Product Collection. Most of these experiments were carried out in the general manner previously described,[4] except that cooling with ordinary ice was found to be sufficient during the outgassing procedure. As before, most of these reaction mixtures were physically heterogeneous. In most of these experiments, also, allylmercuric chloride was the starting material, and a twofold excess of iodide ion was used. It was assumed that the reaction actually takes place in solution and that allylmercuric chloride is rapidly converted to the iodide in a solution containing excess iodide ion. In a kinetic experiment identical cleavage rates were observed with allylmercuric iodide and chloride as starting materials and an excess of iodide ion. In addition one of the product collection experiments in which RH/RD was determined was carried out with predissolved allylmercuric iodide. The result is indistinguishable from the others.

The Effect of Charge-Transfer Complexation on the Hydrolysis of Some Carboxylic Acid Derivatives[1]

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Contribution from the Department of Chemistry, Northwestern University, Evanston, Illinois. *Received September 13, 1965*

Abstract: 3,5-Dinitrobenzoate ion has been shown to form a complex in aqueous solution with N-(indole-3-acryloyl)imidazole, *p*-nitrophenyl 3-indoleacrylate, and *p*-nitrophenyl 3-indoleacetate. The association constant for the first complex was determined both spectrophotometrically and kinetically, while the association constants of the other two complexes were only determined kinetically. Kinetic analysis indicates that, when complexed with 3,5-dinitrobenzoate ion, all three substrates are unreactive to hydroxide ion, or more specifically react with hydroxide ion less than 3% as fast as the uncomplexed substrate. The lack of reactivity of the complex between N-(indole-3-acryloyl)imidazole and 3,5-dinitrobenzoate ion is probably not due to electrostatic repulsion of the hydroxide ion by the carboxylate ion of the complexing agent, because the complex is also inert to reaction with the neutral nucleophile, *n*-butylamine. The inhibition of the hydrolysis of N-(indole-3-acryloyl)imidazole can not be attributed to steric effects due to complexation with the imidazole portion of the substrate since *p*-nitrophenyl 3-indoleacrylate is likewise inhibited and possesses a similar association constant. The results are rationalized in terms of the relative stabilization of the ground and transition states due to complexation.

The reactivities of labile compounds in solution have often been found to change in the presence of reagents that complex with them. For example, Higuchi and Lachman[3] found that caffeine will complex with ethyl *p*-aminobenzoate and inhibit its hydrolysis. Later Lach and Chin[4] discovered an even larger retardation of the hydrolysis of ethyl *p*-aminobenzoate, using β-cyclodextrin as the complexing agent. Recently Connors and Mollica[5] demonstrated a small inhibition of the hydrolysis of methyl cinnamate by imidazole. Ross and Kuntz[6] showed that the decrease in the bimolecular rate constants for the reaction between aniline and 2,4-dinitrochlorobenzene with increasing aniline concentration was due to molecular compound formation. While most of the examples in the literature involve rate inhibitions, rate increases due to complexation are also possible. One of the most notable of these is the work of Colter and coworkers[7] who studied the catalysis of the acetolysis of 2,4,7-trinitro-9-fluorenyl *p*-toluenesulfonate by the donor molecule, phenanthrene. Also Cramer and Kampe[8] have shown that the association of cyclodextrins with β-keto acids will facilitate decarboxylation of these compounds. In most of the studies mentioned above the determination of association constants by kinetic methods was possible. In some instances information about the complexes was obtained that would be difficult to get otherwise. Thus these reactions serve as an important probe into the chemistry of complex formation. Furthermore, since all enzymatic processes involve reactions of substrates in the complexed state, the study of reactions of simple complexes may be very useful in the elucidation of enzymatic mechanism.

This research is concerned with the chemical behavior of carboxylic acid derivatives when subjected to charge-transfer complexation. It is well known that electronegative substituents on the acyl portion of benzoate esters greatly enhance their susceptibility to hydrolysis. If a bound complexing agent is regarded as a substituent of unknown location,[9] then it might be expected that a strong electron acceptor, which is able to bind with an aromatic acid derivative, would also increase its reactivity. Of course, other factors such as steric hindrance by the complexing agent may be important. It was hoped here to effect catalysis of the hydrolysis of a carboxylic acid derivative by proper complex formation between a donor substrate and an acceptor complexing agent.

The present study primarily involves an investigation of the hydrolysis of N-(indole-3-acryloyl)imidazole (I) in the presence of the complexing agent, 3,5-dinitrobenzoate ion (II) in aqueous solutions. The latter compound was chosen because it is known that poly-

(1) This research was supported by a grant from the National Science Foundation.

(2) National Institutes of Health Postdoctoral Research Fellow.

(3) T. Higuchi and L. Lachman, *J. Am. Pharm. Assoc.*, **44**, 521 (1955).

(4) J. L. Lach and T. Chin, *ibid.*, **53**, 924 (1964).

(5) K. A. Connors and J. A. Mollica, *J. Am. Chem. Soc.*, **87**, 123 (1965).

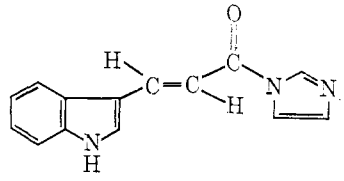
(6) S. D. Ross and I. Kuntz, *ibid.*, **76**, 3000 (1954).

(7) A. K. Colter, S. S. Wang, G. H. Megerle, and P. S. Ossip, *ibid.*, **86**, 3106 (1964).

