65
0.03			2.73	29.0	0.79	71.0	1.94
0.04			3.14	31.4	0.99	68.6	2.15
0.05			3.90	33.7	1.31	66.3	2.59
0.06			4.23	35.8	1.51	64.2	2.72
0.08			4.77	38.4	1.83	61.6	2.94
0.10			5.68	41.6	2.36	58.4	3.32
0.12			6.59	42.3	2.79	57.7	3.80
0.15			7.35	44.3	3.26	55.7	4.09
0.20			8.46	46.9	3.97	53.1	4.49

[a] Initial concentration of isatoic anhydride *ca.* 2.5 × 10^{-5} M.
[b] Temperature, 5.2°.

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[12] k_A' concerns formation of anthranilamides II. k_U' concerns formation of ureidobenzoic acids III.

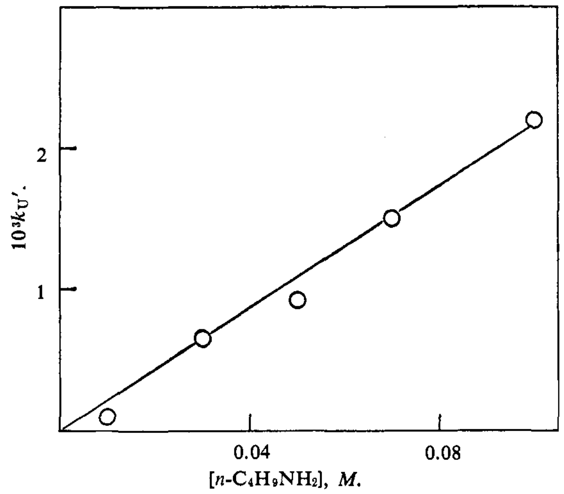

Figure 3. Dependence of k_U' on n-butylamine concentration, with n-butylammonium chloride constantly 0.1 M (data of Table I, series C).

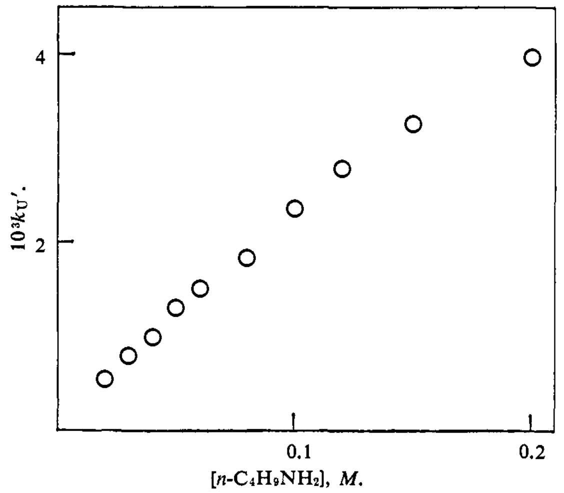

Figure 4. Dependence of k_U' on n-butylamine concentration, in the absence of salts (data of Table I, series D).

pH's was nearly constant; the average value is 86 l. mole^{-1} sec^{-1} at 1.3°.

Table II. Reactions of N-Methylisatoic Anhydride with n-Butylamine in Water at 1.3°

$[B(OH)_3]$, M	$[NaB(OH)_4]$, M	pH	$[C_4H_9NH_2]$ (calcd), M	10^3k_ψ, sec^{-1}	$k_\psi/[C_4H_9NH_2]$, l. mole^{-1} sec^{-1}
0.041	0.059	9.14	8.3×10^{-5}	7.58	91
0.041	0.059	9.14	8.3×10^{-5}	7.58	91
0.057	0.043	8.82	4.0×10^{-5}	3.64	91
0.057	0.043	8.82	4.0×10^{-5}	3.32	83
0.072	0.028	8.51	1.96×10^{-5}	1.45	74

Reaction of Isatoic Anhydride with t-Butylamine. In a series of runs without added amine hydrochloride or other salts, the reaction rate was determined as a function of t-butylamine concentration (Table III). Again the disappearance of substrate followed the first-order law. Examination of ultraviolet spectra of acid-quenched infinity samples showed, however, that hydrolysis to anthranilic acid was extensive. There was clear evidence that IIIb was formed as a minor product, but no indication of IIIa. It was possible to account quantitatively for the spectra as mixtures of IIIb and anthranilic acid.

