bridge, at 25°. The cell constant was determined using 0.001000 M KCl. The equivalent conductance (Λ) of each detergent solution containing urea was multiplied by the ratio of the viscosity of the urea solution to that of water. When this correction is made, the equivalent conductance of the detergent at infinite dilution is essentially independent of urea concentration in the range we employed.

Critical micelle concentrations (c.m.c.) were determined by plotting $\Lambda\eta_\mu/\eta_{H_2O}$ vs. the square root of detergent concentration, the c.m.c. being obtained from the break in the curve. Results for four solutions are presented in Table I. The

TABLE I

Urea concn., moles/l.	0.0	0.5	2.0	6.0
C.m.c. moles/l.	0.0142	0.0156	0.0204	0.0454

results in pure water agree with those of other investigators,[12,13] and the data show a clear increase in c.m.c. with increasing urea concentration. Thus, urea does break hydrophobic bonds in aqueous solution. The effect of urea is modest, however, as was shown by measurements made with aqueous solutions of detergent in 6.6 M acetone. The latter experiments showed no evidence of micelles even at detergent concentrations as high as 0.12 M.

The mechanism by which urea may act as a breaker of hydrophobic bonds is by no means clear. However, since the average dielectric constant of the medium is not the determining factor (urea and acetone having opposite effects on the dielectric constant), we are led to hypothesize that the urea acts to stabilize the molecularly dispersed system, perhaps indirectly, by some favorable interaction with the "iceberg" regions that presumably form about the exposed hydrocarbon tails of the detergent,[14,15] or by formation of structures similar to urea–hydrocarbon clathrates.[7] Spelling out the details of the interaction will have to await further elucidation of the effect of urea on the structure of water.

Direct application of these results to protein, deoxyribonucleic acid, or polypeptide denaturation is not possible in view of the absence of definitive equilibrium data on the denaturing effect of organic molecules, such as acetone, at concentrations comparable to those used in studies of urea action. If its effect on hydrophobic bonds is responsible for the denaturing action of urea, then acetone, at comparable concentrations, should be a more effective denaturant. If acetone is not more effective, then urea must be capable of destroying other sources of stabilization (e.g., hydrogen bonds) in addition to hydrophobic bonds.[16]

(12) A. Scott and H. Tarter, J. Am. Chem. Soc., 65, 692 (1943).

(13) P. Debye, Ann. N. Y. Acad. Sci., 51, 587 (1949).

(14) H. S. Frank and M. W. Evans, J. Chem. Phys., 13, 507 (1945).

(15) I. Klotz and V. Stryker, J. Am. Chem. Soc., 82, 5169 (1960).

(16) The authors wish to acknowledge stimulating and informative discussions with G. Colacicco, E. P. Geiduschek, L. Kotin, T. Layloff, M. Nagasawa, C. Tanford and D. Wetlaufer.

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A CASE OF INTRAMOLECULAR ASSISTANCE OF AMIDE HYDROLYSIS BY A NEIGHBORING AMIDE GROUP[1]

Sir:

We have obtained evidence for an amide hydrolysis which is strongly assisted by a *neighboring amide function*. In the course of our work[2] on intramolecular hydrogen transfer during diazonium ion decomposition, we observed hydrolysis of o-benzamido-N,N-dicyclohexylbenzamide (I) under (acidic) conditions which had failed to cause hydrolysis of much less sterically hindered amides. Furthermore, the basic and acidic hydrolyses of this compound gave different products. Whereas the basic cleavage in aqueous ethanol occurred, as expected, at the benzoyl group, the acidic hydrolysis in acetic acid took place at the more sterically hindered *tert.* amide linkage to yield N-benzoylanthranilic acid (IV) and dicyclohexylamine.

In acetic acid which was 6.9 M in water and 0.89 M in sulfuric acid, I hydrolyzed to the extent of 87% in five hours at 80°. On the other hand, N,N-dicyclohexylbenzamide (II) yielded no detectable benzoic acid when subjected to the same reaction conditions for one week. Assuming that as little as one half per cent. yield of benzoic acid would have been detected, the rate of hydrolysis of I is *at least* 10^4 times greater than that of the much less sterically compressed model compound II.