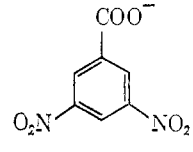
(8) F. D. Cramer and W. Kampe, *ibid.*, **87**, 1115 (1965).

(9) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

nitroaromatics are good electron acceptors.[10] The carboxylate ion of this compound is necessary in order to obtain a high concentration of the acceptor in the aqueous solvent. Since the Hammett σ constant of the carboxylate ion is close to 0 it would be expected that the acceptor properties of the complexing agent would be very similar to those of *m*-dinitrobenzene. The substrate was chosen because of its many attractive features: (1) it hydrolyzes at a convenient rate at pH 10.4; (2) the hydrolytic reaction is accompanied by a large change in absorbance, at around 400 mμ; (3) the substrate possesses an indole ring whose donor properties are well documented[11]; (4) the indole ring is conjugated with the reactive carbonyl group; and (5) the hydrolyzable bond of the substrate is situated far from the binding site, the indole ring, so that a complexing agent lying flat on the indole ring for maximum

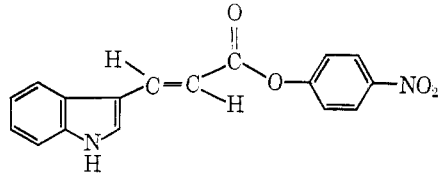


I

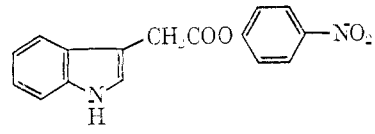


II

orbital overlap will not inhibit the reaction by sterically blocking the approach of the nucleophile. It was also desirable to compare the reaction of this substrate with that of the *p*-nitrophenyl ester of 3-indoleacrylic acid (III) and with that of a corresponding unconjugated system. For this reason the reaction of *p*-nitrophenyl 3-indoleacetate (IV) is also described.



III



IV

Experimental Section

Materials. N-(Indole-3-acryloyl)imidazole (I). This compound was prepared by the mixed anhydride method from 3-indoleacrylic acid (Aldrich), triethylamine, and ethyl chloroformate, followed by the addition of imidazole. The product was recrystallized repeatedly from ethyl acetate–hexane to give a crystalline solid, m.p. 199–200.5° dec. (lit.[12] m.p. 190°). *Anal.* Calcd. for $C_{14}H_{11}N_3O$: C, 70.88; H, 4.67; N, 17.71. Found: C, 70.61; H, 4.92; N, 17.60.

***p*-Nitrophenyl 3-Indoleacetate (IV).** 3-Indoleacetic acid (Eastman) (1.75 g., 0.01 mole) and *p*-nitrophenyl trifluoroacetate (Aldrich) (2.63 g., 0.011 mole) were mixed in 10 ml. of dry pyridine.[13] The solution became warm and was allowed to stand for 15 min. The light brown solution was then added to 40 ml. of ice water with rapid stirring which resulted in a yellow oil. The aqueous layer was decanted and the oil was dissolved in ether, followed by a thorough drying with two portions of calcium sulfate. The drying agent was removed by filtration and the solution was reduced to 25 ml. on a steam bath. Petroleum ether was added until the cloud point was reached. Cooling in a refrigerator produced 2.22 g. (75% yield) of tan colored crystals, m.p. 108–109°. Recrystallization using the same solvents and activated charcoal, and once more with no charcoal, produced crystals, m.p. 108–108.5°. *Anal.* Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 65.25; H, 4.17; N, 9.24.

***p*-Nitrophenyl 3-Indoleacrylate (III).** This compound was prepared by the method described for *p*-nitrophenyl 3-indoleacetate. Repeated recrystallization of the product resulted in yellow needles, m.p. 179.5–181°. *Anal.* Calcd. for $C_{17}H_{12}NO_4$: C, 66.22; H, 3.92; N, 9.08. Found: C, 66.43; H, 3.99; N, 8.68.

3,5-Dinitrobenzoic Acid (II). Material from a newly opened bottle of Eastman White Label product was recrystallized repeatedly from hot, aqueous ethanol, m.p. 205–207° (lit.[14] m.p. 205–207°).

All inorganic compounds used were of reagent quality. The acetonitrile was distilled repeatedly from phosphorus pentoxide. The *n*-butylamine was distilled repeatedly from potassium hydroxide and finally from zinc dust. Distilled water was used to prepare all buffers.

Kinetics. The hydrolysis of N-(indole-3-acryloyl)imidazole (I) was followed in a thermostated Cary 14 PM recording spectrophotometer by measuring the decrease in absorbance with time at 390.0 mμ. Experiments were performed in Borax buffers of pH 10.40 with varying amounts (0 to 0.15 *M*) of 3,5-dinitrobenzoate and with a constant ionic strength of 0.50. The solutions were prepared by adding 0.015 mole of 3,5-dinitrobenzoic acid and an equal molar amount of 1.00 *M* potassium hydroxide to about 50 ml. of 0.025 *M* Borax buffer, pH 10.40, in a 100-ml. volumetric flask, and stirring until all the acid dissolved. The proper amount of potassium chloride was added and the solution was brought to the mark with more buffer, after which it was adjusted to a pH of 10.40 using a Radiometer 4C pH meter. The solutions with a smaller concentration of complexing agent were prepared by serial dilution of this solution with Borax buffer with an ionic strength of 0.50. Small additions of 1.0 *M* hydrochloric acid or potassium hydroxide brought the pH values to 10.40.