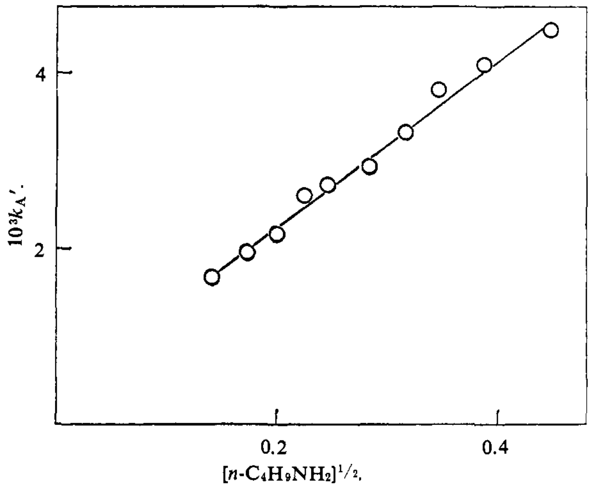

Figure 5. Dependence of k_A' on the square root of n-butylamine concentration, in the absence of added salts (data of Table I, series D).

Table III. Reactions of Isatoic Anhydride with t-Butylamine in Water at 25.1°

$[t\text{-}C_4H_9NH_2]$, M	10^3k_ψ, sec^{-1}	IIIb, %	Anthranilic acid, %	$10^3k_U'$, sec^{-1}	$10^3k_H'$ sec^{-1}
0.02	1.65	5	95	0.08	1.57
0.05	2.03	9	91	0.18	1.85
0.10	2.63	12	88	0.32	2.31
0.15	3.16	15	85	0.48	2.68
0.20	3.49	18	82	0.63	2.86

In the usual way, the k_ψ values were dissected, with use of fractional yields of IIIb and anthranilic acid derived from infinity spectra, into k_U' and k_H'. The latter pertains to the hydrolysis reaction. The resulting values are listed in Table III.

It is clear in Table III that k_U' increases linearly with t-butylamine concentration. The linear relationship is exact at 0.1–0.2 M amine, and the small deviations at lower concentrations can be attributed to the low relative precision of the IIIb yields upon which the k_U' are based.

Hydrolysis of Isatoic Anhydride. Rates of reactions of I with aqueous sodium hydroxide at several concentrations and temperatures were determined. The pseudo-first-order coefficients (k_H') obtained are listed in Table IV, together with second-order coefficients (k_H) which represent $k_H'/[OH^-]$. The k_H values were substantially independent ot hydroxide ion concentration. From the average values of k_H at 1.3 and 15.0°,[13] ΔH^* was reckoned to be 10.8 kcal/mole and ΔS^* −24.6 cal deg^{-1} mole^{-1}.

[13] The datum at 23.1° was neglected in computation of activation parameters because of its low statistical weight.

Table IV. Reactions of Isatoic Anhydride with NaOH in Water[a]

	1.3°		15.0°		23.1°	
[NaOH], M	$10^3k_H'$, sec^{-1}	k_H, M^{-1} sec^{-1}	$10^3k_H'$, sec^{-1}	k_H, M^{-1} sec^{-1}	$10^3k_H'$, sec^{-1}	k_H, M^{-1} sec^{-1}
0.01	0.47	0.047	1.16	0.116	2.27	0.227
0.05	2.46	0.049	6.75	0.135		
0.10	5.30	0.053	16.0	0.160		
0.15	7.82	0.052	21.3	0.142		
0.20	10.5	0.052				
Average		0.051		0.138		0.227

[a] Ionic strength held constant at 0.2 by compensation with NaCl, as required. Initial concentration of I *ca.* 2.5×10^{-5} M.

