mesh Chromosorb P. Helium (120 ml./min.) was used as the carrier gas, and the temperature was raised at the rate of 8°/min. over the range 100–320°. Peaks were identified by retention times and by infrared, n.m.r., and mass spectral analysis of trapped samples. Phenyl 3,3-diphenylpropionate, 1,1,2-triphenylethane, and 1,1,1-triphenylethane[36] were shown to be absent by comparing the chromatograms of fraction C containing added samples of these materials with those of the original mixtures. Calibration runs on standard mixtures showed that compositions could be determined to within ±3% of the actual values. It was necessary to include chlorobenzene in these standards, since a few per cent of this material always remained in fraction C obtained from runs where it was used as the solvent. Chromatograms of fraction C invariably exhibited a few minor peaks in addition to those that were identified. On the assumption that the g.c. sensitivity factors of these components were identical with that of IV, they were estimated to comprise 4–8% of the weight of C, and none of them ever amounted to more than 2% of this weight. For purposes of calculation it was always necessary to correct the weight of C for the amounts of III that were isolated, since this compound gave no chromatographic peak under the conditions used.

The principal errors in the analysis of C would appear to be those arising from failure of the chromatographic technique to account for small amounts of benzene and sodium 3,3,3-triphenylpropionate present in the samples and for the acetic acid formed from V during the analysis. Another possible source of error would be failure to account for acetic acid formed *in situ* from phenyl 3-acetoxy-3,3-diphenylpropionate. Although no firm evidence for the presence of this compound was obtained, in some preliminary qualitative experiments it was noticed that the peaks in the n.m.r. spectra of the C fractions at about 6 and 8 τ were broader and more intense (relative to the olefinic hydrogen peak of II, which appears at 0.40 τ in $CDCl_3$) than they should have been if they were due entirely to compound V. The presence of phenyl 3-acetoxy-3,3-diphenylpropionate would account for this observation if the resonances of its methyl and methylene protons were sufficiently close to those of the corresponding protons of V. In any event, the fairly good material balances obtained for most of the experiments summarized in Table I can be taken as evidence for the general reliability of the analytical scheme. It is apparent that none of the sources of error just cited will affect the accuracy of the relative percentages of (II + IX):IV:VI (assuming, of course, that the chromatographic conversion of acetates to the corresponding olefins was always quantitative). Therefore, since III is only a small fraction of [II + (III/2) + IX] it is believed that the numbers of principal interest, namely, those for the ratio given in the last column of Table I, are not seriously in error.

(36) M. Gomberg and L. H. Cone, *Ber.*, **39**, 2963 (1906).

Reactions of Ib and Ic with Lead Tetraacetate. Migratory Aptitudes.—These reactions were carried out in the way described in part B, above, using 5.00 mmoles each of acid and lead tetraacetate and 25 ml. of solvent. Fractions A and B were examined in the usual way. Fraction C was saponified by refluxing and stirring for at least 6 hr. with 2.8 g. (50 mmoles) of potassium hydroxide and 25 ml. of 95% ethanol. Most of the solvent was removed under vacuum, and the residue was dissolved by adding 25 ml. of water and 25 ml. of ether. The layers were separated, and the aqueous portion was extracted with 75 ml. of ether in three portions. After two washings with 40-ml. portions of saturated sodium chloride solution, the combined ether layers were evaporated under vacuum to give a viscous, oily residue (0.05–0.15 g.) which was shown (by a variety of analytical techniques) to contain no aryl esters. The aqueous layer was acidified (pH 2) with concentrated hydrochloric acid, extracted at least twice with an equal volume of ether, and then continuously extracted with ether for a day or longer. In experiments with Ib the aqueous moiety gave a negative test for phenols with brominating solution[33] at the end of this time. For reactions starting with Ic several drops of the solution were decolorized, and the mixture became cloudy. However, since experiments with standard mixtures of phenol and *p*-nitrophenol (see below) showed that these compounds would have been completely removed by the extraction procedure, the positive test must have been due to reaction of the reagent with a nonphenolic product (perhaps 3-phenyl-3-*p*-nitrophenylacrylic acid?). Following treatment with Drierite and removal of solvent *in vacuo*, the ratios of phenolic products contained in the residue from the combined ether extracts were determined by programmed temperature gas chromatography (temperature increase 8°/min. from 125 to 260°, helium flow rate 120 ml./min.), usually on a 4 ft. × 0.25 in. column containing 15% Carbowax 20,000 on 40–60 mesh Chromosorb P. In some of the experiments starting with Ib, equally good results were obtained with the column used in the analysis of fraction C from acid Ia (see above). The peaks corresponding to phenol, *p*-methoxyphenol, and *p*-nitrophenol were shown to be homogeneous by infrared and mass spectral analysis of trapped samples. No peaks having the correct retention times for the *ortho* and *meta* isomers of the substituted phenols were detected. The analytical scheme was checked by carrying standard mixtures of phenol with *p*-methoxy- or *p*-nitrophenol through the entire procedure, beginning with the alcoholic caustic treatment. Recoveries were essentially quantitative, and the percentages found never differed from the original values by more than ±1%.