In a typical run, 3.00 ml. of buffer containing the complexing agent was placed in the sample and reference compartments of the spectrophotometer and thermostated at 25.0 ± 0.1° for more than 15 min. The spectrophotometer was then balanced and, by means of a small glass stirrer, 25 μl. of a solution of N-(indole-3-acryloyl)-imidazole in acetonitrile was added to the sample cell (preceded by addition of 25 μl. of pure acetonitrile to the reference cell). The spectrophotometer was turned on within 10 sec. after addition of the substrate and the reaction was generally followed to 8 half-lives. The absorbance at completion of the reaction was always within 0.01 unit of the original base line. The first-order plots were linear to greater than 80% of the reaction. Duplicate runs always agreed to better than 3%. The concentration of the 3,5-dinitrobenzoate ion was limited by the severe blanking problems at 390.0 mμ above 0.15 *M* as well as by the solubility of the complexing agent. Buffer and substrate solutions were stored in a refrigerator.

A single run was performed in a similar manner using an *n*-butylamine buffer with a total amine concentration of 0.40 *M* and a pH of 10.40. The 3,5-dinitrobenzoate ion concentration was 0.0757 *M* and the ionic strength was again 0.50. The buffer was used 1 hr. after preparation because it seemed to be unstable, turning to a light brown color after 24 hr.

The hydrolysis of *p*-nitrophenyl 3-indoleacetate was studied in the same manner as described above except that the wave length was 400.0 mμ. The hydrolysis of *p*-nitrophenyl 3-indoleacrylate at various 3,5-dinitrobenzoate ion concentrations was examined in phosphate buffers of pH 11.90 and ionic strength of 0.50, at 400.0 mμ. Neither the Borax nor the phosphate buffer made a significant contribution to the observed rate.

Spectrophotometric Determination of the Association Constant. The equilibrium constant for the association of N-(indole-3-acryloyl)-imidazole with 3,5-dinitrobenzoate ion was determined by measuring the increase in absorption at 420.0 mμ with increasing 3,5-dinitrobenzoate ion concentration, while keeping the substrate con-

(10) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(11) I. Isenberg, A. Szent-Gyorgyi, and S. L. Baird, *Proc. Natl. Acad. Sci., U. S.*, **46**, 1307 (1960); R. Foster and P. Hanson, *Tetrahedron*, **21**, 255 (1965).

(12) S. A. Bernhard and Z. H. Tashjian, *J. Am. Chem. Soc.*, **87**, 1806 (1965).

(13) S. Sakakibara and N. Inukai, *Bull. Chem. Soc., Japan*, **37**, 1231 (1964).

(14) R. Q. Brewster and B. Williams, *Org. Syn.*, **22**, 48 (1942).

centration constant. A pH of 7.00 was used in order to minimize the hydrolysis of the substrate. Phosphate buffers of pH 7.00 and ionic strengths of 0.50 containing varying amounts of 3,5-dinitrobenzoate ion were prepared in a manner identical with that described for the Borax buffers. The buffers were also filtered through sintered glass to remove dust and improve the accuracy of the spectrophotometric measurements. Two 1.00-cm. cuvettes were filled with 3.00 ml. of buffer and equilibrated in the sample and reference chambers of a Cary 14 PM spectrophotometer at 25.0 ± 0.1°. The acetonitrile and substrate solution were added exactly as in the kinetic runs and the optical density was determined at 420.0 mμ using a 0–2.0 slide-wire and a substrate concentration of 1.73×10^{-4} *M*. The optical density difference between no complexing agent and 0.10 *M* complexing agent was 0.46 absorbance unit. A single micropipet was used to deliver the substrate solution for all the determinations, and all the determinations were done in duplicate. Duplicate determinations agreed to within 3%. Since there seemed to be a very small amount of hydrolysis under the conditions of the experiment, the absorbance readings were taken within 30 sec. after addition of the substrate. The use of 380.0 mμ would have been advantageous because of the large absorbance change in this region were it not for the fact that at the higher 3,5-dinitrobenzoate ion concentrations the large slit widths made the readings unreliable. It was not possible to obtain a spectrophotometric association constant for the other two substrates.

Results

The effect of varying concentrations of 3,5-dinitrobenzoate ion (A = acceptor) on the rate of hydrolysis of N-(indole-3-acryloyl)imidazole (D = donor) was determined. The results of such experiments are shown in Table I and in Figure 1. It is seen that the

Table I. The Observed Rate Constants for the Hydrolysis of N-(Indole-3-acryloyl)imidazole in the Presence of Varying 3,5-Dinitrobenzoate Ion Concentrations[a]

(A), *M*	$k_{obsd} \times 10^4$ sec.$^{-1}$
0.000	20.4
0.0120	16.3
0.0180	14.8
0.0300	12.4
0.0420	11.0
0.0601	8.71
0.0814	7.68
0.120	6.15
0.150	5.80

[a] pH 10.40; 25.0°; 0.83% acetonitrile–water (v./v.); substrate = 3.87×10^{-5} *M*; *I* = 0.50; Borax buffer.

complexing agent causes a sizeable rate *decrease*, contrary to our predicted analogy between a bound complexing agent and an electronegative substituent. The rate decrease is much too large to be explained by a change in the bulk dielectric properties of the solvent due to the addition of an organic compound. The rate decrease is very apparent at 0.012 *M* 3,5-dinitrobenzoate ion whereas 0.16 *M* acetonitrile has no effect on the observed rate constant. Furthermore the general shape of the curve of Figure 1 indicates that the expected complexing is taking place: if complexing occurs, the rate should change and level off as the substrate becomes saturated with the complexing agent; in the limit, addition of more complexing agent should not change the rate constant at all. At this point, of course, all the substrate will be present in the bound (complexed) form. Such a system is described by eq.