From the pK_a of *t*-butylamine[14] and the pK_w of water, the hydroxide ion concentrations prevailing in the several experiments of Table III were reckoned. A plot of k_H' against these hydroxide ion concentrations is presented as Figure 6. A linear relationship obtains. The slope is 0.22 l. mole^{-1} sec^{-1} and should represent k_H at 25.1°. This figure is slightly lower than the measured k_H at 23.1°. In view of uncertainties in the pK_a used to reckon hydroxide ion concentration, the agreement is regarded as satisfactory.

It is noteworthy that there is a nonzero intercept in Figure 6 of magnitude 9×10^{-4} sec^{-1}. This represents a pH-independent component of hydrolysis rate, within the pH range covered by the experiments of Table III. Preliminary studies of hydrolysis rate in triethylamine–triethylammonium chloride buffers also indicate an appreciable pH-independent component.

Reaction of Isatoic Anhydride with Aniline. In a series of runs without added aniline hydrochloride or other salts, the pseudo-first-order coefficient was determined by a photometric procedure which involved absorbance measurements on acid-quenched samples. Infinity spectra indicated that IIc was the only product formed. The reaction was essentially first order in aniline, as shown (Table V) by the near-constancy of the second-order rate coefficients, k_A, which represent $k_\psi/[C_6H_5NH_2]$.

Table V. Reactions of Isatoic Anhydride with Aniline in Water at 29.7°

$[C_6H_5NH_2]$, M	10^4k_ψ, sec^{-1}	10^3k_A, l. mole^{-1} sec^{-1}
0.03	1.8	6.1
0.06	3.3	5.6
0.09	4.7	5.2
0.12	6.3	5.3
0.15	7.3	4.9
0.18	8.8	4.9

The reactions of isatoic anhydride with aniline and with *n*-butylamine to form anthranilamides (II) differ remarkably in their kinetic dependence on amine concentration. Whereas the former is first order in amine, the latter is half-order except in the presence of *n*-butylammonium chloride where it is zero order.

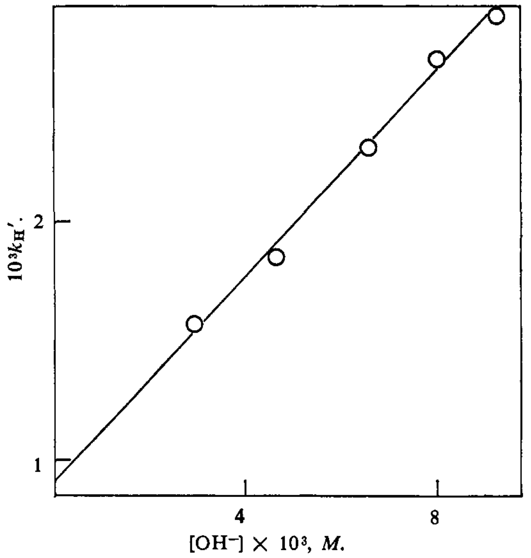

Figure 6. Dependence of hydrolysis rate coefficient, k_H', on calculated hydroxide ion concentration in reactions of isatoic anhydride with *t*-butylamine solutions (data of Table III).

The second-order rate coefficients in Table V diminish somewhat with increasing aniline concentration. Similar effects have been noted in reactions of aniline with 2,4-dinitrohalobenzenes, and they have been attributed to charge-transfer complex formation between aniline and the aromatic substrate.[15]

An effort was made to determine the rate of reaction of I with aniline at 29.7° as a function of aniline concentration in 1 : 1 triethylamine–triethylammonium chloride buffers. Each buffer constituent was 0.18 M and aniline varied from 0.03 to 0.15 M. The photometric first-order rate varied only randomly with aniline concentration (average $k_\psi = 3.12 \times 10^{-3}$ sec^{-1}), and the spectra of infinity samples gave no indication that IIc or IIIc had been formed. Substantially the same pseudo-first-order rate coefficient was obtained when I was allowed to react in a triethylamine–triethylammonium chloride buffer of similar composition in the absence of aniline. Aniline was thus, under the conditions employed, an unsuccessful competitor with water and/or hydroxide ion for isatoic anhydride or reactive intermediates derived therefrom.

These observations contrast with our preparative experience (see Experimental Section) that reactions of I with aniline in the presence of a slight excess of sodium hydroxide afforded appreciable yields of both IIc and IIIc.