Acknowledgment.—The author is indebted to Professors W. von E. Doering, G. W. Griffin, H. B. Jonassen, and R. Pettit for stimulating discussions, to Mr. H. J. Tarski for competent technical assistance, and to Dr. R. H. Perry, Jr., for his support of this work.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PENNSYLVANIA]

Acid-Catalyzed Amide Hydrolysis Assisted by a Neighboring Amide Group[1]

BY THEODORE COHEN AND JONATHAN LIPOWITZ

RECEIVED AUGUST 13, 1964

The acid-catalyzed hydrolysis of *o*-benzamido-N,N-dicyclohexylbenzamide (I) in aqueous acetic acid containing sulfuric acid at 80° occurs at the N,N-dicyclohexylamide linkage and is at least 10^4 times faster than the hydrolysis of the less sterically hindered model compound, N,N-dicyclohexylbenzamide (IV), under the same conditions. Several mechanisms are presented by which the *o*-benzamido group may participate in the hydrolysis by acting as a general base, a nucleophile, or, when protonated, as a general acid. Support for the intermediate formation of benzoylanthranil (V) has been obtained by isolating this compound from a reaction in which compound I was cleaved in dry dioxane containing hydrogen chloride, and by showing that V rapidly hydrolyzes to the acid obtained from the hydrolysis of I.

Because of the great biological importance of proteolytic reactions, there has been considerable interest in intramolecular assistance to amide hydrolysis.[2] In cases in which the amide group has not undergone prior protonation, intramolecular assistance can be afforded either by strong basic groups, such as an alkoxide anion[3] or the nitrogen atom of the conjugate base of another amide function,[4] or by general acids,

(1) (a) This work was supported by Grant NSF G-9475 from the National Science Foundation. (b) Based on the Ph.D. Thesis of J. Lipowitz, University of Pittsburgh, July, 1964.

(2) M. L. Bender, *Chem. Rev.*, **60**, 88 (1960); T. C. Bruice, *Brookhaven Symp. Biol.*, **No. 15**, 52 (1962).

(3) T. C. Bruice and F. H. Marquardt, *J. Am. Chem. Soc.*, **84**, 365 (1962).

TABLE I

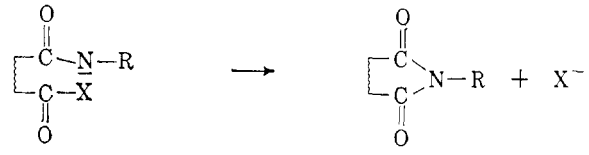
AMIDE HYDROLYSES

Amide	[M]	Solvent	T,°C	Time (hr.)	Products	Yield, %
I	0.090	[a]	80 ± 1	5	Starting material	13[b]
					Dicyclohexylamine	73[c]
					N-Benzoylanthranilic acid	84[b]
N-Cyclohexyl-benzamide	0.056	[a]	80 ± 1	5.5	Starting material	98[b]
					Benzoic acid	None
IV	0.101	[a]	80 ± 2	168	Starting material	89[b]
					Dicyclohexylamine	None
					Benzoic acid	None
I	0.086	[a]	110–113[e]	0.5	Starting material	Trace[b]
					Dicyclohexylamine	90[c]
					N-Benzoylanthranilic acid	91[b]
I	0.081	Acetic acid, 0.093 M in H_2SO_4 6.7 M in H_2O[d]	108–111[e]	0.5	Starting material	58[b]
					Dicyclohexylamine	46[c]
					N-Benzoylanthranilic acid	48[b]
IV	0.090	[a]	110–112[e]	168	Starting material	None
					N-Cyclohexylbenzamide	39[b]
					Cyclohexylamine	19[c,f]
					Benzoic acid	34[b]
I	0.083	Dioxane satd. with HCl	80 ± 1	20	Starting material	None
					Dicyclohexylamine	94[c]
					N-Benzoylanthranilic acid	17
					Benzoylanthranil	80
V	0.11	[a]	82–85	0.33	Starting material	None
					N-Benzoylanthranilic acid	98[b]
I	0.045	Ethanol, 2.0 M in KOH, 11 M in H_2O	80 ± 1	5	Starting material	44
					o-Amino-N,N-dicyclohexylbenzamide	46[c]

[a] Acetic acid, 0.91 M in sulfuric acid and 7.1 M in water; in these runs acid was present in large excess. [b] Yield corrected for ether decomposition products. [c] Isolated as the hydrochloride. [d] Sulfuric acid was present at the start to the extent of 2 equiv. to 1 of amide. [e] Reflux temperature. [f] Some amine salt was probably lost during work-up; see text.

which are capable of functioning mechanistically as combination nucleophile-electrophiles.[2] Among the intramolecular general acids which have been found effective are the un-ionized carboxyl group,[5] the hydroxyl group,[3] and the positively charged imidazolium group.[6] One case is known in which the protonated amide group is apparently attacked by the weakly nucleophilic alcohol function which is suitably situated on the same molecule.[7]

There are numerous examples of the intramolecular participation of amide groups both in nucleophilic substitutions at saturated carbon atoms[8,9] and in the hydrolysis of carboxylic acid derivatives.[4,10] In the known cases[3] in which a neutral amide group is involved, it is the carbonyl oxygen atom which acts as the nucleophile. When the conjugate base of the amide is the participating group,[4,9,10] either the oxygen or nitrogen atom may act as the nucleophile, but the latter is strongly favored when either would lead to the same size ring.[11] Except for the subject of this paper,[12] all known examples of amide participation in the hydrolysis of carboxylic acid derivatives occur by way of the conjugate bases and involve attack by nitrogen, leading to imides.[4,10]



In this paper, we describe the first example of an *acid*-catalyzed reaction in which one amide function aids in hydrolysis of another amide group in the same molecule.[12] During our work on hydride transfer reactions occurring during diazonium ion decomposition,[13] it was noted that o-benzamido-N,N-dicyclohexylbenzamide (I), dissolved in aqueous acetic acid containing sulfuric acid, hydrolyzes under conditions that had been shown by previous control tests to be ineffective in the hydrolysis of the much less hindered N-cyclohexylbenzamide (Table I). Furthermore, the products of the hydrolysis of I are dicyclohexylamine (III) and N-benzoylanthranilic acid (II), indicating that the hydrolysis occurs at the more sterically hindered of the two carbonyl groups.[14]

(4) B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. soc. chim. Belges*, **69**, 616 (1960); P. Crooy and A. Bruylants, *ibid.*, **73**, 44 (1964); J. A. Shafer and H. Morawetz, *J. Org. Chem.*, **28**, 1899 (1963).