In an attempt to obtain a finite rate difference between I and II, the reactions were run in the same solvent at reflux (112°). At that temperature, I hydrolyzed to the extent of 89% in one half hour whereas II yielded N-cyclohexylbenzamide (53%) and benzoic acid (47%) after one week. Since in the latter case, the basic fraction contained no appreciable dicyclohexylamine,[3] it appears likely that the benzoic acid arose from partial hydrolysis of N-cyclohexylbenzamide which presumably was formed by acid catalyzed solvolysis of II.[4] No attempt was made to isolate the other likely products, cyclohexanol, cyclohexylacetate, and cyclohexene. The data are summarized in Table I.
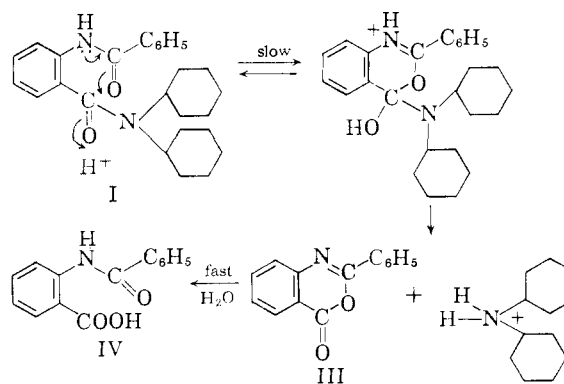

Fig. 1.

A reasonable reaction path compatible with the large rate enhancement caused by the *ortho*-benzamido group, the acid catalysis (compare runs 3 and 5 in Table I) and the fact that cleavage

TABLE I

HYDROLYSIS OF AMIDES IN 6.9 M ACETIC ACID, IN WATER

Amide	T, °C.	Time, hr.	Acidity, M^a	Cleavage,[b] %
I	80	5	0.89	87
II	80	168	0.89	<0.5
I	112	0.5	0.89	89
II	112	168	0.89	[c]
I	111	0.5	0.089	44

[a] Molarity of sulfuric acid. In all runs except the last the acid was present in large excess over the reactants. In the last run, sulfuric acid was present at the start to the extent of two equivalents to one of amide. [b] Based on isolated carboxylic acid. In all cases the yield of amine hydrochloride was within 2% of that of the acid. [c] A different reaction occurred; see text.

occurs at the more crowded of the two carbonyl groups is shown in Fig. 1. The proposal involves nucleophilic attack of the benzoyl oxygen on the carbon atom of the protonated *tert.* amide carbonyl group with consequent displacement of the dicyclohexylamine and rapid hydrolysis of the resulting six-member ring intermediate.[5]

Some support for this mechanism has been obtained by the isolation in 80% yield of the proposed intermediate benzoylanthranil (III)[6] from a cleavage reaction of I carried out for twenty hours at 80° in a solution of dry dioxane saturated with hydrogen chloride. It was further shown that under the reaction conditions which caused the cleavage of I to the extent of 87% in five hours, III was hydrolyzed to IV to an extent greater than 96% at the end of twenty minutes.

Because amide groups are the most prominent functionality of proteolytic enzymes, the general type of assisted hydrolysis observed here should be considered along with other mechanistic proposals which have been put forth to explain enzymatic hydrolysis.[7] A number of variations of this general scheme can be envisioned and we plan to investigate several of these.

(5) Of the other possible mechanisms which we have considered, the most likely involves general acid catalysis by the protonated benzamido group as in *i*. However, this type of electrophilic assistance is expected to be much less effective than that afforded by direct protonation of the carbonyl group undergoing reaction, a protonation which appears to be at least as favorable as that of the benzoyl oxygen. The complex *i* would also be destabilized by powerful non-bonded repulsions. Further studies which might provide evidence concerning this mechanism are planned.


(6) P. R. Levy and H. Stephen, *J. Chem. Soc.*, 985 (1956).

(7) In a recent review,[8] Bender has discussed the possibility that enzymatic amide groups might assist in the hydrolysis of carboxylic acid derivatives. He has also suggested the use of acylated anthranilic acid derivatives as model systems and has even anticipated the possible involvement of intermediates such as III.