Discussion

A Model for the Reaction System. We shall discuss our results with respect to the reaction scheme presented in Chart I. This scheme bears a close resemblance to one outlined by Staiger and Miller[6] for reactions of isatoic anhydride, and to one proposed by Kopple[16] for reactions of aliphatic N-carboxyamino acid anhydrides.

In this model, conversion of I to its anion (VII) is a mobile acid–base equilibrium with equilibrium constant K_1. The anion (VII) is in rapidly reversible equi-

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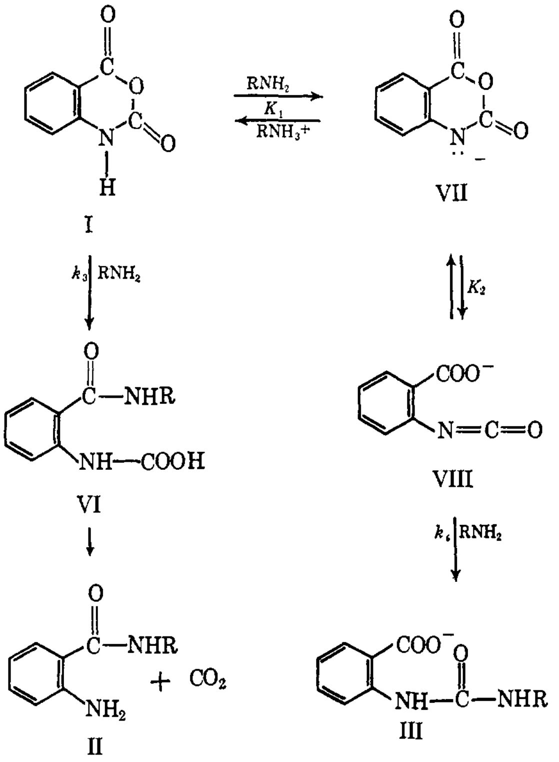
[14] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965, p 36, gives pK_a = 10.81 for *t*-butylamine at 17°; this is an average of two concordant observations and is nearly the same as that of *n*-butylamine. This pK has been corrected to 25° on the assumption that its temperature dependence is the same as for *n*-butylamine;[9] the pK_a at 25° so estimated is 10.63.

[15] S. D. Ross and I. Kuntz, *J. Am. Chem. Soc.*, 76, 3000 (1954); J. F. Bunnett and R. H. Garst, *ibid.*, 87, 3875 (1965).

[16] K. D. Kopple, *ibid.*, 79, 6442 (1957).

librium with the isomeric isocyanate (VIII). Reactions of I with the amine to form carbamic acid VI and of VIII with the amine to form III are both slow and kinetically first order in amine.

Chart I



Step 3, reaction of I with amine to form carbamic acid VI, is postulated to be irreversible. The model requires no commitment as to whether the carbamic acid accumulates as such (or as its anion) or whether it proceeds to II at a rate comparable to or greater than its rate of formation. However, as discussed below, this question is significant in respect to obtaining rate coefficients from photometric data.

Let $[I]_{st} = [I] + [VII] + [VIII]$. From Chart I and our method of evaluating experimental rate coefficients, it follows that

$$d[VI]/dt = k_A'[I]_{st} = k_3[I][RNH_2]$$

$$d[III]/dt = k_U'[I]_{st} = k_4[VIII][RNH_2]$$

If we set up equilibrium expressions appropriate for the equilibria involved in the model, and make appropriate substitutions in the above equations, we obtain

$$k_A' = \frac{k_3[RNH_3^+][RNH_2]}{[RNH_3^+] + K_1(1 + K_2)[RNH_2]} \qquad (1)$$

$$k_U' = \frac{k_4K_1K_2[RNH_2]^2}{[RNH_3^+] + K_1(1 + K_2)[RNH_2]} \qquad (2)$$

If $[RNH_3^+] >> K_1(1 + K_2)[RNH_2]$, these equations simplify to

$$k_A' = k_3[RNH_2] \qquad (3)$$

$$k_U' = k_4K_1K_2[RNH_2]^2/[RNH_3^+] \qquad (4)$$

If $K_1(1 + K_2)[RNH_2] >> [RNH_3^+]$, eq 1 and 2 simplify to

$$k_A' = \frac{k_3[RNH_3^+]}{K_1(1 + K_2)} \qquad (5)$$

$$k_U' = \frac{k_4K_2[RNH_2]}{1 + K_2} \qquad (6)$$

The extreme situation of eq 3 and 4 is that in which equilibrium 1 lies nearly entirely on the side of undissociated I. The extreme situation of eq 5 and 6 is that in which it lies nearly entirely on the side of anion VII and/or isocyanate VIII.