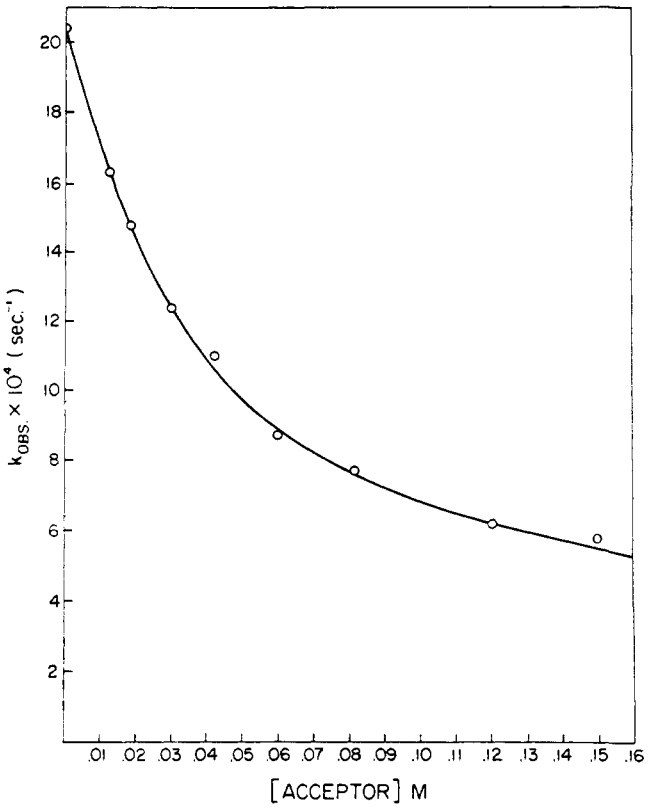


Figure 1. The observed rate constants for the hydrolysis of N-(indole-3-acryloyl)imidazole at pH 10.40 and 25.0° with varying concentrations of 3,5-dinitrobenzoate ion.

1. In this scheme DA represents the complex and P

$$\begin{array}{ccc} D + A & \overset{K}{\rightleftharpoons} & DA \\ \downarrow k_1 & & \downarrow k_2 \\ P & & P \end{array} \qquad (1)$$

the products. The complex DA is related to the free species D and A by the association constant *K*. Both the complexed donor, DA, and the uncomplexed donor, D, may conceivably react to give hydrolyzed product. Using eq. 1 the observed first-order rate constant of the hydrolysis may be related to the individual rate constants k_1 and k_2 as well as the equilibrium constant *K* as shown in eq. 2.[7] The value of k_1 is known; it is

$$\frac{1}{(k_1 - k_{obsd})} = \frac{1}{(k_1 - k_2)} + \frac{1}{(k_1 - k_2)K(A)} \qquad (2)$$

simply the observed rate constant in the absence of complexing agent. It is then possible to obtain k_2 and *K* by plotting $1/(k_1 - k_{obsd})$ *vs.* 1/(A). The intercept of such a plot gives k_2 and, knowing this constant, *K* may be calculated from the slope. Figure 2 shows such a graph based on the data of Table I. The linearity of the plot is excellent. The difference $(k_1 - k_2)$ obtained from the reciprocal of the intercept is found to be 20.0×10^{-4} sec.$^{-1}$ which differs from the known k_1 by only 2%. Since this difference is within experimental error, it indicates that k_2 is immeasurably small in this system. Since the experimental error is about 3%, the rate of hydrolysis of the complex is equal to or less than 3% of the rate of hydrolysis of the uncomplexed substrate.

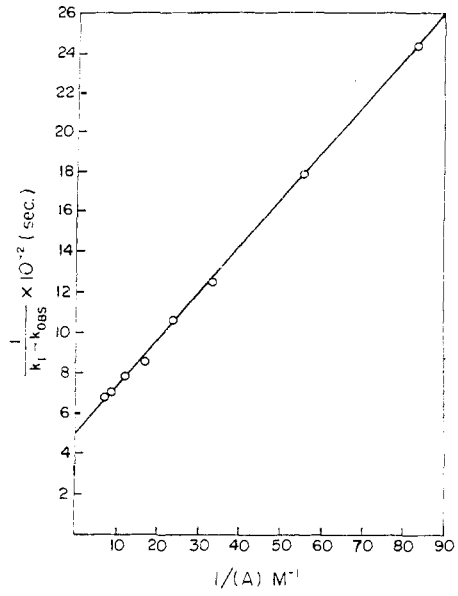


Figure 2. The determination of the formation constant of the N-(indole-3-acryoyl)imidazole 3,5-dinitrobenzoate ion complex and the rate constant of its hydrolysis from the kinetic data of Table I.

The association constant for the complex formation between N-(indole-3-acryloyl)imidazole and 3,5-dinitrobenzoate ion is calculated to be 21.5 M^{-1}, a sizeable equilibrium constant. It can be compared with an association constant of 0.15 M^{-1} for charge-transfer complexation between N,N-dimethylaniline and *s*-trinitrobenzene in dioxane[15] and the value of 33.9 M^{-1} for the interaction of tetracyanoethylene with naphthalene in carbon tetrachloride.[16] It is possible that the large association constant found here is due to the aqueous solvent used in this study. The equilibrium constant should be enhanced by the hydrophobic nature of the substrate and the dinitrobenzene ring.[10] Furthermore, the charge separation that occurs in the complex between the two species should be facilitated by the polar solvent.[17] Unfortunately, most information about charge-transfer complexes is derived from nonaqueous systems. It would be important to chemistry and biology to extend these studies to aqueous solvents through the use of water-solubilizing groups, such as the carboxylate employed here, on the acceptor or donor.

