Modification of the Reactivity of Some Carboxylic Acid Derivatives by Complexation. Effects on Some Intermolecular and Intramolecular Reactions[1,2]

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Abstract: The kinetic method for studying organic complexes utilizes measurements of the reaction rate of a substrate as a function of ligand concentration to establish the stability constant for the substrate–ligand interaction product (the complex) and to determine the chemical reactivity of the complex, which is expressed as q_{11}, the fractional decrease in reactivity of the complex relative to the uncomplexed substrate. Reactions studied include the intramolecular general base catalyzed hydrolysis of *trans*-cinnamoylsalicylic acid anion (CSA anion); intermolecular hydroxide ion catalyzed hydrolysis of CSA anion; sulfite addition to the olefinic double bond of CSA anion; intermolecular nucleophilic reactions of *p*-nitrophenyl benzoate with the nucleophiles hydroxide ion, hydrogen peroxide anion, hydroxylamine, hydrazine, and sulfite; intermolecular reactions of N-*trans*-cinnamoylimidazole with water and acetate; and intramolecular catalyses of the hydrolyses of phthalamic acid, *p*-nitrophenyl glutarate, and methyl hydrogen phthalate. The ligands included theophylline and its anion; the anions of 8-chloro-, 8-bromo-, and 8-iodotheophyllines; caffeine; 8-methoxycaffeine; and 7-(2,3-dihydroxypropyl)-theophylline. Solubility and spectral studies of complex stability were employed for supporting evidence of interaction. All studies were in aqueous solution. Hydroxide attack at the ester function of cinnamate–xanthine and benzoate–xanthine complexes is essentially completely inhibited ($q_{11} = 1$). Sulfite addition to the cinnamate double bond also gives $q_{11} = 1$. These results are interpreted to mean that, in the complex, the ligand is physically near these sites in the substrate. A series of nucleophiles reacting with the *p*-nitrophenyl benzoate–theophylline complex gave q_{11} values ranging from 0.6 to 1. It is suggested that complex formation can result in both lowering of initial-state energy and raising of transition-state energy, with the extent of the transition-state effect (and therefore q_{11}) depending on the fractional displacement of the transition state along the reaction coordinate. Intramolecular catalyses were not significantly inhibited by complex formation. The kinetic method for studying complexes is a useful probe into complex structure.

Nonadditive behavior in the physical and chemical properties of solutions is often accounted for by the hypothesis of "molecular complex" formation when the usual chemical reactions can be ruled out as the responsible processes. Organic complex formation is a facile reversible reaction involving relatively weak forces of interaction; the rate of attainment of equilibrium is much greater than any rates involved in the usual measurements of the solution properties, so the system is considered to be at equilibrium. With the hypothesis of complex formation it becomes possible to utilize quantitative measures of the solution properties to describe the extent of interaction between solute species and to investigate the nature of the complex.

It is not surprising that the chemical reactivity of a species participating in complex formation should be different from that of the uncomplexed molecule, for the proximity of a second species could lead to significant electronic perturbations and steric effects. The most familiar of these phenomena are those observed in enzymatic systems, with complex formation between enzyme and substrate being essential to the catalytic process; in these instances, chemical reactivity of the substrate is enhanced by complex formation. Less familiar, but probably much simpler, are complexes in which substrate reactivity is reduced upon complexation.[2,4]

As an experimental method for studying organic complexes, the measurement of solution kinetics has not yet been highly developed in comparison with more conventional techniques, of which the spectral method is preeminent. Typical applications have been made by Ross and coworkers,[5] Higuchi and Lachman,[6] Wadke and Guttman,[7] and Menger and Bender.[8] All of these examples noted inhibition of substrate reactivity in the presence of ligand. Colter, *et al.*, treated rate enhancements in terms of complex formation.[9] The interpretation of kinetic data obtained in systems containing one or more complexes has been examined in detail,[10] but the thorough exploitation of such data in studying complexes has not yet been attempted. This paper reports experimental studies designed to explore the capabilities and the limitations of the kinetic method for studying organic complexes, with applications to some substrates and reaction types of wide interest.

Principles. We restrict attention to systems in which

(1) Part III in the series "Modification of Reaction Rates by Complex Formation." For part II see ref 2.

(2) J. A. Mollica, Jr., and K. A. Connors, *J. Am. Chem. Soc.*, **89**, 308 (1967).

(3) National Institutes of Health Predoctoral Fellow.

(4) Throughout this paper we use the term *substrate* to mean that species whose properties (chemical reactivity, solubility, electronic absorption) are measured, whereas the *ligand* is the second solute species in the system. The distinction between substrate and ligand is one of convenience, and is arbitrary. Usually ligand concentration is the independent variable.

(5) S. D. Ross, M. Bassin, M. Finkelstein, and W. A. Leach, *J. Am. Chem. Soc.*, **76**, 69 (1954).

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

(7) D. A. Wadke and D. E. Guttman, *J. Pharm. Sci.*, **53**, 1073 (1964).

(8) F. M. Menger and M. L. Bender, *J. Am. Chem. Soc.*, **88**, 131 (1966).

(9) A. K. Colter, S. S. Wang, G. H. Megerle, and P. S. Ossip, *ibid.*, **86**, 3106 (1964); A. K. Colter and S. H. Hui, *J. Org. Chem.*, **33**, 1935 (1968).

(10) K. A. Connors and J. A. Mollica, Jr., *J. Pharm. Sci.*, **55**, 772 (1966).

a single 1:1 complex is formed between substrate S and ligand L, and in which a reagent R reacts in a second-order reaction. The kinetic scheme is shown in eq 1–3 where

$$S + L \underset{}{\overset{K_{11}}{\rightleftharpoons}} SL \quad (1)$$

$$S + R \xrightarrow{k_S} \text{products} \quad (2)$$

$$SL + R \xrightarrow{k_{11}} \text{products} \quad (3)$$

K_{11} is the complex stability constant, k_S is the second-order rate constant for the reaction of uncomplexed S, and k_{11} is the corresponding constant for reaction of the complex SL. From this scheme eq 4 is easily derived[10] where k'_S

$$\frac{k_S - k'_S}{k_S} = \frac{q_{11}K_{11}[L]}{1 + K_{11}[L]} \quad (4)$$

is the apparent second-order rate constant for the reaction in the presence of ligand. The dimensionless quantity q_{11} is defined

$$q_{11} = 1 - k_{11}/k_S \quad (5)$$

therefore q_{11} may be interpreted as the fractional decrease in reactivity upon complexation.