Predictions from the Model. Knowing the basicities of the amines employed and having determined the (apparent) pK_a of isatoic anhydride, we are able to forecast for any experiment whether the extreme of eq 3 and 4 or that of eq 5 and 6 should obtain, or whether the situation should be intermediate. If VII is in equilibrium with VIII with equilibrium constant K_2, as in Chart I, $K_{app} = K_a(1 + K_2)$, where K_{app} is the measured and K_a is the true acid dissociation constant of isatoic anhydride. Accordingly, $\log K_1(1 + K_2) = pK_{Am} - pK_{app}$, where pK_{Am} is the dissociation constant of RNH_3^+. Using $pK_{Am} = 11.52$ for *n*-butylamine and *t*-butylamine and 4.6 for aniline,[17] we reckon $K_1(1 + K_2)$ to be 830 for the two butylamines and 1×10^{-4} for aniline. In consideration of the amine and amine hydrochloride concentrations used in our experiments, it follows that the inequality which calls for eq 5 and 6 should prevail in the experiments with the butylamines.

The situation with aniline is less extreme. Taking account of the pK's of aniline and of isatoic anhydride and of their concentrations in the reaction solutions, one reckons that the anilinium ion concentration should exceed $K_1(1 + K_2)[C_6H_5NH_2]$ about 12-fold at 0.03 *M* aniline and about fivefold at 0.18 *M* aniline; see Table V. This approaches the extreme which calls for eq 3 and 4 to be obeyed at the lowest aniline concentration, but at the highest aniline concentration some deviation might be expected in the sense of a decreasing response of k_A' to increasing aniline concentration.

Comparison of Predictions with Observations. Our observations are in excellent accord with the predictions of this model. In the *n*-butylamine reactions (Table I), k_A' should according to eq 5 depend linearly on butylammonium ion concentration and be independent of butylamine concentration. In fact k_A' was essentially invariant at constant *n*-butylammonium ion concentrations despite changes in amine concentration (series C) and it depended linearly on amine hydrochloride concentration whether or not the amine concentration was varied (series A and B; Figures 1 and 2). In solutions free of added salts, the butylammonium ion concentration should depend on the square root of the amine concentration, and indeed k_A' was found to be linearly related to the half-power of butylamine concentration (series D; Figure 5).

With *n*-butylamine, k_U' should according to eq 6 be linear with amine concentration and independent of butylammonium ion concentration. Experimentally (Table I, series B), k_U' varied only randomly when the amine concentration was held constant and the amine hydrochloride concentration was varied. k_U' depended linearly on amine concentration in series A and C (Figures 1 and 3) whether or not the butylammonium ion concentration was changed, and when amine hydrochloride was omitted from the reaction mixture (series D; Figure 4).[18]

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[17] R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," 2nd ed, Butterworths, London, 1959, p 532.

The same pattern is expected for *t*-butylamine reactions. In conformity to eq 6, k_U' in reactions not containing added salts was found to depend linearly on *t*-butylamine concentration (Table III).

We have seen that in aniline reactions, the extreme of eq 3 and 4 should be approached, more closely at lower than at higher aniline concentrations. In our experiments, we were able only to measure k_A' (k_ψ in Table V); it was very nearly linear with aniline concentration as called for by eq 3. The modest decrease in k_A with increasing aniline concentration may represent increased significance of the second term in the denominator of eq 1; if so, it matches an expectation from the model, as discussed above.