In order to get an independent check of the hypothesis given in eq. 1, the equilibrium constant between donor and acceptor was determined by an independent, nonkinetic method. This determination was carried out spectrophotometrically at pH 7.00 where the hydrolysis was negligible. Equation 3 describes the

$$\frac{(D_t)}{(O.D. - O.D._0)} = \frac{1}{(\epsilon_{DA} - \epsilon_D)} + \frac{1}{(\epsilon_{DA} - \epsilon_D)K(A)} \quad (3)$$

system.[18] The symbol D_t is the total amount of donor

(15) R. Foster and D. L. Hammick, *J. Chem. Soc.*, 2685 (1954).
(16) G. Briegleb, J. Czekalla, and G. Reuss, *Z. physik. Chem.* (Frankfurt), **30**, 333 (1961).
(17) R. Foster and T. J. Thompson, *Trans. Faraday Soc.*, **58**, 860 (1962).
(18) J. A. A. Ketelaar, C. van de Stolpe, A. G. Goundsmit, and W. Dzcubar, *Rec. trav. chim.*, 71, 1104 (1952).

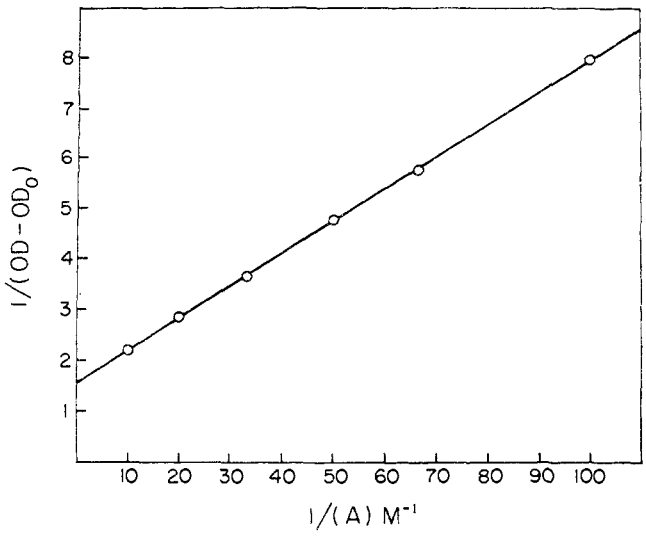


Figure 3. Spectrophotometric determination of the formation constant of the N-(indole-3-acryloyl)imidazole-3,5-dinitrobenzoate ion complex.

present; O.D. represents the absorbance of the donor in the presence of 3,5-dinitrobenzoate ion; $O.D._0$ is the absorbance of the same species in the absence of the acceptor A; the ϵ values refer to those of the complex DA and the donor D; and K is the association constant for complex formation. The spectrophotometric data at 420.0 mμ with changing 3,5-dinitrobenzoate ion concentrations are given in Table II. By plotting $1/(O.D. - O.D._0)$ *vs.* 1/(A) one may calculate the association constant K. A plot of this sort is given in Figure 3. The association constant from this plot is 23.6 M^{-1}, in excellent agreement with the value of 21.5 M^{-1} obtained kinetically, confirming the hypothesis of eq. 1.[19]

Table II. The Absorbance (O.D.) of 1.73×10^{-4} M Solutions of N-(Indole-3-acryloyl)imidazole at 420.0 mμ in Various Concentrations of 3,5-Dinitrobenzoate Ion (A)[b]

(A), M	O.D.
0.000	0.968[a]
0.0100	1.094
0.0150	1.142
0.0200	1.178
0.0300	1.245
0.0500	1.322
0.100	1.428

[a] 0.968 = $O.D._0$. [b] pH 7.00; 25.0°; 0.83% acetonitrile–water (v./v.); I = 0.50; phosphate buffer.

It has been assumed here that the complex between donor and acceptor has a 1:1 stoichiometry. Since the acceptor A is in such large excess, it is possible that a higher order complex, such as DA_2, is present in solution. Unfortunately, the excellent linear plot of Figure 3 cannot be used as evidence to exclude such species,

(19) W. P. Person, *J. Am. Chem. Soc.*, **87**, 167 (1965), has shown that the accuracy of the determination of an equilibrium constant for the complex formation using a spectrophotometric technique requires that the highest concentration of the acceptor (or donor, whichever is in excess) must be greater than about $0.1/K$. The value of this quantity in this work is 4.2×10^{-3} M so that the highest concentration of 3,5-dinitrobenzoate ion, 0.1 M, exceeds this value by a factor of more than 20. It is therefore believed that the spectrophotometric association constant is a reliable one.