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

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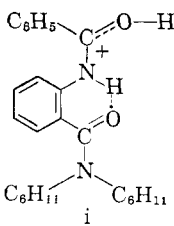
1,3 π-INTERACTION IN A CYCLOBUTANE SYSTEM

Sir:

Although 1,3 π-interaction has been invoked in the cyclobutane ring system to explain various chemical phenomena,[1,2] no experimental proof of its existence has appeared despite attempts[3] to provide such evidence by the examination of the ultraviolet spectra of 1,3-diexocyclic unsaturated cyclobutanes. We wish to report that, using this approach, evidence indicating 1,3 π-interaction[4] in the cyclobutanes I–IV has been obtained.

The dione I with malononitrile (1:2.4 molar ratio) in pyridine solution at 25° for one week gave bis - (dicyanomethylene) - 2,2,4,4 - tetramethylcyclobutane (II) in 97% yield, m.p. (sinters 250°) 305–310° (dec.); λ_{max}^{KBr} 4.48 and 6.14 μ. (Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.17; N, 5.12; N, 23.71. Found: C, 71.39; H, 5.25; N, 23.85). By lowering the amount of malononitrile (1:1.1) and decreasing the reaction time (three days) dicyanomethylene-2,2,4,4-tetramethylcyclobutanone (III) was ob-

tained as the major product (46%) along with the bis-dicyanomethylene compound II (21%). The cyclobutanone (III) had m.p. 108–108.5°; λ_{max}^{KBr} 4.48, 5.55, and 6.14 μ; (Anal. Calcd. for $C_{11}H_{12}$-
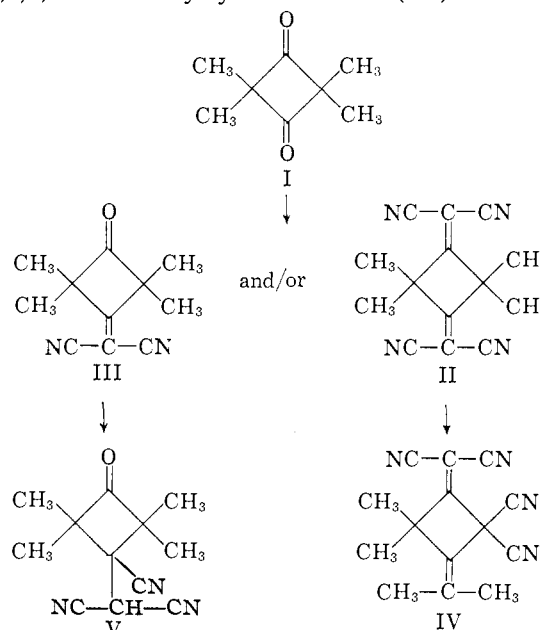
(1) E. F. Silversmith and J. D. Roberts, *J. Am. Chem. Soc.*, 80, 4083 (1958).

(2) E. J. Smutny, M. C. Caserio and J. D. Roberts, *ibid.*, 82, 1793 (1960).

(3) 1,3-Dimethylenecyclobutane failed to show absorption in the ultraviolet attributable to 1,3 π-interaction (F. F. Caserio, Jr., S. H. Parker, R. Piccolini and J. D. Roberts, *ibid.*, 80, 5507 (1958). 3-Methylenecyclobutanone was synthesized but no conclusions could be drawn regarding 1,3 interaction because of the presence of 3-methylcyclobutenone (F. F. Caserio, Jr., and J. D. Roberts, *ibid.*, 80, 5837 (1958).

(4) (a) Recently, the ultraviolet and infrared absorption spectra of 3-thiacyclobutanone were found to be "anomalous," and possible transannular sulfur–carbonyl interaction was considered (J. C. Martin, Abstracts of 139th A.C.S. meeting, St. Louis, Missouri, March, 1961, p. 31-O). Previously the possibility of 1,3 bonding was raised in the case of 3-methylenetrimethylene oxide (D. E. Applequist and J. D. Roberts, *J. Am. Chem. Soc.*, 78, 4012 (1956). (a) An analogous 1,4 π-interaction has been observed in exomethylene derivatives of a boat 1,4-cyclohexanedione derived from quinone and cyclopentadiene (S. Winstein, L. DeVries, and R. Orloski, *ibid.*, 83, 2020 (1961)).