Absolute Values of Rate Coefficients. We have seen that eq 5 should be valid for reactions of I with *n*-butylamine. Knowing k_A' at various butylammonium ion concentrations and having estimated $K_1(1 + K_2)$, we are in a position to compute k_3. For this purpose let us use the average k_A' from Table I, series C, namely 21.4×10^{-3} sec^{-1}. The k_3 so computed is 180 l. mole^{-1} sec^{-1}, at 1.3°.

One would not expect substitution of methyl for hydrogen on the nitrogen atom of isatoic anhydride to have much effect on the rate of nucleophilic attack at C-4. The second-order rate coefficient for reaction of *n*-butylamine with IV should therefore not differ greatly from this k_3 value. It is gratifying that our measured second-order rate coefficient (Table II), 86 l. mole^{-1} sec^{-1}, differs from k_3 for reaction of *n*-butylamine with I by only a factor of 2.

Let us compare the k_3 values for reactions of *n*-butylamine and aniline with I. For this purpose, we shall multiply the above k_3 for *n*-butylamine by a rule-of-thumb factor of 8 to adjust it to 29.7°, and compare it with the k_A values of Table V. The rate coefficient for *n*-butylamine is thus estimated to be 240,000-fold greater than that for aniline. On a logarithmic scale, these rate coefficients differ by 5.4 units; for comparison, the p*K*'s of the two amines differ by 6.9 units.

We were unable to measure any k_A' value for *t*-butylamine. We estimate that were it as high as 0.2×10^{-3} sec^{-1} in the last experiment of Table III, it would have been observed. Taking this value as a maximum, dividing it by 6 (for a crude correction to 1.3°), and comparing it with the last k_A' in Table I, series D, we estimate that *n*-butylamine is *at least* 130 times as reactive as *t*-butylamine in reaction at C-4 of isatoic anhydride. (The legitimacy of this comparison follows from eq 5 and the near-identity of the p*K*'s of the two butylamines.) It is evident that the bulkiness of *t*-butylamine is unfavorable to its reactivity.

k_U' values were measureable for both butylamines. With attention to eq 6 and the last entries in Tables I, series D, and Table III, and again employing a factor of 6 to correct for the difference in temperatures, we estimate that *n*-butylamine is about 40 times as reactive as *t*-butylamine with isocyanate intermediate VIII. Nucleophilic attack at the isocyanate carbon of VIII is evidently less sensitive to the steric requirements of the nucleophile. This is easily rationalized; a transition state approaching trigonal character with three groups attached should involve less crowding than one approaching tetrahedral character with four groups attached.

Hydrolysis. At pH >9.6, isatoic anhydride exists in solution mainly as VII and VIII. If hydrolysis occurred *via* attack of hydroxide ion on VII or VIII, the overall reaction would be first order in hydroxide ion. If it occurred *via* attack of hydroxide ion on I, it would be zero order in hydroxide ion. The constancy of k_H in Table IV shows that it is first order in hydroxide ion. It is probable that the rate-limiting step is attack on the isocyanate carbon of VIII.

The pH-independent component of hydrolysis (*vide supra*) plausibly represents nucleophilic attack of water on the isocyanate group. Alternatively, it may represent hydroxide attack at C-4 (or C-2) of I.

From comparison of k_U' and k_H' values from experiments in Tables I, III, and IV at equal nucleophile concentrations, and on the basis that IIIa, IIIb, and anthranilic acid all result from nucleophilic attack on the same intermediate (probably VIII), hydroxide ion may be reckoned to be 2.5 times as reactive as *n*-butylamine at 1.3° and 70 times as reactive as *t*-butylamine at 25°.

The Carbamic Acid Intermediates. The mechanistic model of Chart I does not provide for the carbamic acid intermediate (VI) to revert to I and amine. It involves no commitment as to how rapidly VI progresses to II.

Phenylcarbamic acid is known to decompose rapidly in acidic solution, forming aniline and CO_2.[19] We are therefore confident that VI decomposed to II on acidification to pH 1, an operation performed on every sample in our kinetic investigation with aniline and on the infinity samples (for product analysis) from reactions of I with *n*-butylamine. However, during the kinetic runs with *n*-butylamine, it is likely that VI (as its anion) was stable during the period of photometric observation.[20] In neither procedure did decarboxylation of VI complicate our kinetic measurements.