(5) (a) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958); (b) S. J. Leach and H. Lindley, *Trans. Faraday Soc.*, **49**, 921 (1953); (c) Vigneron-Voortman, P. Crooy, and A. Bruylants, *Bull. soc. chim. Belges*, **73**, 241 (1964).

(6) T. C. Bruice and J. M. Sturtevant, *J. Am. Chem. Soc.*, **81**, 2860 (1959).

(7) L. Zürn, *Ann.*, **631**, 56 (1960); R. B. Martin, R. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 158 (1964).

(8) S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950); W. B. Lawson, E. Gross, C. M. Foltz, and B. Witkop, *ibid.*, **84**, 1715 (1962); H. W. Heine, *ibid.*, **79**, 907 (1957); A. Singh, L. J. Andrews, and R. M. Keefer, *ibid.*, **84**, 1179 (1962); J. Sicher, M. Tichy, F. Sipos, and M. Pankova, *Proc. Chem. Soc.*, 384 (1960); A. T. Austin and J. Howard, *Chem. Ind.* (London), 1413 (1959).

(9) C. Zioudrou and G. L. Schmir, *J. Am. Chem. Soc.*, **85**, 3258 (1963); H. W. Heine, P. Love, and J. L. Bove, *ibid.*, **77**, 5420 (1955); F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957).

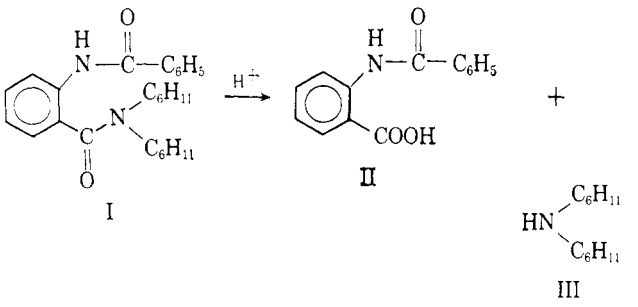
(10) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954); E. Sondheimer and R. W. Holley, *ibid.*, **79**, 3767 (1957); S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *ibid.*, **84**, 2421 (1962).

(11) C. J. M. Stirling, *J. Chem. Soc.*, 255 (1960); B. Capon, *Quart. Rev.* (London), **18**, 71 (1964).

(12) For a preliminary account of this work, see T. Cohen and J. Lipowitz, *J. Am. Chem. Soc.*, **83**, 4866 (1961).

(13) T. Cohen and J. Lipowitz, *ibid.*, **86**, 2514 (1964).

(14) This observation alone does not indicate neighboring group participation since it is possible that this very unfavorable steric situation could be overcome by electronic effects.



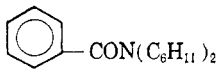
I II III

A study was thus undertaken in order to determine the approximate rate enhancement caused by the *o*-benzamido group and, if possible, to throw some light on the general nature of the interaction involved. It was most convenient to use the same solvent and temperature as had been used in the preliminary experiment referred to above since the approximate extent of hydrolysis was already known. The extent of hydrolysis in each experiment was determined gravimetrically after separation of the acidic, basic, and neutral products, utilizing appropriate extraction procedures. Because it was necessary to add a large amount of water to the reaction mixtures in order to perform these extractions, large volumes of ether were required. Early experiments showed that the neutral and acidic fractions, which were obtained by evaporation of the appropriate ether extract, contained appreciable amounts of resinous material. Based on the weights of the crude extracts, yields considerably in excess of theoretical were obtained. Recrystallizations of the acidic and neutral extracts afforded products which were free of contamination, but this procedure resulted in considerable product losses.

The same resinous materials (by infrared comparisons) were obtained when the work-up procedure was repeated in the absence of amides. They apparently arise by a minor degree of degradation of the (purified) ether in the acid solution. The weights of these materials, obtained in the neutral and acidic extracts of the blank, were subtracted from the weights of the appropriate crude fractions in the hydrolysis experiments in order to obtain corrected yields.

Justification for this correction procedure was based on the fairly good agreement between the corrected yield of N-benzoylanthranilic acid and the yields of dicyclohexylamine hydrochloride (Table I). No correction was applied to the yield of the latter compound because it was precipitated from ether, thereby avoiding contamination. This procedure also produced a fairly good mass balance (89 to 104%), based on the yield of acid and recovery of starting material.

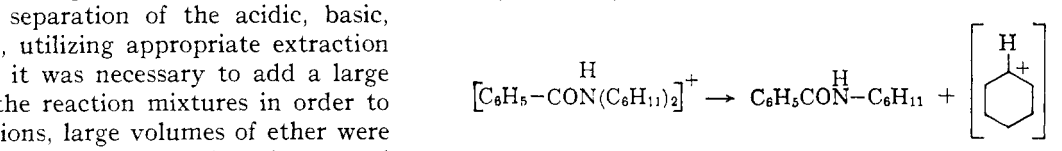
Hydrolysis of the model compound N,N-dicyclohexylbenzamide (IV) was attempted. This compound



IV

did not hydrolyze to any detectable extent in 168 hr. under the same conditions in which the more sterically hindered amide I cleaved to the extent of 84% in 5 hr. It is estimated that about 0.5% of the hydrolysis product, benzoic acid, could have been detected. Assuming that 0.5% hydrolysis had occurred, the ratio of the pseudo-first-order rate constants (k_I/k_{IV}) can be calculated to be 1.4×10^4. This rate ratio is, of course, a bare minimum figure since it is possible that the actual extent of hydrolysis of the model compound IV was much less than 0.5%.