The experimental method involves measurement of k'_S as a function of [L]. The basic quantities obtained are K_{11} and q_{11}. These are readily evaluated from a rearranged form of eq 4, namely[8,10]

$$\frac{k_S}{k_S - k'_S} = \frac{1}{q_{11}K_{11}[L]} + \frac{1}{q_{11}} \quad (6)$$

Thus a plot of $k_S/(k_S - k'_S)$ against $1/[L]$ should be linear. The intercept on the ordinate axis is $1/q_{11}$, and the intercept on the abscissa is $-K_{11}$. The stability constant can also be obtained as the ratio (ordinate intercept)/slope. When multiple complexes or complexes of higher stoichiometry are present, the intercepts and slope are more complicated quantities, and their interpretation is not usually practicable, though equations are available to describe these systems.[10]

Of the systems that have been investigated by the kinetic technique the most numerous have been alkaline hydrolyses, usually of carboxylic acid derivatives (that is, R = OH^- in the above symbolism).[2,6,8,11] As noted earlier, the interpretation of the reciprocal of the intercept of the kinetic plot (eq 6) as q_{11} requires that a single 1:1 complex be present, and this simple situation is not always satisfied. It appears, however, within the limitations imposed by this restriction, and taking account of the uncertainty in experimental q_{11} values, that when the attacking agent is hydroxide ion q_{11} is essentially unity; that is, the complexed form is resistant to attack by OH^-. The present investigation considerably extends the types of reactions subjected to kinetic scrutiny in the presence of complexes. The substrates are all carboxylic acid derivatives, with reaction taking place at an ester, an amide, or an olefinic double bond group. The ligands are xanthines, selected for their appreciable complexing ability with these substrates. The reagents are generally classifiable as nucleophiles, though the reaction mechanisms may follow nucleophilic or general base patterns. Both intermolecular and intramolecular reactions have been studied.

(11) (a) L. Lachman, L. J. Ravin, and T. Higuchi, *J. Am. Pharm. Assoc.*, **45**, 290 (1956); L. Lachman and T. Higuchi, *ibid.*, **46**, 32 (1957); L. Lachman, D. Guttman, and T. Higuchi, *ibid.*, **46**, 36 (1957); J. L. Lach and W. A. Pauli, *Drug Std.*, **27**, 104 (1959); J. L. Lach and T. Chin, *J. Pharm. Sci.*, **53**, 924 (1964); D. A. Wadke and D. E. Guttman, *ibid.*, **54**, 1293 (1965); D. E. Guttman, *ibid.*, **51**, 1162 (1962); H. Morawetz and J. A. Shafer, *Biopolymers*, **1**, 71 (1963); K. A. Connors and J. A. Mollica, Jr., *J. Am. Chem. Soc.*, **87**, 123 (1965); A. Bruylants and J. B. Nagy, *Bull. Soc. Chim. Belges*, **75**, 246 (1966); D. Brooke and D. E. Guttman, *J. Pharm. Sci.*, **57**, 1677 (1968); (b) B. J. Kline, Ph.D. Dissertation, University of Wisconsin, 1968.

Experimental Section

Materials. The purification and preparation of many of the reagents have been described.[2] Reagent grade chemicals were used directly. Hydrogen peroxide solutions in phosphate buffer were titrated with standard potassium permanganate before and after kinetic studies. Nessler's reagent was prepared according to the Jackson modification.[12] Salicylic acid was sublimed; mp 158–159°. Acetylsalicylic acid (Mallinckrodt, USP) was recrystallized from chloroform; mp 134° (lit.[13] 135°).

Phthalamic acid was prepared according to Chapman and Stephen.[14] Crystals were precipitated by adding concentrated hydrochloric acid to a solution of the ammonium salt in cold water; neut equiv 164.2 (theoretical 165.13); mp 147–149°, resolidifies at 155–157°, remelts as an imide at 238° (lit.[15] mp 147–148°, resolidifies at 153–157°, remelts at 230°). Methyl hydrogen phthalate was prepared by refluxing phthalic anhydride in methanol[16a] and was recrystallized from 1:1 benzene–ligroin; neut equiv 179.0 (theoretical 180.15), mp 83.0–84.5° (lit.[16b] 82–82.5°, 83–84.5°). *p*-Nitrophenyl glutarate[17] was recrystallized twice from benzene; mp 97–98° (lit.[17] 96–97°). N-*trans*-Cinnamoylimidazole was prepared according to Schonbaum, *et al.*;[18] after three recrystallizations from benzene the compound had mp 132–133.5° (lit.[18] 133–133.5°). *p*-Nitrophenyl benzoate was prepared from *p*-nitrophenol and benzoyl chloride in pyridine solution; it was recrystallized once from ethanol and once from chloroform–Skellysolve B; mp 144° (lit.[19] 145°).

O-*trans*-Cinnamoylsalicylic acid was prepared by the method of Einhorn, *et al.*[20] The product was recrystallized twice as needles from 1:1 methanol–water; mp 154–155° (lit.[20] 150–152°). The nmr spectrum yielded τ 3.39 and 2.12 (olefinic proton doublets, J = 16 Hz), 2.5 (aromatic protons), and 1.63 (carboxylic acid proton). The integrated spectrum indicated nine aromatic protons. The pK_a of the compound in water at 25.0° was found to be 3.89 ± 0.07 (spectrophotometric determination).

8-Iodotheophylline was synthesized after Knoll[21] and recrystallized from ethanol; mp 305° (lit.[21] 294–296° dec). Its purity was checked by titration in N,N-dimethylformamide with standard lithium methoxide in benzene–methanol (thymol blue indicator). The pK_a determined spectrophotometrically in water at 24.0° was 6.20 ± 0.01.

The spectrophotometrically determined pK_a (water, 24.0°) of 8-bromotheophylline was 5.64 ± 0.02.

Apparatus. Temperatures in the range 25–50° were maintained to within 0.05° with water baths. Higher temperatures were held to within 0.1° in an oil bath. Thermometers were calibrated against thermometers carrying ASTM or NBS certificates.

pH measurements at room temperature were made with either a Radiometer Model 25 pH meter with scale expander and wide-range glass electrode G202B, or a Sargent Model DR with glass–calomel combination electrode S-30072-15. Measurements above room temperature were made with the Sargent meter equipped with a miniature glass–calomel combination electrode S-30070-10. The electrode–meter systems were always calibrated against NBS-

(12) F. D. Snell and C. T. Snell, "Colorimetric Methods of Analysis," Vol. 2, 3rd ed, D. Van Nostrand Co., Inc., New York, N. Y., 1949, p 815.
(13) T. J. Carswell, *J. Am. Pharm. Assoc.*, **16**, 306 (1927).
(14) E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1793 (1925).
(15) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).
(16) (a) E. L. Eliel and A. W. Burgstahler, *ibid.*, **71**, 2151 (1949); (b) J. W. Thanassi and T. C. Bruice, *ibid.*, **88**, 747 (1966).
(17) E. Gaetjens and H. Morawetz, *ibid.*, **82**, 5328 (1960).
(18) G. R. Schonbaum, B. Zerner, and M. L. Bender, *J. Biol. Chem.*, **236**, 2930 (1961).
(19) W. P. Jencks, *J. Am. Chem. Soc.*, **80**, 4581 (1958).
(20) A. Einhorn, L. Rothlauf, and R. Seuffert, *Ber.*, **44**, 3311 (1911).
(21) A. Knoll (to G. Chemische Fabriken.), German Patent 1,136,339 (1962); *Chem. Abstr.*, **58**, P4585*a* (1963).

recommended standard buffers prepared from reagent grade chemicals.

Most spectral data and rate constants were obtained with a Cary Model 14 recording spectrophotometer with thermostated cell compartment; some measurements were made on Cary 11 or Cary 15 instruments. Nmr spectra were obtained with a Varian Model A-60-A spectrometer.

Procedures. Complex formation was studied by the kinetic,[10] spectral,[22] and solubility[23] techniques. Most procedures were identical with, or similar to, those described elsewhere.[2] Some significant differences will be described.