General Comments. The mechanistic model of Chart I gives a good account of quite a variety of kinetic observations. It accounts for the fact that higher amine concentrations favor formation of *o*-ureidobenzoic acids (III), in that either of two extreme kinetic expressions based on the model (eq 4 and 6) calls for a kinetic order in amine one unit higher than do the corresponding expressions (eq 3 and 5) for forma-

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(18) The requirement of eq 5 and 6, of equal k_A' at equal butylammonium ion concentrations and equal k_U' at equal amine concentrations, should also be satisfied in comparison of appropriate runs between the four series of Table I. This requirement is well satisfied with respect to k_A' values; the seeming deviation in early runs of series B is associated with the nonzero intercept in Figure 2, and is obviously due to the fact that butylammonium ion is also formed by basic dissociation of the amine. With respect to k_U' values, some discrepancies are evident at low amine concentrations; the main difficulty is that the early k_U' values in series C are based on small differences between large experimental quantities, and are therefore somewhat uncertain.

With reference to eq 5 and the average k_A' value in series C, one may estimate the butylammonium ion and butylamine concentrations present in each reaction solution in series D, and from them the K_b of the amine at 1.3°. The K_b value so estimated is substantially constant at $3.1 \pm 0.3 \times 10^{-3}$ *M* for the last eight experiments of series D. However, K_b should be 3.8×10^{-4} *M* if pK_a is 11.52 at 1.3°. The eightfold difference seems rather large to attribute to uncertainties in the pK_a estimate; we cannot fully explain it.

(19) E. Mohr, *J. Prakt. Chem.*, [2] 73, 177 (1906).

(20) In the *n*-butylamine reaction solutions, the pH was *ca.* 11.5 or greater. In carbonate buffers at pH 10.6, sodium phenylcarbamate has a half-life of 850 sec at 18° and is even more stable in 0.1 *M* sodium hydroxide: A. Jensen, M. B. Jensen, and C. Faurholt, *Acta Chem. Scand.*, 6, 1073 (1952).

tion of anthranilamides (II). It accounts for the fact that the rate law for formation of IIc from I and aniline is different from that for formation of IIa from I and *n*-butylamine. It conveniently accommodates the fact that bulkiness in an amine favors formation of type III rather than type II products, in that C-4 of I would be expected to be more sensitive to the steric requirements of an attacking nucleophile than the isocyanate carbon of VIII.

We caution that this agreement of experiment with predictions from the model does not prove that the model is correct. However, we feel that it justifies using the model as a basis for prediction and interpretation unless and until it is shown to be inadequate.

If the model is right in its broader aspects, it may yet be faulty in detail. To be specific, our experiments do not require the isocyanate intermediate VIII. We cannot exclude the possibility that III is formed by direct nucleophilic attack on C-2 of VII, although we find this alternative unattractive on several grounds.[21] (Also, we note Kopple's infrared evidence that an isocyanate is produced by action of sodium hydride on the N-carboxy anhydride of α-aminoisobutyric acid in dioxane solution.[16])

A point of interest is that our kinetics do not provide any indication that reactions of amines with either C-4 of I or the isocyanate carbon of VIII requires base catalysis. Probably C–N bond formation is rate limiting in the I → VI and VIII → III transformations.[22]

Acknowledgment. We thank the Maumee Chemical Co. for a large measure of financial support of this research, and for assistance in many ways.

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[21] Professor W. P. Jencks has pointed out in private conversation that VIII would be required as a discrete intermediate if it could be demonstrated that the rate of formation of ureidobenzoic acids III from VII was independent of the concentration or identity of the amine nucleophile. Transformation of VII to VIII would then be indicated as the rate-limiting step. If k_2 and k_{-2} are rate coefficients for the VII → VIII transformation and its reverse, one expects $k_U' = k_2k_4[\mathrm{RNH_2}]/(k_{-2} + k_4[\mathrm{RNH_2}])$. In appropriate cases, a plot of k_U' against $[\mathrm{RNH_2}]$ should diminish in slope as amine concentration increases, and a plot of $1/k_U'$ *vs.* $1/[\mathrm{RNH_2}]$ should be linear with intercept $1/k_2$. Curvature of this sort is evident in Figure 4, and the inversion plot is linear. The reciprocal of its intercept (possibly k_2) is 13.2×10^{-3} sec^{-1}. We caution, however, against accepting the slight curvature in Figure 4 as evidence of a change in rate-limiting step. If the alkaline hydrolysis occurs *via* attack of hydroxide ion on VIII, similar but more pronounced curvature should be evident in a plot of k_H' against $[\mathrm{OH^-}]$, but there is no suggestion of such curvature in the data of Table IV.