In order to obtain a more meaningful rate difference between I and IV, each was heated in the same solvent at a temperature 30° higher than that used in the previous experiments. At the higher temperature, the hydrolysis of I to N-benzoylanthranilic acid and dicyclohexylamine was essentially complete at the end of 30 min. Under the same conditions, N,N-dicyclohexylbenzamide was consumed completely at the end of 168 hr. However, the products formed—N-cyclohexylbenzamide, cyclohexylamine, and benzoic acid (no dicyclohexylamine could be isolated)—clearly indicate that hydrolysis at the acyl linkage did not occur. Instead, a cleavage at the cyclohexyl C–N bond occurred. It is likely that this reaction is an SN1 type solvolysis of the protonated amide.



The heterolysis is then followed by some normal hydrolysis to benzoic acid and cyclohexylamine.[15] No attempt was made to isolate the cyclohexanol, cyclohexyl acetate, and cyclohexene which would be expected to be produced from the cyclohexylcarbonium ion.

A precedent for this heterolysis is found in the work of Lacey,[16] who reported that N-*t*-alkylamides in strongly acidic solution produce the corresponding dealkylated amide as well as alcohol and olefin arising from the further reactions of the *t*-alkylcarbonium ion.

The actual rate enhancement caused by the benzamido group is undoubtedly much higher than 1×10^4, the minimum ratio k_I/k_{IV}. While the electronic effect of the *o*-benzamido group of I is expected to have only a negligible effect[17] on the rate of hydrolysis of the N,N-dicyclohexylbenzamide group, the steric effect would be expected to depress the rate of this hydrolysis appreciably.[18]

Three general types of reaction paths compatible with the large rate enhancement caused by the *o*-benzamido group, the acid catalysis (compare runs 4 and 5 in Table I), and the fact that cleavage occurs at the more crowded of the two carbonyl groups are shown in Fig. 1.

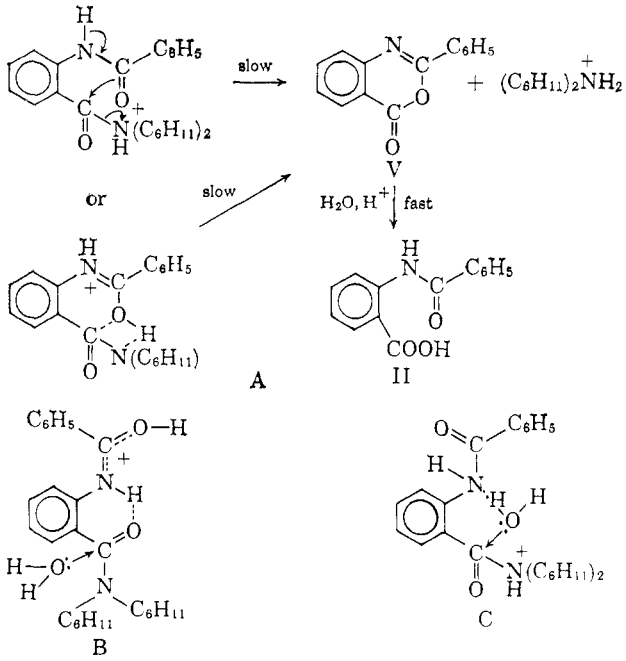
In mechanism A, the benzamido group, participating as a nucleophile, attacks the protonated N,N-dicyclohexylamide groups. Protonation can occur on either the oxygen or nitrogen atom; only the latter is shown. This mechanism is presumably related, in principle, to the internally assisted, acid-catalyzed hydrolysis of γ-hydroxybutyramide.[7] A variation of this mech-

(15) The fact that the cyclohexylamine yield is considerably less than that of benzoic acid is probably caused by loss of cyclohexylamine during work-up. The ether suspension of the hydrochloride of this amine became cloudy soon after the hydrogen chloride was added and it appeared that the hygroscopic precipitate was dissolving in the water that it had absorbed.

(16) R. N. Lacey, *J. Chem. Soc.*, 1633 (1960).

(17) The effects of aromatic substituents on acid-catalyzed hydrolyses of benzamides have been found to be very small.[18]

(18) J. A. Leisten, *J. Chem. Soc.*, 765 (1959), and papers cited therein.



anism involves O-protonation of the benzamido group, followed by concerted attack of the –OH group, acting as a general acid, on the C—N or C=O group of the amide being cleaved.[19] In this mechanism (A), benzoylanthranil (V) is postulated as a slowly formed intermediate which is rapidly hydrolyzed to product.

In mechanism B, the protonated benzamido group behaves as a general acid. By hydrogen bonding to the oxygen or nitrogen atom of the group being cleaved, it activates this group to nucleophilic attack by water.

In mechanism C, the benzamido group behaves as a general base, aiding in the nucleophilic attack of a water molecule on the protonated amide group.

Some support for mechanism A was obtained by the isolation in 80% yield of the proposed intermediate, benzoylanthranil (V), from a cleavage reaction of I carried out for 20 hr. in dry dioxane saturated with hydrogen chloride. Accompanying the benzoylanthranil was a 17% yield of its hydrolysis product, N-benzoylanthranilic acid (II), and a 94% yield of dicyclohexylamine hydrochloride. A control experiment established that N-benzoylanthranilic acid (II) forms only a trace quantity of benzoylanthranil under the reaction conditions used to cleave I. It was further demonstrated that the proposed intermediate, benzoylanthranil (V), is hydrolyzed to the acid II essentially quantitatively in 20 min. under conditions (aqueous acetic–sulfuric acid) in which *o*-benzamido-N,N-dicyclohexylbenzamide is hydrolyzed to the extent of 84% in 5 hr.