Kinetic Measurements. In methyl hydrogen phthalate systems sufficient ester to give a 4×10^{-3} *M* solution and the desired amount of ligand were brought to volume with a standard hydrochloric acid buffer. The solution was brought to 25.0° and, if the pH was to be above 1, adjusted with small volumes of concentrated hydrochloric acid or sodium hydroxide. At pH's below 1 no electrometric activity measurements were made and titration data were used as a measure of hydrogen ion concentration. The rate of hydrolysis of this ester is only slightly affected by the addition of KCl;[16b] therefore ionic strength was not controlled in these solutions. Portions (8 ml) of the solution were sealed in 10-ml Pyrex ampoules, which were immersed in a constant-temperature bath. Ampoules were withdrawn at appropriate intervals, quenched in ice water, and stored at refrigerator temperature until all samples were taken. They were then brought to 25° and a 5.0-ml aliquot was diluted to 25.0 ml with pH 7.5 1 *M* phosphate buffer. If no caffeine was present, the absorbance was measured directly against a suitable reference at 279 mμ. If caffeine was present, 10.0 ml was extracted four times with 10-ml portions of chloroform and the absorbance of the aqueous phase was then measured.

The hydrolysis of phthalamic acid was followed by monitoring the release of ammonia with Nessler's reagent. Samples (1.0 ml) were withdrawn at intervals and were added to 1.0 ml of Nessler's reagent and about 20 ml of water. The alkaline reagent served as a quench by elevating the pH to levels where the rate of hydrolysis of phthalamic acid was negligible.[24] The solution was brought to volume and, after 15 min, the absorbance was measured at 420 mμ. Although both phthalamic and phthalic acids develop colors with Nessler's reagent, a linear working curve can be established. The initial concentration of phthalamic acid in the kinetic studies was 5×10^{-3} *M*.

All *p*-nitrophenyl ester studies were followed spectrophotometrically at 400 mμ; initial substrate concentrations were *p*-nitrophenyl glutarate, 1×10^{-4} *M*, and *p*-nitrophenyl benzoate, 8×10^{-6} *M*.

Cinnamoylsalicylic acid anion studies at 50.0° were carried out by pipetting 0.25 ml of ester solution (in acetonitrile) into a 25-ml volumetric flask and diluting to volume with a buffer–ligand solution. Aliquots (4.0 ml) were sealed in 5-ml ampoules and placed in a constant-temperature bath. Ampoules were quenched in ice–water and then equilibrated at 25°. Absorbance was immediately measured. The initial substrate concentration was in the range $5\text{–}20 \times 10^{-4}$ *M*, and the analytical wavelength was 320–335 mμ; the precise conditions depended upon the pH and the properties of the ligand.[25]

Sulfite Addition Product. About 900 mg of sodium sulfite was dissolved in 100 ml of water and the pH was adjusted to 7.80 at 25°. Fifty milligrams of cinnamoylsalicylic acid was added to a 50-ml volumetric flask, the solid was dissolved in sulfite solution to the mark, and the reaction was allowed to proceed for 3 hr. The solution was lyophilized for 5 hr and the dry powder was analyzed by infrared and nmr spectrometry. The ir spectrum (KBr pellet) showed an ester carbonyl at 1745 cm^{-1} as compared with 1710 cm^{-1} for the unreacted compound. This shift is reasonable for loss of the α,β unsaturation. The olefinic double bond of the unreacted compound appears at 1630 cm^{-1}, and this peak does not appear in the spectrum of the product.

The nmr spectrum of the product (in D_2O) showed nine aromatic protons and did not exhibit the olefinic proton doublets shown by the starting material. Instead, two nonequivalent protons appeared at τ 6.46 and 6.92. A third proton could not be distinguished, probably because of exchange with the solvent. These data (as well as uv data to be considered later) are all consistent with sulfite addition across the double bond.

Treatment of Data. Solubility phase diagrams were constructed by plotting total apparent molar solubility of substrate (S_t) against total molar concentration of ligand ($[L]_t$). The best straight line was fitted by the method of least squares, all points being given equal weight. The calculation of stability constants from solubility data is treated elsewhere.[10,23]

Spectral data were plotted as $b/\Delta A$ against $1/[L]_t$, where b is path length and ΔA is the difference in absorbance between solutions containing the total molar concentration of ligand and no ligand.[2,10,22] Straight lines were fitted by a least-squares method with weighting of points being dependent upon ligand concentration, as described below for the kinetic method.

Kinetic results were analyzed in terms of eq 6; the good approximation $[L] = [L]_t$ is made. Although two other linear forms of this equation can be written,[10] our experience suggests that they offer no advantages over eq 6. Equation 6 is particularly convenient as written because it normalizes all data for a system, it permits q_{11} to be estimated by inspection, and it allows pseudo-first-order rate constants to be used directly (without prior conversion to second-order constants) if [R] is constant in a series of determinations. Equation 6 leads to a "double-reciprocal" type of plot (as in the spectral method), and this plot is extremely sensitive to data variation at low ligand concentrations. A weighted regression analysis was therefore used to fit the best straight line to the data, with greater weight being given to data at high ligand concentration. The abscissa, $1/[L]_t$, was taken as exact, and the ordinate, $k_S/(k_S - k'_S)$, was weighted in proportion to the reciprocal of its variance at the appropriate value of $1/[L]_t$. It was observed that $1/(k_S - k'_S)^2$ is reasonably proportional to the variance in the ordinate, so a normalized weighting factor w (eq 7) was employed.[25,26] All regression analyses were carried out on a Control Data Corp. 1604 digital computer.

$$w = \frac{(k_S - k'_S)^2}{\sum_{[L]_t} (k_S - k'_S)^2} \tag{7}$$

The stability constant values estimated by the kinetic method have a reproducibility of 10–15%. (This range also applies to constants obtained by other methods.) The quantity q_{11}, which is constrained (for 1:1 systems) to lie in the range 0–1, can be determined with an uncertainty of about 0.1. Since it is not known *a priori* that the systems studied yield simple 1:1 complexes, the data are treated as if this simple situation existed, the apparent 1:1 stability constant evaluated as described above being labeled K'_{11}. Whether or not K'_{11} is in fact the stability constant K_{11} must be established by comparative methods and independent evidence.[10]

Results

Intermolecular Reactions. Cinnamoylsalicylic Acid (CSA). This half-ester, *trans*-$C_6H_5CH{=}CHCOOC_6H_4COOH$, was selected because it is capable of undergoing an intramolecular reaction, to be discussed later. Spectral complexation studies were performed with both the unionized and the anion forms of the ester as substrates and with various xanthines as ligands. That spectral shifts occurred indicates the probable participation of the cinnamoyl group in the complex, since neither acetylsalicylic acid nor salicylic acid exhibits detectable spectral changes in the presence of xanthines, though these compounds are known to form complexes. Typical plots are shown in Figure 1 for the CSA anion with 7-(2,3-dihydroxypropyl)theophylline (**1c**) and Table I lists the stability constants obtained spectrally with CSA. Most of these constants were determined at 325 mμ. Some of the ligands were studied at several wavelengths and substrate concentrations. The necessary (not sufficient) criterion

(22) H. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, **70**, 2832 (1948); **71**, 2703 (1949).

(23) T. Higuchi and K. A. Connors, *Advan. Anal. Chem. Instr.*, **4**, 117 (1965).

(24) M. L. Bender, *J. Am. Chem. Soc.*, **77**, 348 (1955).

(25) P. A. Kramer, Ph.D. Dissertation, University of Wisconsin, 1968.