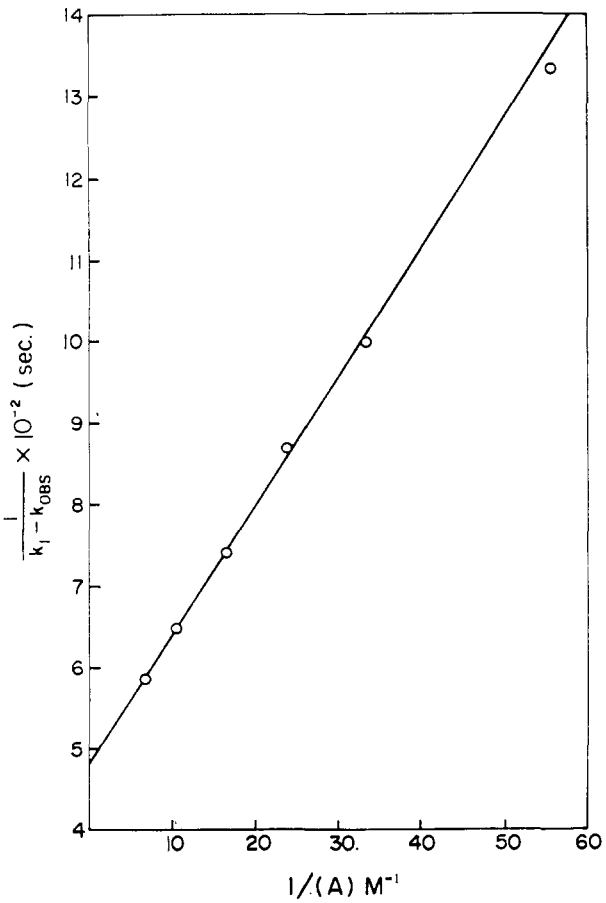


Figure 4. The determination of the formation constant of the *p*-nitrophenyl 3-indoleacetate-3,5-dinitrobenzoate ion complex and the rate constant of its hydrolysis from the kinetic data of Table IV.

as was recently shown.[20] Likewise, the linear plot of the kinetic data of Figure 2 is no assurance of the absence of such complications. However, formation of a complex with more than one 3,5-dinitrobenzoate ion would necessitate bringing two negative charges in close proximity, and for this reason such a species is considered unlikely.

The effect of varying concentrations of 3,5-dinitrobenzoate ion on the hydrolysis of *p*-nitrophenyl 3-indoleacrylate and *p*-nitrophenyl 3-indoleacetate was also determined. The results of such experiments are shown in Tables III and IV, respectively. These data

Table III. The Observed Rate Constants for the Hydrolysis of *p*-Nitrophenyl 3-Indoleacrylate in the Presence of Varying 3,5-Dinitrobenzoate Ion Concentrations[a]

(A), *M*	$k_{obsd} \times 10^3$ sec.$^{-1}$
0.000	2.36
0.0180	1.61
0.0300	1.36
0.0421	1.21
0.0601	1.01
0.0961	0.816
0.150	0.658

[a] 25.0°; pH 11.90; 0.83% acetonitrile–water (v./v.); I = 0.50; phosphate buffer; substrate = 5.15×10^{-6} *M*.

(20) G. D. Johnson and R. E. Brown, *J. Am. Chem. Soc.*, 87, 1655 (1965).

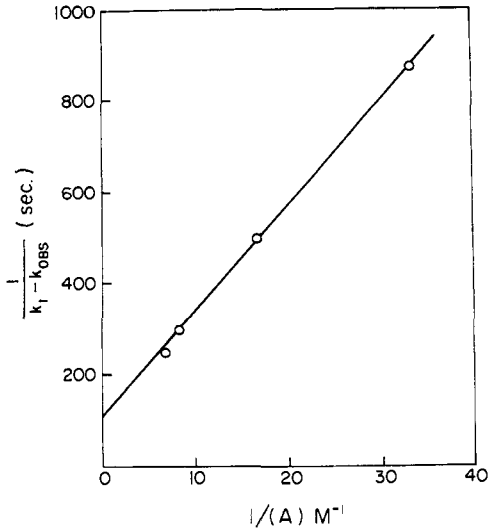


Figure 5. The determination of the formation constant of the *p*-nitrophenyl 3-indoleacrylate-3,5-dinitrobenzoate ion complex and the rate constant of its hydrolysis from the kinetic data of Table III.

are plotted in Figures 4 and 5 in the same manner as the data for the N-(indole-3-acryloyl)imidazole hydrolysis in order to obtain the parameters K and k_2. If is found that for *p*-nitrophenyl 3-indoleacrylate and *p*-nitrophenyl 3-indoleacetate the K values are 29.7 and 4.80 M^{-1}, respectively, and that both k_2 values are again within an experimental error of 0. Unfortunately it was not possible to check these values of K spectrophotometrically since the absorbance changes were in a wave length region made inaccessible by the high concentration of 3,5-dinitrobenzoate ion. There is somewhat more error in these equilibrium constants than in the previous one because the experimental data are fewer. The values are probably accurate to within 10%.

Table IV. The Observed Rate Constants for the Hydrolysis of *p*-Nitrophenyl 3-Indoleacetate in the Presence of Varying 3,5-Dinitrobenzoate Ion Concentrations[a]

(A), *M*	$k_{obsd} \times 10^3$ sec.$^{-1}$
0.000	8.06
0.0300	6.91
0.0601	6.05
0.120	4.69
0.150	3.98

[a] 25.0°; pH 10.40; 0.83% acetonitrile–water (v./v.); I = 0.50; Borax buffer; substrate = 4.10×10^{-5} *M*.

Discussion

All previous studies of the complexation of carboxylic acid derivatives have shown an inhibition of the hydrolysis of the complexed material. The present study has led to the same results.