While these experiments demonstrate that benzoylanthranil is a very reasonable intermediate in this assisted hydrolysis, mechanisms B and C cannot be definitely excluded from consideration on the basis of any experiments reported here.

Bender, Schonbaum, and Hamilton[20] have recently discussed the possibility that enzymatic amide groups might assist in the hydrolysis of carboxylic acid derivatives. They have also suggested the use of acylated anthranilic acid derivatives as model systems and have even anticipated the possible involvement of intermediates such as V.

In view of these results, it became of interest to determine the site of basic hydrolysis of I. Hydrolysis at 80° for 5 hr. in aqueous ethanolic potassium hydroxide resulted in the production of 46% *o*-amino-N,N-dicyclohexylbenzamide and the recovery of 44% starting material. This hydrolysis thus appears to be normal. It occurs at the least hindered amide group, the one bearing the best leaving group and the carbonyl group which is expected on electronic grounds to be the most receptive to nucleophilic attack.

(19) Concerted attacks of this general type have been proposed previously.[3,5a]

(20) M. L. Bender, G. R. Schonbaum, and G. A. Hamilton, *J. Polymer Sci.*, **49**, 75 (1961).

Experimental[21]

Solvent Purification.—Acetic acid (b.p. 117–117.5°) was prepared by distilling glacial acetic acid twice from chromium trioxide. Dioxane was purified by heating it at reflux for 24 hr. over sodium and distilling through a 4-ft. column packed with glass helices. The fraction, b.p. 99.5–100.5° (740 mm.), was collected and stored in a nitrogen atmosphere.

***o*-Amino-N,N-dicyclohexylbenzamide.**—Thionyl chloride (24.0 g., 0.20 mole) was added to a refluxing solution of *o*-nitrobenzoic acid (30.0 g., 0.18 mole) in 150 ml. of purified dioxane and refluxing was continued until hydrogen chloride evolution had stopped (3 hr.). A ⅔ aliquot of this cooled solution was added over a 10-min. period to a magnetically stirred solution of freshly distilled dicyclohexylamine (21.8 g., 0.12 mole) and triethylamine (36 g., 0.36 mole) in 200 ml. of purified dioxane. Stirring was continued until the tan reaction mixture had cooled to room temperature (45 min.). Dioxane and triethylamine were evaporated on a rotary evaporator, and the red-brown viscous residue was triturated with several portions of ether. The combined ether extract was dried with sodium sulfate and evaporated on a steam bath. One crystallization of the residue from aqueous alcohol produced pale yellow needles of *o*-nitro-N,N-dicyclohexylbenzamide, m.p. 142–145° (30.0 g., 76%). Its infrared spectrum in chloroform exhibited absorption at 2900 (s), 2850 (s), 1625 (s), and 1345 cm.$^{-1}$ (s).

A solution of this amide (15.0 g., 0.046 mole) in 150 ml. of alcohol containing several grams of No. 28 Raney nickel (Raney Catalyst Co., Inc., Chattanooga, Tenn.), which had been stored under water, was hydrogenated in a Parr aparatus at an initial pressure of 3 atm. After the uptake of hydrogen had stopped (2 hr.), the solution was filtered free of catalyst through a fine filter, evaporated to a small volume, and the residue crystallized from aqueous alcohol to afford a powder, m.p. 136–138° (12.7 g., 93%). Two crystallizations from distilled Skellysolve B (b.p. 65–67°) afforded microcrystals, m.p. 138.5–139.5°. The infrared spectrum of the amine in chloroform exhibited absorption at 3310 (w), 2880 (m), 2833 (m), and 1608 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{19}H_{28}N_2O$: C, 75.95; H, 9.40; N, 9.33. Found: C, 76.10; H, 9.32; N, 9.10.

***o*-Benzamido-N,N-dicyclohexylbenzamide (I).**—A solution of benzoyl chloride (5.2 g., 0.037 mole) in 50 ml. of purified benzene was added over a 5-min. period to a magnetically stirred solution of *o*-amino-N,N-dicyclohexylbenzamide (11.0 g., 0.037 mole) and triethylamine (11 g., 0.11 mole) in 250 ml. of purified benzene. The solution was heated at reflux for 1 hr., allowed to cool, and filtered to remove amine hydrochloride. The filtrate was evaporated on a rotary evaporator and the white solid residue was recrystallized from alcohol to produce a white solid, m.p. 205.5–207.0° (14.0 g., 95%). Two additional recrystallizations from absolute alcohol afforded an analytical sample, m.p. 209.0–209.8°. Its infrared spectrum in chloroform exhibited absorption at 2915 (m), 2849 (w), 1669 (m), and 1618 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.97; N, 6.93. Found: C, 77.47, 77.59; H, 7.68, 7.72; N, 6.75, 6.67.

N,N-Dicyclohexylbenzamide (IV).—A solution of benzoyl chloride (7.7 g., 0.055 mole) in 40 ml. of purified dioxane was added over a 5-min. period to a magnetically stirred solution of dicyclohexylamine (10.0 g., 0.055 mole) and triethylamine (15 g., 0.15

(21) Unless otherwise stated, melting points were taken on a Kofler block utilizing a stage calibrated thermometer and they are therefore corrected.

mole) in 100 ml. of purified dioxane. The reaction mixture was stirred for 1.5 hr. and then evaporated to dryness on a rotary evaporator. Trituration of the brown residue with several portions of ether and evaporation of the ether extract afforded a brown oil. A charcoal decolorization (Darco) and recrystallization from aqueous alcohol afforded an oil which crystallized (m.p. 92–98°) on standing in a refrigerator for several days. Recrystallization from Skellysolve B afforded material (6.0 g.), m.p. 96.0–99.5°. Additional product (2.1 g.), m.p. 94–99°, was obtained from the concentrated mother liquor (8.1 g., total 51%). Repeated recrystallizations from absolute ethanol and Skellysolve B produced material, m.p. 96.0–99.5° (lit.[22] m.p. 77°). Its infrared spectrum in chloroform exhibited absorption at 3040 (m), 2950 (w), and 1639 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{19}H_{27}NO$: C, 79.95; H, 9.53; N, 4.91. Found: C, 79.81; H, 9.12; N, 5.06.