(26) P. A. Kramer and K. A. Connors, *Am. J. Pharm. Educ.*, in press.

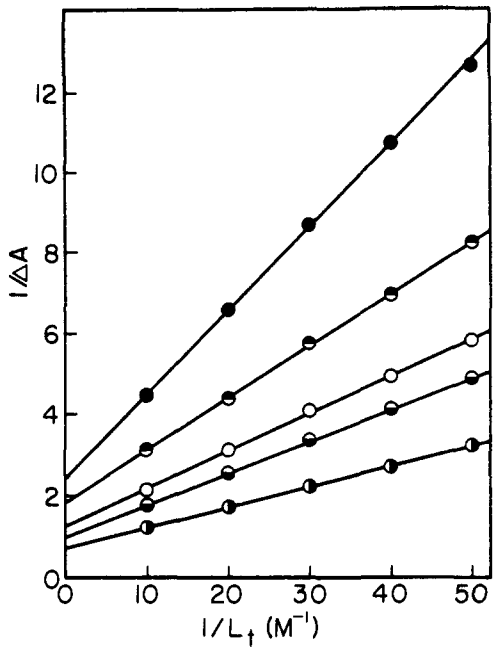


Figure 1. Plots of spectral data for CSA anion–7-(2,3-dihydroxypropyl)theophylline system: pH 6.84, 25.0°, ionic strength 0.3. Wavelength (mμ), S_t (M), K_{11}' (M^{-1}), top to bottom: 335, 1×10^{-3}, 14; 325, 5×10^{-4}, 13; 330, 1×10^{-3}, 14; 328, 1×10^{-3}, 12; 325, 1×10^{-3}, 14.

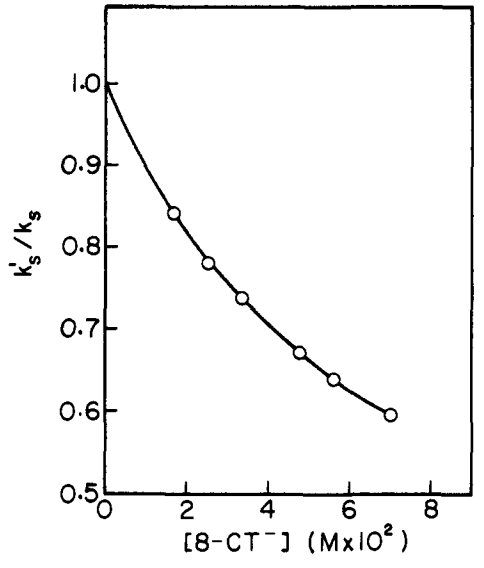


Figure 2. Relative rate of alkaline hydrolysis of CSA anion in the presence of 8-chlorotheophyllinate: 25.0°, pH 12.80, 0.83% acetonitrile, ionic strength 0.3.

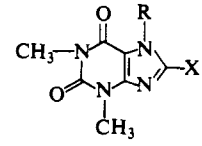
for the existence of only 1:1 stoichiometry is that the apparent stability constant be independent of both wavelength and substrate concentration.[10,27] It appears that 7-(2,3-dihydroxypropyl)theophylline satisfied these requirements. The 8-bromotheophyllinate (**1b**) system, however, appears to yield stability constants that vary significantly with wavelength, suggesting that multiple complexes may be present.

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

Table I. Spectrally Determined Stability Constants for Complexation of Cinnamoylsalicylic Acid in Water[a]

Ligand	Substrate form	K_{11}' (M^{-1})
7-(2,3-Dihydroxypropyl)theophylline	Anion	14[c]
Theophylline	Anion	20
	Acid	18
Protonated theophylline	Acid	12
Theophyllinate[b]	Anion	9.3
8-Chlorotheophyllinate	Anion	17
8-Bromotheophyllinate	Anion	19–24[d]
8-Iodotheophyllinate	Anion	32
Caffeine	Acid	24
8-Methoxycaffeine	Anion	30
	Acid	37

[a] 25.0°, ionic strength 0.3. [b] Monoanions of theophylline and its derivatives will be called theophyllinates. [c] Independent of wavelength and substrate concentration; see Figure 1. [d] Varies with wavelength.



1a, R = X = H (theophylline)
b, R = H; X = Cl, Br, I (8-halotheophyllines)
c, R = $CH_2CH(OH)CH_2OH$; X = H [7-(2,3-dihydroxypropyl-theophylline]
d, R = CH_3; X = H (caffeine)
e, R = CH_3; X = OCH_3 (8-methoxycaffeine)

A significant decrease in complexing tendency, relative to the neutral ligand, is observed for theophylline (**1a**) possessing either a positive or a negative charge. In contrast, ionization of the ester produces no significant alteration in K_{11}' for the theophylline complex. This may indicate that the complexation closely involves the entire xanthine molecule with the cinnamoyl function, whereas the phenol portion of the ester is not intimately involved. 8-Halotheophyllinates interact more strongly than does theophyllinate itself, with effectiveness increasing as the 8 substituent radius increases. It is significant that CSA complexes somewhat less effectively than does methyl *trans*-cinnamate with common ligands, indicating that the alcohol portion of the substrate, though perhaps not directly involved in the complex bonding, can influence complex stability.

Caffeine solutions are complicated by the presence of self-aggregated species,[2,28] which render uncertain an interpretation of the apparent stability constant. Theophylline appears to be substantially free of such self-association.[28] 8-Chlorotheophyllinate solutions were found, by the partition method, to undergo detectable self-association in the aqueous phase in 0.05 M solutions of the anion.

The studies described established the degree of interaction between CSA and various ligands. These systems were next subjected to kinetic study, with the ester undergoing hydroxide attack and subsequent hydrolysis. Figure 2 shows the type of effect observed; here the relative rate of hydrolysis, k'_s/k_s, is plotted against concentration of 8-chlorotheophyllinate. The inhibition is sub-

(28) D. Guttman and T. Higuchi, *J. Am. Pharm. Assoc.*, **46**, 4 (1957).

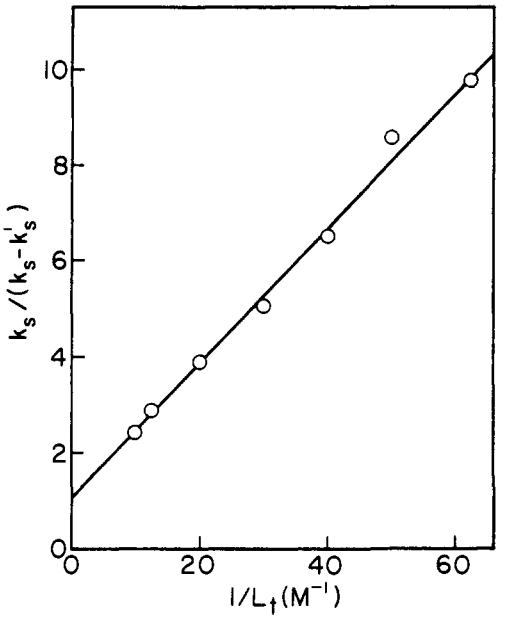


Figure 3. Plot of kinetic data for alkaline hydrolysis of CSA anion in the presence of theophyllinate: 25.0°, pH 12.80, 0.83% acetonitrile, ionic strength 0.3.