The nature of the rate inhibitions found previously is understood only incompletely. A rationale may be presented for the inhibition when β-cyclodextrin was used as complexing agent.[4] In this system, the substrate is presumably absorbed into a nonpolar region within the ring of sugar residues of the cyclodextrin, and its rate of hydrolysis is inhibited just as it would be if the medium were made less polar by the addition

of an organic solvent to the aqueous medium. In the inhibition of the hydrolysis of ethyl *p*-aminobenzoate by caffeine, an association involving a π-electron charge-transfer complex may be taking place.[3] If this is indeed the proper description of the complex, the inhibition of the ester hydrolysis may be explained in terms of either steric hindrance by the complexing agent or by electronic changes in the complex which lead to a diminution in the rate of reaction.

The forces involved in the complex between N-(indole-3-acryloyl)imidazole and 3,5-dinitrobenzoate ion are postulated here to be due to a charge-transfer interaction between two π-electron systems, the indole ring of the substrate, and the dinitrobenzene ring of the complexing agent. As mentioned previously, the former is known to be a good donor while the latter is a good acceptor. Independent evidence of the charge-transfer nature of this complex is, however, missing. A charge-transfer band, if present, would probably lie in a wave length region well below 390.0 mμ and thus be obscured by the absorbance of the 3,5-dinitrobenzoate ion, which is present in high concentrations. (Nevertheless, the spectrophotometric equilibrium constant was determined from the absorption band characteristic of the free donor which is perturbed to somewhat longer wave lengths upon complexation.) Both the magnitude of the association constant and the chemical composition of the participants point to a charge-transfer type of interaction.

The stereochemistry of the complexation of the donor to the substrate in solution is not known; nor is it known in many other similar systems. Electronically, the most likely stereochemistry would involve direct ring–ring interaction between the indole ring of the N-(indole-3-acryloyl)imidazole and the dinitrobenzene ring of the complexing agent. Of course, there are other possible ways in which the substrate and complexing agent may bind to one another, for example, by an interaction of the complexing agent with the acylimidazole group of the substrate or with its double bond. However, these kinds of associations should not be nearly as favorable with respect to π-orbital overlap and hydrophobic stabilization. The experiment with *p*-nitrophenyl 3-indoleacrylate was carried out in order to obtain information on this question. This ester has a nitrophenyl group which undoubtedly does not participate in complexation as a donor with the dinitrobenzoate ion acceptor. However, the substrate is still rendered inactive by complexation, and its association constant is very similar to that of the corresponding imidazole derivative. This is good evidence that the indole ring rather than the imidazole ring of N-(indole-3-acryloyl)imidazole engages in the binding process.

On the basis of the above description of the complex, the possible causes of the rate retardation may be discussed. If in fact the stereochemistry of the interaction between the donor and the acceptor has been properly described above, it is very unlikely that complex formation can result in steric hindrance. The carbonyl group and the indole ring of N-(indole-3-acryloyl)imidazole are *trans* to each other and quite far apart. It would be surprising if the complexing agent, situated above the indole ring, could reduce the rate of hydrolysis by steric hindrance alone to 3% or less of that of the free substrate. This conclusion is supported by the observation that the rate of basic hydrolysis of isopropyl acetate is 27% that of ethyl acetate.[21] It is seen that placement of a methyl group in close vicinity of the ester group cannot hinder its hydrolysis as much as is observed in the complexing system.

The presence of a negative charge on the acceptor, in the form of a carboxylate ion, must also be considered. It is certainly possible that this anionic charge on the complex inhibits attack by another negative species, hydroxide ion, even though the distance between the two may be fairly large. This explanation, however, was excluded by an experiment using *n*-butylamine as a nucleophile. It was shown that 0.0757 *M* concentration of 3,5-dinitrobenzoate ion reduces the rate constant for the reaction between *n*-butylamine and N-(indole-3-acryloyl)imidazole to 34% of its value in the absence of complexing agent. The corresponding inhibition for hydroxide attack is 37%, within experimental error of the other number. This indicates that the complex is as inert to a neutral nucleophile, *n*-butylamine, as it is to a negatively charged one, hydroxide ion. The conclusion must therefore be reached that the inhibition is not electrostatic in origin.

A third explanation for the inhibition of hydrolysis is that electronic changes within the complex reduce the susceptibility of the substrate to nucleophilic attack. It appears that the complexing agent must stabilize the ground state of the substrate more than the transition state and hence raise the activation energy of reaction. This statement implies that the ground state of the substrate is a better donor than its transition state, a somewhat surprising conclusion. The electronically perturbed state of the substrate in the complex, probably involving an electron in its highest filled orbital, might be stabilized by the presence of the carbonyl group. If this is the case, then the carbonyl stabilization of the complex would be lost in the transition state which resembles the tetrahedral intermediate believed present in basic hydrolyses of this sort. The reaction would thus be retarded. The surprising feature of this rationale is that the carbonyl group, an electron withdrawer, stabilizes the perturbed electronic state of the substrate in the complex in which one of its electrons is being donated to the complexing agent. In fact, our expectation that the carbonyl group would destabilize such a system led us to predict that the complexing agent would perhaps accelerate the hydrolysis. The electronic explanation given here is similar to that encountered in metal ion catalysis where a metal ion complex which stabilizes the ground state decelerates the reaction, whereas a metal ion complex which stabilized the transition state accelerates it.[22]

In any complete analysis of the relative energies of the ground and transition states of a reaction, it is necessary to include solvent interactions. It is quite possible that complexation, which brings a large hydrophobic dinitrobenzene ring in the vicinity of the substrate, orients ("freezes") the solvent in the region of the carbonyl group. Attack of the carbonyl by hydroxide ion could then be inhibited because of the inability

(21) M. S. Newman in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 4, p. 222.

