may simply be that of converting the cyclic hypomanganate ester to the corresponding cyclic manganate ester.

It is not likely that the ester, **5**, would undergo decomposition to give hydroxy ketones as has been suggested elsewhere.[8a] The transfer of electrons that must occur during such a decomposition will proceed most readily if all of the orbitals involved are in the same plane. Since the C–C bond of **5** is in the same plane as the –O–Mn–O– bonds, cleavage could easily take place. On the other hand, cleavage of a C–H bond, which is required for formation of the α ketol, would not likely occur with the cyclic manganate ester because of the impossibility of the appropriate orbitals all becoming planar. Of course, if the ester were to be hydrolyzed before electron transfer took place the reaction depicted in eq 4 would probably take place.

Acknowledgment. The authors are pleased to acknowledge the financial assistance of the National Research Council of Canada in the form of an operating grant (D. G. L.) and a scholarship (J. R. B.). D. G. L. is also grateful for the hospitality of the Department of Chemistry at the University of Oslo where this paper was written.

Intramolecular General Base Catalyzed Hydrolysis and Tertiary Amine Nucleophilic Attack *vs.* General Base Catalyzed Hydrolysis of Substituted Phenyl Quinoline-8- and -6-carboxylates

Paula Yurkanis Bruice and Thomas C. Bruice*

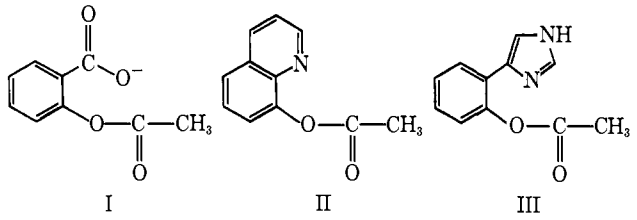
Contribution from the Department of Chemistry, University of California, Santa Barbara, California 93106. *Received May 4, 1974*

Abstract: The reaction of a series of substituted (p-CH_3O, H, p-Cl, p-CN, o-NO_2, p-NO_2, and 2,4-diNO_2) phenyl quinoline-8- and -6-carboxylates (Q-8 and Q-6, respectively) with lyate species and tertiary amines has been investigated (20% (v/v) acetonitrile–H_2O, μ = 0.5, 30°). The Hammett ρ values for HO^- attack on the Q-8 (ρ = 0.93) and Q-6 (ρ = 0.88) esters are of a magnitude anticipated for rate-determining nucleophilic addition to the ester group. The rate ratio $k_{HO^-}{}^{Q-8}/k_{HO^-}{}^{Q-6} \simeq 0.2$ is attributed to the greater steric hindrance of the 8 isomers. Spontaneous hydrolysis (k_{H_2O}) of the Q-8 esters greatly exceeds that for the Q-6 esters and exhibits a ρ value of 0.97. Employing two alternate means of approximation, $k_{H_2O}{}^{Q-8}/k_{H_2O}{}^{Q-6} \cong 10^4$. The enhanced rate of hydrolysis of the 8 isomers is attributed to intramolecular quinoline nitrogen general base assistance to nucleophilic attack of H_2O in the case of the Q-8 esters. The reaction of tertiary amines with the Q-8 and Q-6 esters provides Hammett plots having ρ = 1.2–1.5 with the 2,4-diNO_2 substituted esters exhibiting marked positive deviations. From the similarity of the ρ values to those for HO^- and H_2O catalyzed hydrolysis, values of $k_n{}^{H_2O}/k_n{}^{D_2O}$ = 1.5–1.6, and β = 0.69 for reaction of p-NO_2-Q-6 with quinuclidine derivatives, tertiary amine catalysis of ester hydrolysis (except for the most reactive 2,4-diNO_2 substituted esters) is best ascribed to general base catalyzed attack of water. For tertiary amine catalyzed hydrolysis of the 2,4-diNO_2 substituted esters direct nucleophilic attack upon the esters is in effect: positive deviation from the $\sigma\rho$ plot indicating a change in mechanism rather than a change in the rate-limiting step, $\rho > 2.0$, $k_n{}^{H_2O}/k_n{}^{D_2O}$ = 0.8–0.9, and β = 0.95 for reaction of quinuclidines with 2,4-diNO_2-Q-6. Steric hindrance to approach of a tertiary amine to the 2,4-diNO_2 substituted esters (triethylamine and 4-morpholineethanesulfonic acid) brings about a change in the role of the tertiary amine from a nucleophilic to a general base catalyst. The rate ratios $k_n{}^{Q-8}/k_n{}^{Q-6}$ range from 0.6 to 0.8 for the less reactive esters. For the 2,4-diNO_2 substituted esters the rate ratios increase with decreasing amine pK_a and range from 1.4 to 79. This observation has led to the suggestion that the transition state of the 2,4-diNO_2 substituted 8 isomer is electrostatically stabilized by the quinoline nitrogen lone pair. Reaction with imidazole is characterized by a linear Hammett plot with the 2,4-diNO_2 substituted esters, unlike with other tertiary amines, evidencing no deviation. The ρ values of 2.3 and 2.4 for imidazole catalyzed hydrolysis of the Q-8 and Q-6 esters, respectively, suggest that departure of phenoxide is at least partially rate limiting. The p-CH_3O, H, p-Cl, and p-NO_2 substituted Q-6 esters are subject to imidazole catalysis of imidazole attack indicating that imidazole reacts directly with the esters as a nucleophile. This [imidazole]^2 rate term is seen only with the least reactive Q-8 ester (p-CH_3O). The decreased importance of general base catalysis and the slight increase in bimolecular rate evidenced by the Q-8 esters in their reaction with imidazole suggest that the lone pair of the quinoline nitrogen may serve to stabilize the zwitterionic tetrahedral intermediate thereby increasing k_n sufficiently to make k_{gb} undetectable.