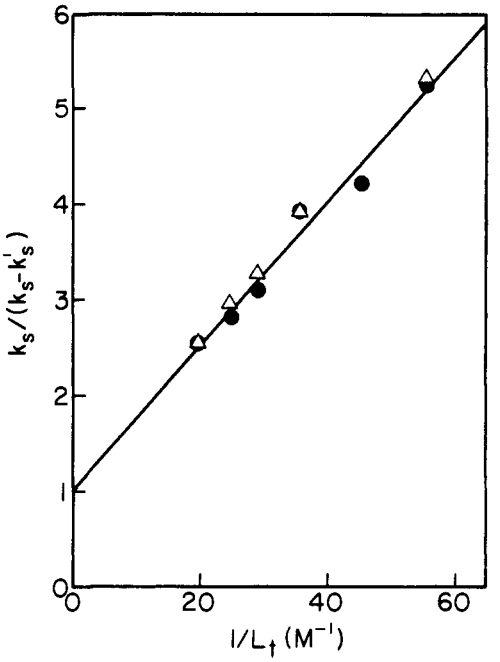


Figure 4. Plot of kinetic data for sulfite addition to CSA anion in the presence of 8-chlorotheophyllinate: 25.0°, pH 7.70, 0.83% acetonitrile, ionic strength 0.65, 0.5% ethanol as preservative; △, 0.2 M Na_2SO_3; ●, 0.08 M Na_2SO_3.

stantial, being about 40% at 0.07 M ligand. Figure 3 shows the double-reciprocal kinetic plot according to eq 6 for the CSA anion–theophyllinate system. The results are (conditions are given in Figure 2) for theophyllinate, $K_{11}' = 8\ M^{-1}$, $q_{11} = 0.94$; for 8-chlorotheophyllinate, $K_{11}' = 14\ M^{-1}$, $q_{11} = 0.81$; and for 8-bromotheophyllinate, $K_{11}' = 15\ M^{-1}$, $q_{11} = 0.66$.

Theophyllinate provides the best example of a simple system. K_{11}' by the kinetic method is in fair agreement with that determined spectrally. The value of q_{11} is essentially unity, indicating nearly complete loss of reactivity toward hydroxide ion in the complexed state. These results are similar to those for the methyl *trans*-cinnamate–theophyllinate–hydroxide system.[2] The halogenated xanthines present a more complicated situation. In each case the kinetic K_{11}' appears to be significantly smaller than the spectral K_{11}', which is evidence[10] that multiple complexes are present. This is strengthened by the partition study described above. The q_{11} values listed therefore cannot be considered fully valid indicators of the 1:1 complex reactivity for the 8-bromo- and 8-chlorotheophyllinate systems.

CSA anion was treated with sulfite, which is known to catalyze the hydrolysis of *p*-nitrophenyl acetate.[29] When CSA anion was treated with sodium sulfite at 25° at pH 7.70, the uv spectrum of the product solution did not correspond to that of a mixture of cinnamate, sulfite, and salicylate ions. Much of the absorption above 270 mμ was lost. Acetylsalicylic acid anion has no appreciable uv absorption above 280 mμ, whereas salicylate has a substantial peak at 296.5 mμ. When CSA anion was placed in 0.1 M sulfite at pH 7.70, a reaction occurred that destroyed most of the uv absorption above 280 mμ. Upon heating the sample for a few hours at 50°, a peak appeared at 296.5 mμ. Addition of sulfite to the cinnamate double bond at 25°, followed by sulfite-catalyzed cleavage of the ester linkage at 50°, accounts for these results.

The addition reaction to CSA anion is first order with respect to sulfite up to 0.12 M sulfite; the second-order constant (pH 7.70, 25.0°, ionic strength 0.65, calculated on the basis of SO_3^{2-}) is $6.2 \times 10^{-3}\ M^{-1}\ sec^{-1}$. At higher sulfite concentration the order appears to fall below unity.

The reaction was studied in the presence of 8-chlorotheophyllinate, with two different sulfite concentrations being used. Figure 4 shows the kinetic plot. That two nucleophile concentrations gave superimposable lines and that no spectral change was observed when sulfite was added to solutions of 8-chlorotheophyllinate indicated that no extensive reagent–ligand interaction occurs. The apparent stability constant from Figure 4 is 13 M^{-1}, in good agreement with the value of 14 found from hydroxide data, but significantly smaller than the value 17 found by spectral study. From Figure 4 q_{11} is found to be 1.0, suggesting that the complex is essentially unreactive toward sulfite addition.

The experiments described in this section appear to be the first in which functional groups in different parts of the same complexed substrate molecule have been subjected to attack and kinetic analysis. The results indicate that the ligand is effective in causing nearly complete loss of reactivity for attack by hydroxide at the ester group and by sulfite at the olefinic double bond. It may be inferred that, in the complex, the ligand molecule is physically near this region of the substrate molecule.

***p*-Nitrophenyl Benzoate.** As a reference study, a kinetic investigation was made of this substrate with theophyllinate as the ligand and hydroxide as the attacking nucleophile. The results were $K_{11}' = 12\ M^{-1}$ and $q_{11} = 1.0$ (25.0°, pH 11.9, 0.2% acetonitrile, ionic strength 0.3).

(29) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **82**, 1778 (1960).

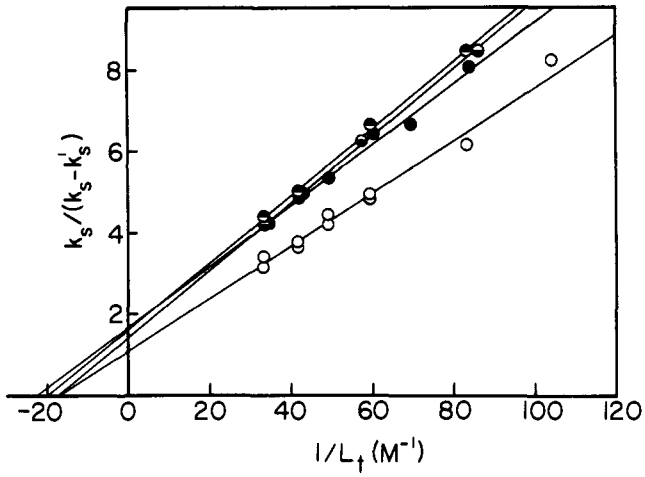


Figure 5. Plot of kinetic data for the *p*-nitrophenyl benzoate–theophylline system: ○, sulfite; ●, hydrogen peroxide anion; ◓, hydroxylamine; ◒, hydrazine.

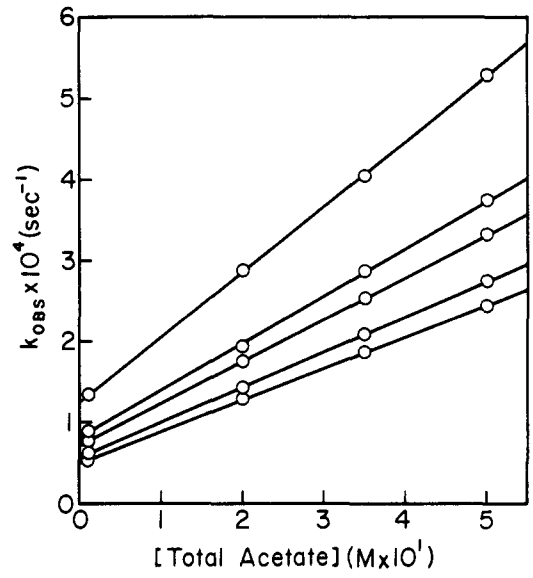


Figure 6. Plot of first-order rate constants for the acetate-catalyzed hydrolysis of cinnamoylimidazole in the presence of caffeine: 25.0°, pH 5.05, 0.63% acetonitrile, ionic strength 0.33. Caffeine concentration ($M \times 10^2$), top to bottom: 0.00, 2.34, 3.60, 6.48, 9.00.