(22) M. L. Bender, Advances in Chemistry Series, No. 37, American Chemical Society, Washington, D. C., 1963, p. 19.

of the water molecules to properly solvate the transition state.

This solvation argument might explain why the complex of *p*-nitrophenyl 3-indoleacetate is unreactive hydrolytically. The inhibition found with this substrate could not be electronic in origin because the carbonyl group is separated from the complexing site, the indole ring, by a methylene group. On the other hand, in opposition to the complex of N-(indole-3-acryloyl)imidazole, the complex of *p*-nitrophenyl 3-indoleacetate could show steric hindrance and electrostatic inhibition, and these effects may also contribute to the unreactivity.

Thus, in the search for a synthetic catalyst which will first complex with the substrate and then effect a catalysis, factors such as stereochemical, electrostatic, solvent, and electronic effects on the ground state *vis-a-vis* the transition state must be taken into account.

Azocumene. I. Preparation and Decomposition of Azocumene. Unsymmetrical Coupling Products of the Cumyl Radical

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Abstract: Azocumene (2,2′-diphenyl-2,2′-azopropane) has been prepared from cumylamine and iodine pentafluoride. It undergoes thermal decomposition with $\Delta H^* = 29.0 \pm 0.3$ kcal. and $\Delta S^* = 11.0 \pm 1.0$ e.u. The products of photodecomposition in solution at 20° and of thermal decomposition up to 60° are nitrogen and the result of 5–6% disproportionation and 94–95% coupling of cumyl radicals. A portion of the coupling product, estimated as about 2%, is quinoid dicumyl (III), formed by α-to-*para* coupling of the cumyl radicals. It undergoes thermal redissociation with $\Delta H^* \cong 26$, $\Delta S^* \cong 11$. This quinoid dicumyl is detected by its strong ultraviolet absorption (Figure 2B) which appears during low-temperature photolysis. It reacts rapidly with bromine, and it consumes Koelsch's stable free radical VI at a first-order rate identical with that of its own thermal disappearance, the rate being unaffected by pyridine or by HCl in ether. Similar, but more stable, products are formed when azoisobutane is photolyzed in cumene, ethylbenzene, and toluene (with intensity of absorption decreasing in that order) but not in benzene. Photolysis of azocumene in frozen toluene, in contrast to that in solution, gives more disproportionation than coupling of cumyl radicals by a factor of 1.5–3.

The thermal or photolytic decomposition of azoalkanes (RN=NR) has proved to be a useful source of alkyl radicals, and possesses the advantage that only one type of radical is formed initially. It is generally believed that except in special cases[1] decompositions of azo compounds involve concerted, two-bond cleavages without any intermediate diazoalkyl radical formation.[2] Convincing evidence for this lies in the fact that both groups substituted on the azo linkage substantially affect the decomposition rate. A striking example is phenylazotriphenylmethane, which has a half-life at 50° of 51 min.,[3] while azobenzene does not decompose to radicals thermally, and azotriphenylmethane decomposes so rapidly that it cannot be isolated even at −40°.[4]

Many radical reactions are run in cumene because it is an excellent hydrogen donor and dicumyl, the main reaction product of the cumyl radicals formed, is conveniently handled. The cumyl radical is also of interest in autoxidation work.[5] Azocumene (2,2′-diphenyl-2,2′-azopropane) was expected to be a useful generator of cumyl radicals for study, and also to be free from the side reactions observed in secondary azo compounds (isomerization to hydrazones[6] and induced decomposition by abstraction of α-hydrogen[7]) or in azonitriles (formation of unstable ketenimines by coupling of two α-cyano radicals). The present paper describes the preparation of azocumene and the kinetics and products of its decomposition; the following paper reports a study of factors which influence the cage effect.[8]

The activation parameters for thermal decomposition of some azoalkanes which have been studied previously (Table I[9–13]) form a regular pattern which invites a prediction of the decomposition rate of azocumene.

(1) As in perester decomposition, phenyl and methyl radicals are not well enough stabilized to contribute to a concerted decomposition. The decomposition of monophenylazomethane, $C_6H_5CH_2N{=}NCH_3$, is initiated by cleavage of the benzyl–N bond alone: S. Seltzer, *J. Am. Chem. Soc.*, **87**, 2628 (1965).

(2) (a) R. K. Lyon, *ibid.*, **86**, 1907 (1964); (b) C. Steel and K. J. Leidler, *J. Chem. Phys.*, **34**, 1827 (1961); (c) S. G. Cohen and C. H. Wang, *J. Am. Chem. Soc.*, **77**, 3628 (1955).

(3) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 576.

(4) H. Wieland, H. von Hove, and K. Börner, *Ann.*, **446**, 31 (1926).

(5) P. D. Bartlett and T. G. Traylor, *J. Am. Chem. Soc.*, **85**, 2407 (1963), and references cited there.

(6) S. G. Cohen and C. H. Wang, *ibid.*, **77**, 2460 (1955).

(7) T. G. Traylor and R. D. Swigert, unpublished results in these laboratories.

(8) S. F. Nelsen and P. D. Bartlett, *J. Am. Chem. Soc.*, **88**, 143 (1966).

(9) C. Steel and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 975 (1959).

(10) Reference 2, Table VI.

(11) A. V. Blackham and N. L. Eatough, *J. Am. Chem. Soc.*, **84**, 2922 (1962).

(12) G. Williams and A. S. Lawrence, *Proc. Roy. Soc.* (London), **A156**, 455 (1936).

(13) Calculated from unpublished results of I. V. Berezin in this laboratory. See also ref. 3.