In a study of the hydrolysis of I, Fersht and Kirby found that the reaction proceeded *via* rate-limiting nucleophilic attack of water with intramolecular general base assistance from the carboxylate group.[1] Felton and Bruice[2] found that the hydrolysis of II and III occurred more rapidly than electronically equivalent isomers in which the nitrogen base is not located at the reaction site. Although this finding strongly suggested

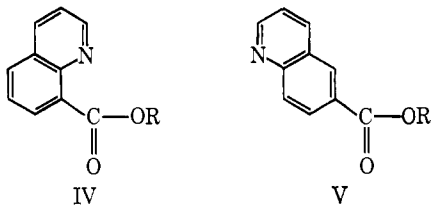
(1) A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 89, 4853 (1967).

(2) (a) T. C. Bruice and S. M. Felton, *J. Amer. Chem. Soc.*, 91, 2799 (1969); (b) S. M. Felton and T. C. Bruice, *ibid.*, 91, 6721 (1969).



I II III

the participation of the quinoline and imidazole nitrogen atoms as intramolecular general base catalysts, the possibility of the enhanced reaction rate being due to an O → N acyl shift followed by general base catalysis of the N-acyl compound by the phenolate group could not be conclusively eliminated. In order to determine whether amines can act as intramolecular general base catalysts additional systems need be examined in which there is no possibility of an acyl shift. For this reason we have undertaken an examination of the comparative rates of hydrolysis of several phenyl quinoline-8-carboxylates (IV) and phenyl quinoline-6-carboxylates (V). The leaving group of the ester pair



IV V

R		
CH_3O	(*p*-CH_3O-Q-8)	(*p*-CH_3O-Q-6)
H	(Q-8)	(Q-6)
Cl	(*p*-Cl-Q-8)	(*p*-Cl-Q-6)
CN	(*p*-CN-Q-8)	(*p*-CN-Q-6)
NO_2	(*o*-NO_2-Q-8)	(*o*-NO_2-Q-6)
NO_2	(*p*-NO_2-Q-8)	(*p*-NO_2-Q-6)
NO_2, NO_2	(2,4-diNO_2-Q-8)	(2,4-diNO_2-Q-6)

was varied to determine the nature of the rate-limiting step.

In the intramolecular amine catalyzed hydrolysis of phenyl γ-(*N*,*N*-dimethylamino)butyrates and phenyl δ-(*N*,*N*-dimethylamino)valerates and in the intermolecular tertiary amine (trimethylamine) catalyzed hydrolysis of phenyl acetates, the tertiary amine was found to act as a nucleophile with the rate-limiting step being breakdown of the tetrahedral intermediate.[3] Since the results of the hydrolysis studies of IV and V showed that the quinoline nitrogen acts as a general base to catalyze the attack of water with attack being rate limiting, it was of interest to determine in the intermolecular tertiary amine catalyzed hydrolysis of IV and V whether the amine would function as a nucleophile or as a general base and whether its role would change with increasing ester reactivity.