Hydroxylamine, hydrazine, hydrogen peroxide, and sulfite were added individually to a system containing *p*-nitrophenyl benzoate as substrate and theophylline as ligand at pH's near neutrality. Measurements were made at 25.0° and the concentration of reagent was selected to provide an observed rate at least 100 times the background hydrolysis rate.[30] Inhibition of these nucleophilic reactions by theophylline occurred in all cases. The kinetic data are plotted according to eq 6 in Figure 5. K_{11}' (x intercept) should be the same for all lines, and within the experimental uncertainty this is so. Table II gives the K_{11}' and q_{11} values for these systems. The complex is essentially unreactive toward sulfite, but retains considerable reactivity (up to 40% of that of the uncomplexed ester) toward the other nucleophiles. This appears to be the first example of the same functional group in the same complex displaying a spectrum of reactivities to different reagents. It may be noted that all of these nucleophiles with q_{11} values significantly below unity exhibit the so-called α effect,[32] which is an enhanced nucleophilicity (relative to basicity) associated with unshared electrons on the atom α to the nucleophilic atom. In contrast with this observation is the lack of a smooth correlation between q_{11} values and absolute reactivities of the nucleophiles, expressed as the second-order rate constants for their reactions with *p*-nitrophenyl benzoate; these are, under the conditions of the complexation experiments, hydroxide ion, 4.3 $M^{-1}\,sec^{-1}$; hydrogen peroxide anion, 4.3 × 10^3 $M^{-1}\,sec^{-1}$; hydroxylamine, 0.24 $M^{-1}\,sec^{-1}$; hydrazine, 5.1 $M^{-1}\,sec^{-1}$; sulfite, 0.43 $M^{-1}\,sec^{-1}$. A Brønsted-type plot (log k_2 *vs.* pK_a) for these reactions gives a line with slope about 0.75 for HO_2^-, NH_2OH, NH_2NH_2, and SO_3^{2-}; the point for OH^- falls about six orders of magnitude below this line.

Table II. Stability Constants and q_{11} Values for Nucleophilic Reactions of *p*-Nitrophenyl Benzoate in the Presence of Theophylline[a]

Nucleophile	$K_{11}'\,(M^{-1})$	q_{11}
Hydroxylamine	20	0.61
Hydrazine	17	0.71
Hydrogen peroxide anion[b]	22	0.59
Sulfite[c]	17	0.93

[a] Conditions except as noted differently: 25.0°, pH 7.7, 0.2% acetonitrile, ionic strength 0.3. [b] 0.8% acetonitrile. [c] Ionic strength 0.65.

N-Cinnamoylimidazole. This substrate was chosen to establish the effects of complexing on rates of general acid–base reactions. It is assumed that cinnamoylimidazole undergoes reactions by the same mechanistic routes as does acetylimidazole, which has been well studied.[32b] Thus acetylimidazole hydrolyzes with the rate equation $v = k[AcIMH^+] + k'[AcIM] + k''[AcIm][OH^-]$, where AcIM represents acetylimidazole. The spontaneous hydrolysis (k and k' terms) may be described as general acid–base catalyzed reactions by water on AcIM and its conjugate acid $AcIMH^+$.[33]

The pK_a of cinnamoylimidazole cation is 3.65.[18] Rate measurements in acid solution showed a pH-independent region between pH 1 and 2; this behavior strengthens the assumption that acetylimidazole is a good model for cinnamoylimidazole. The observed first-order rate constant (25°, ionic strength 0.3) in this pH region is 2.0 × $10^{-3}\,sec^{-1}$; 0.09 M caffeine (**1d**) produced an 18% decrease in this constant at pH 2, and 0.03 M theophylline gave a 13% decrease. These decreases are not nearly as

(30) Bergmann[31] has shown that hydroxylamine does not react significantly with xanthine carbonyls at 25° near neutrality. Solubility studies were performed using the nucleophiles as ligands and theophylline as substrate. Ligand concentrations were comparable with those used in rate studies. In all cases no measurable change in theophylline solubility was noted, indicating the probable absence of specific interactions between these species.

(31) F. Bergmann, *Anal. Chem.*, **24**, 1368 (1952).

(32) (a) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966.

(33) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959); R. Wolfenden and W. P. Jencks, *J. Am. Chem. Soc.*, **83**, 4390 (1961).

large as expected; for example, one can calculate that, if a 1:1 complex is formed, and if q_{11} is 1.0, K_{11} must be 5 for the theophylline complex. All available evidence on the complexes of cinnamates with theophylline[2,34] suggests that the stability constant is larger than this, and therefore that q_{11} is smaller than unity.

The water hydrolysis was studied at pH 5, where most of the substrate is in the un-ionized form. The reaction was carried out in acetate buffers of varying concentration so concurrent water and acetate reactions were observed. It has been shown that acetate catalyzes the hydrolysis of acetylimidazole with 78% of the reaction occurring *via* a general base mechanism.[35] Figure 6 shows the observed first-order rate constants for the hydrolysis of cinnamoylimidazole as a function of acetate concentration in solutions containing varying concentrations of caffeine. The intercepts (representing rate constants for water attack) and slopes (rate constants for acetate catalysis) of these lines could be treated according to eq 6; the resulting linear plots gave $K_{11}' = 26\ M^{-1}$ from the acetate data and $27\ M^{-1}$ from the water data. q_{11} was 0.72 and 0.83, respectively. Because caffeine is known to undergo self-aggregation and to form complexes of higher stoichiometry than 1:1 with cinnamates,[2] these numerical values cannot be interpreted in a simple way. It is apparent, however, that both the water and the acetate reactions are substantially inhibited by complexation with caffeine.[36]

Intramolecular Reactions. The possibility that intramolecular catalytic efficiency might be affected by complex formation was investigated with four substrates known to undergo intramolecularly catalyzed hydrolysis. Some small effects were found.

Until recently the pH-independent region of the acetylsalicylic acid hydrolysis pH–rate profile (shown by Edwards[37] to occur between pH 4 and 8) had been generally considered to be the consequence of an intramolecular nucleophilic catalysis by the ionized carboxyl group. Fersht and Kirby,[38a] St. Pierre and Jencks,[38b] and Kemp and Thibault[38c] have now shown that the reaction is actually an intramolecular general base catalysis by the carboxylate anion. This mechanism is probably the same for cinnamoylsalicylate (CSA anion), since its leaving group is the same as for aspirin.

Un-ionized aspirin is known to complex appreciably with caffeine in aqueous solution.[39] Kinetic studies on the aspirin anion in the pH region corresponding to intramolecular catalysis showed that caffeine concentrations up to 0.08 M had no significant effect on the rate of intramolecular catalysis.[40] Since it is possible that this absence of rate modification was the result of an insufficient degree of complexing between the ligand and the ionized substrate, a study was carried out with CSA anion. In this substrate the cinnamoyl function provides the principal site for the complex interaction, and this remains largely unchanged when the *o*-carboxyl group ionizes. As shown in the earlier discussion, CSA anion complexes fairly strongly with numerous xanthines, and these complexes are resistant to intermolecular attack by hydroxide ion at the ester group and by sulfite at the olefinic double bond.