Determination of Decomposition Products of Ether in Organic Extracts.—The acid, neutral, and basic fractions of the hydrolysis experiments conducted in acetic–sulfuric acid solution were contaminated with appreciable amounts of resinous material which caused melting point depressions and errors in yields. The resinous material exhibited infrared bands in chloroform at 3030 (s), 1747 (vw), 1625 (w), 1480 (m), 1392 (m), and 1142 cm.$^{-1}$ (s).

Two liters of purified ether (Mallinckrodt Chemical Works) was evaporated to a small volume on a steam bath and the rest of the ether was evaporated in a stream of dry air, leaving 3 mg. of yellow semisolid. Therefore the appreciable amount of residue found was not initially present in the ether.

An experiment was conducted in which a sulfuric–acetic acid solution was subjected to the same extraction procedures employed in working up the hydrolysis reactions. A solution of 50 ml. of acetic acid, 1.0 *M* in sulfuric acid, was added to a mixture of 150 ml. of water and 200 ml. of purified ether (Mallinckrodt). The aqueous layer was made basic with 10 *M* sodium hydroxide and extracted 5 times with ether. The organic phase was extracted with three 150-ml. portions of 1 *M* hydrochloric acid. The "neutral" ether extract was dried with sodium sulfate, evaporated to a small volume on a steam bath, and the remainder of the ether was evaporated in a stream of dry air leaving a yellow-green semisolid residue (0.143 g.). The aqueous acid extract was made basic and extracted 5 times with ether. The "basic" ether extract was dried and evaporated in the same way, leaving a yellow semisolid (0.062 g.). The initial basic solution was acidified with sulfuric acid and extracted 5 times with ether. The "acidic" ether extract was dried with sodium sulfate and evaporated on a rotary evaporator. The last trace of acetic acid was evaporated in a stream of dry air, leaving a brown solid residue (0.082 g.). The infrared spectra (chloroform) of these residues were very similar to spectra of residues obtained in the following hydrolysis experiments. The weights of the neutral and acidic residues obtained in this experiment were subtracted from the weights of the corresponding extracts in the hydrolysis experiments to provide corrected yields.

Hydrolysis of I at 80° for 5 Hr., 0.91 *M* Sulfuric Acid.—A solution of *o*-benzamido-N,N-dicyclohexylbenzamide (2.00 g., 4.97 mmoles) in 55 ml. of acetic acid, 0.91 *M* in sulfuric acid and 7.1 *M* in water (7.0 ml. of water added to 50 ml. of acetic acid, 1.0 *M* in sulfuric acid), was heated at 80 ± 1° for 5 hr. The reaction mixture was cooled to room temperature in an ice bath, washed into a mixture of ether and water, and worked up in the same way as the blank run. The neutral extract provided impure starting material (0.265 g., 13% corrected), identified by infrared analysis. The dry basic fraction in ether was treated with ethereal hydrogen chloride, producing dicyclohexylamine hydrochloride (0.792 g., 73%) as a powder, which sublimed above 250° (lit.[23] sublimes 300–315°). An infrared spectrum (Nujol mull) was identical with that of an authentic sample, prepared by treating an ethereal solution of dicyclohexylamine with ethereal hydrogen chloride. The acidic ether extract afforded N-benzoylanthranilic acid as a light tan solid, m.p. 170–185° (0.998 g., 84% corrected). Reprecipitation of this material by acidification of its alkaline solution produced acid of m.p. 181–183°. One recrystallization from aqueous alcohol afforded needles, m.p. 182–183° (lit.[24] m.p. 182°). Its infrared spectrum as a Nujol mull exhibited absorption at 2700–2300 (w, very broad), 1692 (s), and 1650 (s) cm.$^{-1}$. By treatment with refluxing thionyl chloride,[25] this acid was converted to benzoylanthranil, m.p. 124.5–125.0° (lit.[26] m.p. 124.5°), after one recrystallization from ethanol. A mixture with an authentic sample of benzoylanthranil, m.p. 120.5–121.5° (capillary m.p., uncorrected), prepared by the treatment of anthranilic acid with benzoyl chloride,[25] had m.p. 120.5–122.0° (capillary m.p., uncorrected).

Hydrolyses of I at Higher Temperature.—The procedures were essentially the same as for the hydrolysis at 80°. After the appropriate solution was heated at reflux for 30 min., it was rapidly cooled in an ice bath. In the run using 0.91 *M* sulfuric acid, the neutral extract (0.125 g. from 1.90 g. of amide) was mainly resinous impurities from the ether, but it appeared to contain a trace of starting material. The remainder of the results can be found in Table I.

Attempted Hydrolysis of N,N-Dicyclohexylbenzamide (IV) at 80°.—A solution of N,N-dicyclohexylbenzamide (1.580 g., 5.55 mmoles) in 55 ml. of acetic acid, 0.91 *M* in sulfuric acid and 7.1 *M* in water, was heated at 80 ± 2° (oil bath) for 1 week. The solution was allowed to cool to room temperature and worked up in the same way as the blank extractions.