[22] *Cf.* J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, **87**, 3879 (1965).

Solvent Isotope Effects in Amide Hydrolysis[1,2]

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Contribution from the Department of Chemistry, University of Kansas, Lawrence, Kansas. *Received March 24, 1966*

Abstract: The rate of hydrolysis of 2,2,2-trifluoro-N-methylacetanilide (I) has been determined as a function of lyoxide ion concentration in protium and deuterium oxide solutions at 25.00 ±0.05°. The kinetic law in both media is shown in eq 2, in agreement with a mechanism involving formation of an adduct of I and lyoxide ion, followed by its general base catalyzed decomposition. The observed kinetic isotope effects are $k_a^{\mathrm{H_2O}}/k_a^{\mathrm{D_2O}} = 1.0 \pm 0.2$ (for addition), $k_1^{\mathrm{H_2O}}/k_1^{\mathrm{D_2O}} = 3.3 \pm 0.7$ (for solvent-catalyzed elimination), and $k_2^{\mathrm{H_2O}}/k_2^{\mathrm{D_2O}} = 2.2 \pm 0.3$ (for lyoxide ion catalyzed elimination). The secondary contributions to the latter two effects are estimated to be $(k_1^{\mathrm{H_2O}}/k_2^{\mathrm{D_2O}})_{\mathrm{sec}} = 0.75$ and $(k_2^{\mathrm{H_2O}}/k_2^{\mathrm{D_2O}})_{\mathrm{sec}} = 0.48$, leading to estimates for the primary contributions of $(k_1^{\mathrm{H_2O}}/k_1^{\mathrm{D_2O}})_{\mathrm{pri}} = 4.4 \pm 1$ and $(k_2^{\mathrm{H_2O}}/k_2^{\mathrm{D_2O}})_{\mathrm{pri}} = 4.6 \pm 1$. The rate-determining step appears to involve proton transfer; it is postulated that general base catalyzed reactions are either (a) simple proton-transfer reactions or (b) "solvation rule" reactions, depending on the nature of the leaving group.

Swain, Kuhn, and Schowen[5] recently examined the magnitudes of solvent isotope effects in a number of general base catalyzed reactions, for which the activated complexes can be represented by structure II, where B is the catalyst, X is an electronegative atom

B- - -H- - -X- - -C- - -Y
II

such as O, N, or S, and Y is a generalized leaving group (including the π electrons of double bonds). On the assumption that the secondary contributions to the solvent isotope effects are given by eq 1, where β is the slope of the Brønsted catalysis law[6] plot and

$$(k^{\mathrm{H_2O}}/k^{\mathrm{D_2O}}) = [(k^{\mathrm{H_2O}}/k^{\mathrm{D_2O}})_{\mathrm{max}}]^{\beta} \qquad (1)$$

$(k^{\mathrm{H_2O}}/k^{\mathrm{D_2O}})_{\mathrm{max}}$, the maximum effect, can be estimated according to simple rules,[5] it was found that no primary isotope effect was produced in these reactions, although all are formulated as "proton-transfer" reactions. The authors[5] concluded that, in such processes, the transfer of the proton is not concerted with the reorganization of the heavy atoms, which is occurring in the rate-determining activated complex, but instead takes place relatively rapidly either before or after the transition

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[2] Amide Hydrolysis. III. For part II, see R. L. Schowen, H. Jayaraman, and L. Kershner, *J. Am. Chem. Soc.*, **88**, 3373 (1966).

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[5] C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Am. Chem. Soc.*, **87**, 1553 (1965).

[6] J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, pp 235–242.