Experiments were carried out in the pH range 6.7–8.0 at 50.0°, the temperature being selected to achieve a reasonable rate of hydrolysis. Phosphate buffers were used to control pH, although it is known that phosphate dianion can catalyze the hydrolysis of salicylate esters;[38a] based on results with aspirin, such catalysis would constitute less than 5% of the over-all rate in the plateau region at the phosphate concentrations used.

The standard enthalpy change for the formation of a cinnamate complex was found[2] to be about −3 kcal/mole. This value, applied to CSA anion complexes, implies that a 30% decrease in the K_{11}' values given earlier for CSA could be expected for the same quantities at 50°. For many of the ligands and concentrations used, up to 50% of the substrate would be in the complexed form at 50°. The hydrolytic rate constant was found to be consistently lower in the presence of the ligands, but the decreases were very small and might be partly due to inhibition of an intermolecular attack by phosphate. It must be concluded that the rate of the intramolecular catalysis is not significantly altered in the complexed forms of the substrate.

The amide group of phthalamic acid undergoes an intramolecularly catalyzed nucleophilic attack by the neighboring free carboxyl group in pH regions below its pK_a, which is 3.7 at 47.3°.[15] This region of the pH–rate profile is pH independent. Since the compound's ultraviolet absorption spectrum does not display a shift in the presence of xanthines (nor do most other benzoates that are known to complex with xanthines), complexation was inferred from the ability of benzoic acid, benzamide, and salicylic acid to form complexes.[23,39,41] The stability constants for such complexes are in the range 10–40 M^{-1} at 25°.

The hydrolysis of this amide was studied at pH 1.2–2.2 at 40.0°. In the presence of caffeine, rate increases of a significant magnitude were observed. These figures show the effect (pH, $10^4 k_{obsd}$ in sec^{-1} in the absence of caffeine, $10^4 k_{obsd}$ in sec^{-1} in the presence of 0.09 M caffeine): 2.10, 1.55, 1.75; 1.24, 1.56, 1.93. These results suggest that the intramolecular catalysis is facilitated slightly in the complex.

p-Nitrophenyl glutarate exhibits a pH-independent region between pH 5 and 8 in its pH–rate profile.[17] Hydrolysis in this area occurs *via* an intramolecularly catalyzed nucleophilic attack of the carboxylate on the ester carbonyl. Because of the lability of the anion, spectral and solubility studies could not be made to determine if this substrate forms complexes. A variety of compounds was screened in an attempt to modify the rate in the plateau region by involving the nitrophenyl or carboxylate groups in a complex. No significant rate alterations were observed. Either the substrate did not form complexes, or the complexes retained the reactivity characteristic of the free substrate.

(34) M. H. Infeld, unpublished results, this laboratory.
(35) W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 4464 (1966).
(36) A stability constant of 18 M^{-1} for the methyl cinnamate–caffeine complex has been reported,[2] but replotting of the data according to the present procedures yields the values $K_{11}' = 24\ M^{-1}$ and $q_{11} = 0.74$ for the attack by hydroxide.
(37) L. J. Edwards, *Trans. Faraday Soc.*, **46**, 723 (1950).
(38) (a) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 4853, 4857 (1967); (b) T. St. Pierre and W. P. Jencks, *ibid.*, **90**, 3817 (1968); (c) D. S. Kemp and T. D. Thibault, *ibid.*, **90**, 7154 (1968).
(39) T. Higuchi and D. A. Zuck, *J. Am. Pharm. Assoc.*, **42**, 138 (1953).
(40) K. E. Lederer, unpublished results, this laboratory.
(41) T. Higuchi and J. L. Lach, *J. Am. Pharm. Assoc.*, **43**, 527 (1954); T. Higuchi and M. Nakano, *J. Pharm. Sci.*, **57**, 183 (1968); J. L. Cohen and K. A. Connors, *Am. J. Pharm. Educ.*, **31**, 476 (1967).

Methyl hydrogen phthalate undergoes an intramolecularly catalyzed hydrolysis, probably nucleophilic. Reactions were carried out at 98° in both the plateau and acid-catalyzed regions.[42] Independent evidence for complexing was obtained in a solubility study at 25°. The intramolecular catalytic rate showed small decreases (5–10%) in the presence of caffeine.

These attempts to inhibit intramolecular catalyses have clearly failed to demonstrate meaningful rate decreases. Since, in some of these systems, complex formation assuredly occurred, the failure to alter reactivity is itself a significant finding when combined with the earlier demonstration that intermolecular attacks are readily inhibited in the same complexes.

Discussion

q_{11} and Reaction Mechanism. Sufficient evidence is now available relating to complexes of carboxylic acid derivatives with xanthines and similar ligands[2,11b] to show that complex stability is closely related to planar molecular area. Complexes of 1:1 stoichiometry probably can be roughly described as having substrate and ligand planes in parallel orientation. Nucleophilic attack at carboxyl groups is believed to occur *via* an approach of the incoming nucleophile perpendicularly to the plane of the carboxyl group.[43] If, in a complex SL, the ligand is in close proximity to the carboxyl group in the ester substrate, it is easy to account for a 50% reduction (corresponding to $q_{11} = 0.5$) in reactivity of SL relative to S as a statistical factor. In fact, however, no q_{11} values of 0.5 have yet been reported for intermolecular nucleophilic reactions of carboxylic acid derivatives. When the nucleophile is hydroxide ion, q_{11} is essentially 1.0 for all complexes studied. In the present paper q_{11} values of 0.6 and 0.7 have been described for other nucleophiles. We have, therefore, to consider why q_{11} values between 0.5 and 1.0 are observed instead of the statistically expected value of 0.5.[44] The possibilities are that complexation of the substrate stabilizes the initial state of the system, or that complexation raises the transition-state energy, or that both effects occur. The 50% reduction in reactivity ascribed above to steric restriction of attack may be considered an initial-state effect. In accounting for the further decrease in reactivity the rate-determining reaction to be considered is

$$\mathrm{R\overset{\overset{\displaystyle O}{\|}}{C}OR'} + \mathrm{N^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{R\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle N}{|}}{C}}OR'} \quad (8)$$

with the tetrahedral intermediate being the product. R and R′ are held constant and the nucleophile N^- is varied (as in the experiments with *p*-nitrophenyl benzoate).

The product of this general reaction is much less stable than is the initial state. According to the Hammond postulate,[45] the activated complex will more nearly resemble the tetrahedral intermediate than it does the starting ester. The ester group in the initial state is planar with sp^2-hydridized carbon; the bond angles around this carbon are about 120°. The carbon in the product is sp^3 with bond angles of about 109°, and the configuration is no longer planar. In the activated complex the configuration is intermediate to these extremes. Complex formation by the ester substrate will result in stabilization of the initial state (relative to the uncomplexed ester) by the steric effect of the ligand on one side of the planar group; this should lead to $q_{11} = 0.5$, as noted. The intermolecular interaction may produce electronic perturbations extending to the unblocked side of the ester group and these could result in further initial-state alterations.