Evaporation of the neutral ether extract afforded recovered starting material (1.400 g., 89% corrected), determined by infrared analysis. The acidic ether extract afforded a residue (0.29 g.) which did not contain enough benzoic acid to be detected by infrared analysis. It is estimated that the carbonyl band attributed to a 0.5% yield of benzoic acid could have been detected.

Treatment of an ethereal solution of the basic extract with ethereal hydrogen chloride produced no precipitate.

Heterolysis of N,N-Dicyclohexylbenzamide (IV) at 110–112°.—A solution of N,N-dicyclohexylbenzamide (1.414 g., 4.96 mmoles) in 55 ml. of acetic acid, 0.91 *M* in sulfuric acid and 7.1 *M* in water, was heated at reflux (110–112°) in a nitrogen atmosphere for 1 week. After the solution had cooled to room temperature, it was worked up in the same way as the blank extractions. The neutral extract consisted of N-cyclohexylbenzamide (0.388 g., 39% corrected), m.p. 142–148°. One recrystallization from aqueous alcohol afforded fluffy needles, m.p. 149–152°. The mixture m.p. with an authentic sample,[27] m.p. 152–153° (lit.[27] m.p. 149°), was 150–152°. No N,N-dicyclohexylbenzamide could be detected in the neutral extract by infrared analysis. The acidic extract consisted of benzoic acid (0.203 g., 34% corrected), identified by infrared analysis. Treatment of an ether solution of the basic extract with ethereal hydrogen chloride produced a light gray precipitate of cyclohexylamine hydrochloride (0.128 g., 19%). An infrared spectrum (Nujol mull) of this salt was identical with that of an authentic sample. No dicyclohexylamine hydrochloride could be detected in the precipitate. The low yield of cyclohexylamine hydrochloride relative to that of benzoic acid probably resulted from partial dissolution of the hygroscopic salt in the water which it appeared to absorb.

Attempted Hydrolysis of N-Cyclohexylbenzamide at 80°.—The same general procedure was followed. Evaporation of the neutral ether extract furnished recovered starting material (0.616 g., 98% corrected, from 0.630 g. of amide), m.p. 149–152.5°, identified by infrared analysis. No benzoic acid could be detected by examination of the infrared spectrum of the acidic ether extract.

Anhydrous Acid Cleavage of *o*-Benzamido-N,N-dicyclohexylbenzamide (I).—Purified dioxane (60 ml.) was saturated with hydrogen chloride which had been dried by allowing it to pass through concentrated sulfuric acid. The resulting solution was added to *o*-benzamido-N,N-dicyclohexylbenzamide (2.00 g., 4.96 mmoles) in a flask fitted with an air condenser and a drying tube containing Drierite. The solution was heated at 80 ± 2° in an oil bath for 20 hr., during which time material gradually precipitated as large, shiny plates. Filtration of the solution in a dry nitrogen atmosphere, trituration of the solid precipitate with anhydrous ether, and evaporation of the ethereal extract afforded benzoylanthranil (0.404 g.), m.p. 111–123°. An infrared spectrum (chloroform) of this material was identical with that of the authentic sample. The ether-insoluble material (1.014 g., 94%), which sublimed above 250°, was shown to be dicyclohexylamine hydrochloride by infrared analysis.

The initial filtrate was evaporated to dryness on a rotary evaporator. Precautions were taken to exclude moisture. An ethe-

(22) M. G. Fouque, *Ann. chim.*, **15** [9], 315 (1921).
(23) R. Willstätter and D. Haatt, *Ber.*, **45**, 1476 (1912).
(24) A. Brückner, *Ann.*, **205**, 130 (1880).
(25) P. R. Levy and H. Stephen, *J. Chem. Soc.*, 987 (1956).
(26) M. T. Bogert, R. A. Gortner, and C. G. Amend, *J. Am. Chem. Soc.*, **33**, 952 (1911).
(27) O. Wallach, *Ann.*, **343**, 46 (1905).

real solution of the yellow residue was extracted with two portions of 5% sodium bicarbonate solution. The ether layer was dried and evaporated to dryness on a steam bath, affording a light yellow solid (0.478 g.), m.p. 90–119°. An infrared spectrum was identical with that of benzoylanthranil. The two portions of benzoylanthranil were combined (0.882 g., 80%) and crystallized twice from benzene–Skellysolve B, affording white needles, m.p. 123–124.5° (lit.[26] m.p. 124.5°). The mixture m.p. with an authentic sample, m.p. 122–123°, was 122–125°.

Acidification of the aqueous sodium bicarbonate extract produced crude N-benzoylanthranilic acid (0.201 g., 17%), m.p. 167–183°, identified by infrared analysis. One crystallization from benzene afforded the acid, m.p. 181.5–183°.

Benzoylanthranilic acid was subjected to the same conditions as were used in this reaction. The acid was recovered (m.p. 170–185°) on evaporation of the solvent on a rotary evaporator. Precautions were taken to exclude moisture. An infrared spectrum in chloroform exhibited very weak absorptions which appeared to be attributed to the presence of a small amount of benzoylanthranil.

Acid Hydrolysis of Benzoylanthranil.—A solution of benzoylanthranil (1.340 g., 6.01 mmoles) in 55 ml. of acetic acid, 0.91 *M* in sulfuric acid and 7.1 *M* in water, was heated at 82–85° (oil bath) for 20 min. The solution was quickly cooled in an ice bath and worked up in the same way as the blank extractions. Only resinous material was obtained in the neutral and basic fractions. The acid fraction, m.p. 160–184°, was shown to be N-benzoylanthranilic acid (1.414 g., 98% corrected) by infrared analysis.

Basic Hydrolysis of *o*-Benzamido-N,N-dicyclohexylbenzamide (I).—A solution of *o*-benzamido-N,N-dicyclohexylbenzamide (0.923 g.) in 50 ml. of ethanol, 2.0 *M* in potassium hydroxide and 11 *M* in water (prepared by addition of 10 ml. of 10.0 *M* potassium hydroxide to 40 ml. of absolute ethanol), was heated at reflux (79–81°) for 5 hr. The solution was cooled to room temperature in an ice bath, adjusted to pH 6 with hydrochlroic acid, and evaporated to dryness on a rotary evaporator. The residue was triturated with water to remove potassium chloride. The water-insoluble material was triturated with chloroform. Evaporation of the chloroform extract on a rotary evaporator afforded recovered starting material (0.406 g., 44%).

The chloroform-insoluble material, m.p. 182–186°, was shown to be *o*-amino-N,N-dicyclohexylbenzamide hydrochloride (0.352 g., 46%) by comparison of its infrared spectrum (Nujol mull) with an authentic sample (m.p. 175–185°). Attempts to recrystallize an authentic sample of the amine hydrochloride (prepared by treating an ethereal solution of the amine with ethereal hydrogen chloride) were unsuccessful. Ether extraction of a suspension in aqueous base of the amine hydrochloride obtained in this reaction afforded *o*-amino-N,N-dicyclohexylbenzamide, identified by its infrared specrum. Recrystallizations from aqueous alcohol and Skellysolve B afforded the amine, m.p. 136–138°. The mixture m.p. with an authentic sample, m.p. 138–139°, was 137–139°.

[CONTRIBUTION NO. 320 FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM, MASSACHUSETTS 02154]

The Reaction of Hydroxylamine with Amides. Kinetic Evidence for the Existence of a Tetrahedral Addition Intermediate[1]

BY WILLIAM P. JENCKS AND MARY GILCHRIST

RECEIVED AUGUST 10, 1964

The rate of the reaction of hydroxylamine with simple amides passes through a maximum near pH 6 because of general acid catalysis of the reaction by hydroxylammonium ion. The reaction is also catalyzed by imidazole buffer. Plots of the apparent second-order rate constants at a given pH against catalyst concentration show a break because of a change in rate-determining step and, consequently, provide evidence for the existence of an intermediate in the reaction. The rate constants for the alkaline hydrolysis and hydroxylaminolysis of formamide are approximately 0.40 M^{-1} min.$^{-1}$ and 9 M^{-2} min.$^{-2}$, respectively.

It has recently become apparent that a number of simple substitution reactions at the carbonyl group display a complex dependence of the rate upon catalyst concentration, because of a change in the rate-determining step of the reaction with changing catalyst concentration. A positive deviation in a plot of rate against catalyst concentration demands only the addition of an extra term to the rate law, but a negative deviation (after correction for ionization or complexing of the reactants) is evidence for a change in rate-determining step and, consequently, for the existence of an intermediate of appreciable stability in reactions at the carbonyl group. Examples of such behavior have been reported for acid-catalyzed reactions[2] in which the deviation from linearity in the plot of rate against hydrogen ion concentration often gives rise to bell-shaped pH–rate profiles, and for general acid–base catalyzed reactions, in which a plot of rate against catalyst concentration shows a decrease in slope as the rate-determining step of the reaction changes.[3] In several cases the existence of an addition intermediate in these reactions has been confirmed by independent evidence.[2b,g] The present report describes kinetic evidence for a change in rate-determining step and the existence of an addition intermediate in the reaction of hydroxylamine with amides to form hydroxamic acids.

Hydroxylamine is known to react with amides near neutrality and at alkaline pH. The reaction near neutrality is slow for most amides and is generally carried out at elevated temperatures for analytical purposes.[4–8] The rate of this reaction shows a sharp maximum near pH 6 for a number of simple amides related to glutamine.[6] The alkaline reaction is slower

(1) Supported by grants from the National Science Foundation and the National Institute of Child Health and Human Development of the National Institutes of Health (HD-01247).

(2) (a) A. V. Willi, *Helv. Chim. Acta*, **39**, 1193 (1956); (b) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959); (c) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 832 (1962); (d) E. H. Cordes and W. P. Jencks, *ibid.*, **85**, 2843 (1963); (e) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *ibid.*, **81**, 5089 (1959); R. B. Martin and A. Parcell, *ibid.*, **83**, 4830 (1961); (f) B. Zerner and M. L. Bender, *ibid.*, **83**, 2267 (1961); (g) E. S. Hand and W. P. Jencks, *ibid.*, **84**, 3505 (1962); (h) R. B. Martin and R. I. Hedrick, *ibid.*, **84**, 106 (1962); (i) B. Hanson, *Acta Chem. Scand.*, **17**, 1307 (1963); (j) B. E. Dawson and T. Henshall, *J. Phys. Chem.*, **67**, 1187 (1963); (k) B. Capon and B. E. Connett, *Tetrahedron Letters*, **22**, 1395 (1964); (l) T. C. Bruice and L. R. Fedor, *J. Am. Chem. Soc.*, **86**, 738, 739 (1964).

(3) (a) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962); (b) R. B. Martin, A. Parcell, and R. I. Hedrick, *ibid.*, **86**, 2406 (1964).

(4) F. Lipmann and L. C. Tuttle, *J. Biol. Chem.*, **159**, 21 (1945).

(5) J. Katz, I. Lieberman, and H. A. Barker, *ibid.*, **200**, 417 (1953).

(6) A. Meister, L. Levintow, R. E. Greenfield, and P. A. Abendschein, *ibid.*, **215**, 441 (1955).

(7) C. Hoffman, *Ber.*, **22**, 2854 (1889).

(8) (a) G. Braunitzer, *Biochim. Biophys. Acta*, **19**, 574 (1956); (b) L. K. Ramachandran and K. Narita, *ibid.*, **30**, 616 (1958).