The transition-state energy for reaction of complex SL will be raised relative to that for S because the required change from the planar sp^2 toward the nonplanar sp^3 hybridization will be balked by the ligand in the complex. This simple argument therefore predicts q_{11} values between 0.5 and 1.0.

To rationalize the dispersion of q_{11} values we compare two nucleophiles, A and B, in reaction 8. Let A be the more powerful nucleophile. It seems reasonable to assume that the two initial states (ester + A and ester + B) do not differ appreciably in energy. We anticipate that A will form a more stable tetrahedral product than will B and, from the Hammond postulate, that the transition state for reaction with A will be attained earlier along the reaction path than will the transition state for B. Therefore, the activated state for A will be more characteristic of the planar ester group than it will be for B. The more planar the ester group configuration is in the transition state, the smaller the effect of complexation will be on the attainment of this state; thus in a series of nucleophiles, increase in nucleophilicity is expected to result in smaller q_{11} values. The data for the nucleophiles OOH^-, NH_2OH, NH_2NH_2, and SO_3^{2-} with the *p*-nitrophenyl benzoate–theophylline complex do not show a smooth correlation of nucleophilicity (rate constant of nucleophile with the uncomplexed ester) with q_{11}. It is possible that the series includes additional complicating effects. The experimental results are therefore inconclusive with regard to the speculation of this paragraph.

Failure to inhibit intramolecular catalyses by complexation may be explicable in terms of the plane-to-plane orientation of substrate and ligand in the complex. Consider phthalamic acid. Only one of the two ring substituents can lie in the plane of the ring, for steric reasons. The complex interaction will only involve the ring and the group that is coplanar with it. The catalytic process is facilitated by the perpendicular orientation of the catalytic group (COOH) and the labile group ($CONH_2$). Since complexing cannot disrupt this orientation, the complexed molecule is as capable of undergoing the intramolecular process as is the uncomplexed molecule. Small electronic perturbations of the initial state could lead to minor rate effects in the complexed substrate. (In a benzoate type of intramolecular process, the statistically controlled rate reduction of 50% is not operative because both sides of the labile group are not accessible to the catalytic function.)[46]

(42) The intermolecular acid-catalyzed hydrolysis was very significantly inhibited by complexation with caffeine.

(43) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(44) Note that q_{11} values of 0.0–0.5 are also quite possible; the simple interpretation of such values is that the ligand is not situated closely enough to the reaction site in the substrate to cause steric blockage of the attacking reagent.

(45) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(46) More specific types of substrate–ligand interactions could produce rate alterations in intramolecular reactions by selectively complexing catalytic groups. A very pretty example has been provided by Usher,[47] who found that chelation of cupric ion with 4(5)-(2-amino-3-bromopropyl)imidazole drastically decreased neighboring-group participation in the solvolysis.

(47) D. A. Usher, *J. Am. Chem. Soc.*, **90**, 367 (1968).

No apparent distinction can be made between the effects of complexing on rates of nucleophilic compared with general base mechanisms. For the types of systems described here, it is possible to determine, by the effect of complexing on rate, whether a reaction is intermolecular or intramolecular.

Kinetic Study of Complex Structure. The substrate–ligand complex system is at virtual equilibrium in the applications of the kinetic technique described here because the reactions to which the substrate are subjected are very slow relative to the complex association and dissociation reactions. Thus the kinetic approach yields the equilibrium stability constant in common with other methods for studying complexes. Since, however, the system is perturbed by causing it to undergo reaction, the procedure also permits a nonthermodynamic insight into the complex. This capability is the main reason the kinetic method is an attractive alternative to conventional tools. A second reason is that it provides a method for the study of complexing tendencies of unstable compounds; the instability can be turned to advantage by utilizing it as the property measured in the kinetic study. In this paper the use of the kinetic method as a probe into organic complex structure has been developed. The quantity q_{11} is considered to be determined in part by the proximity of the ligand to the group being attacked. As the earlier discussion makes clear, q_{11} may also be a function of other reaction features, and its full interpretation must be based upon comparative studies with related systems.

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Irradiation of *cis,cis*-1,5-Cyclooctadiene in the Presence of Copper(I) Chloride[1]

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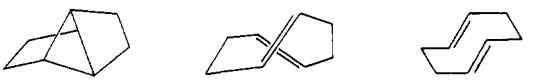
Abstract: Irradiation of an oxygen-free pentane suspension of di-μ-chloro-bis(*cis,cis*-1,5-cyclooctadiene)dicopper-(I) (**4**) at 254-mμ yields, in addition to tricyclo[3.3.0.0^{2,6}]octane (**1**), significant quantities of insoluble copper(I) complexes of *cis,trans*- and *trans,trans*-1,5-cyclooctadienes. Examination of the photochemical behavior of these dienes, and of their yields relative to the yield of **1** during the irradiation of **4**, indicates that a major part of the **1** formed has *cis,trans*-1,5-cyclooctadiene as a precursor. These data further suggest that a significant part of the photoconversion of *cis,trans*-1,5-cyclooctadiene to **1** may take place *via* the intermediacy of *trans,trans*-1,5-cyclooctadiene.

Transition metals catalyze the thermal and photochemical dimerization of a wide variety of olefins.[3-8] One of the most interesting of the metal-catalyzed photochemical reactions is the conversion of *cis,cis*-1,5-cyclooctadiene to tricyclo[3.3.0.0^{2,6}]octane (**1**) by irradiation in the presence of copper(I) chloride, or by photosensitization with mercury ($^3P_1$) atoms.[3,4] Although the basic mechanism of the gas-phase, mercury-photosensitized reaction has been established,[4] neither the mechanism(s) of the condensed-phase, copper-catalyzed photochemical reaction nor the nature of any intermediates in this reaction have yet been clearly defined.

The copper ion in the latter reaction might *a priori* serve a variety of functions: *viz.*, as a photosensitizer, as a "template" controlling the stereochemistry of reaction of coordinated excited olefinic ligands, or as a catalyst facilitating carbon–carbon bond formation through mixing of appropriate metal orbitals with olefinic molecular orbitals.[5] On the basis of quantum yield measurements, Srinivasan has suggested that the primary photochemical step under the homogeneous reaction conditions of his experiments involves absorption of light by uncomplexed *cis,cis*-1,5-cyclooctadiene. He further proposed that the copper(I) atom exerted its influence in the reaction in the subsequent stabilization of the initially formed excited state of the olefin by formation of a complex of unspecified structure (represented schematically by **3**).[3] However, the appealing geometrical relation between **1** and the racemic conformation of *trans,trans*-1,5-cyclooctadiene (**2a**), and the complicated and quite different mechanism suggested for the superficially similar copper-catalyzed photochemical dimerization of norbornene,[8]



1 **2a** **2b**

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(2) (a) National Science Foundation Predoctoral Fellow, 1964–1966; National Institutes of Health Predoctoral Fellow, 1966–1967. (b) Deceased June 4, 1966.

(3) R. Srinivasan, *J. Amer. Chem. Soc.*, **86**, 3318 (1964).

(4) I. Haller and R. Srinivasan, *ibid.*, **88**, 5084 (1966).

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(6) J. J. Mrowca and T. J. Katz, *ibid.*, **88**, 4012 (1966), and references therein.

(7) W. Merk and R. Pettit, *ibid.*, **89**, 4787, 4788 (1967).

(8) D. J. Trecker, R. S. Foote, J. P. Henry, and J. E. McKeon, *ibid.*, **88**, 3021 (1966).