(3) T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **85**, 1 (1963).

Experimental Section

Materials. The hydrochlorides of quinuclidine, trimethylamine, 3-quinuclidinone (Aldrich), and 2-dimethylaminoethyl chloride (Aldrich) were recrystallized from water–ethanol. Triethylenediamine was recrystallized from 95% ethanol and imidazole from acetone–petroleum ether, and 4-morpholineethanesulfonic acid (Aldrich) was used without further purification. Morpholine, *N*-methylmorpholine, *N*-methylpiperidine, and triethylamine were distilled. All solids were dried and stored in a desiccator over P_2O_5.

Preparation of Esters. Method A. One gram (0.0058 mol) of the quinolinecarboxylic acid was dissolved in 10 ml of thionyl chloride and the mixture was heated at ~70° for 4 hr. The excess thionyl chloride was removed under reduced pressure and the residue dissolved in 20 ml of dry benzene and cooled in an ice bath. To this was added dropwise a solution of 0.01 mol of the appropriate phenol and 2 g of triethylamine in 20 ml of benzene. The mixture was heated to ~70° for 2 hr, cooled to room temperature, and filtered. The solvent was removed under reduced pressure, and the residue was dissolved in ether, washed with Na_2CO_3, and dried over $MgSO_4$. Upon filtration and evaporation of solvent a solid remained.

Method B. To a solution of 0.0058 mol of the quinolinecarboxylic acid and 0.0058 mol of the phenol in 10 ml of cold ethylene dichloride was added dropwise 0.0058 mol of *N*,*N*-dicyclohexylcarbodiimide in 10 ml of cold ethylene dichloride. The reaction mixture was maintained at 0° during the addition and for 3 hr following, allowed to slowly warm up to room temperature, filtered, and the solvent was removed under reduced pressure.

Method C.[4] To a cold (−5°) solution of 1 g (0.0058 mol) of the quinolinecarboxylic acid and 0.34 g (0.0058 mol) of freshly distilled triethylamine in dichloromethane was added 0.63 g (0.0058 mol) of ethyl chloroformate, and the mixture was stirred for 0.5 hr. To this was added 0.0058 mol of the appropriate phenol. After stirring for 24 hr, the mixture was washed with a saturated solution of Na_2CO_3, dried over $MgSO_4$, and filtered; the solvent was removed under reduced pressure.

***p*-Methoxyphenyl Quinoline-8-carboxylate. Method C.** The crystals were pressed onto filter paper and washed with ether, and the remaining solid was recrystallized from benzene–hexane; mp 110–111°. *Anal.* Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.01. Found: C, 72.92; H, 4.86; N, 4.99.

***p*-Methoxyphenyl Quinoline-6-carboxylate. Method B.** Purified by sublimation under vacuum; mp 120–121.5°. *Anal.* Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.01. Found: C, 72.87; H, 4.62; N, 5.12.

Phenyl Quinoline-8-carboxylate. Method A. Recrystallized from benzene–hexane; mp 63–64°. *Anal.* Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.49; N, 5.62. Found: C, 77.16; H, 4.42; N, 5.67.

Phenyl Quinoline-6-carboxylate. Method A. Recrystallized from benzene–hexane; mp 65.5–66.5°. *Anal.* Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.49. Found: C, 76.91; H, 4.30.

***p*-Chlorophenyl Quinoline-8-carboxylate. Method A.** Recrystallized from hexane; mp 88–89°. *Anal.* Calcd for $C_{16}H_{10}ClNO_2$: C, 67.73; H, 3.55; Cl, 12.50. Found: C, 67.39; H, 3.58; Cl, 12.24.

***p*-Chlorophenyl Quinoline-6-carboxylate. Method A.** Recrystallized from hexane; mp 125–126°. *Anal.* Calcd for $C_{16}H_{10}ClNO_2$: C, 67.73; H, 3.55; Cl, 12.50. Found: C, 67.79; H, 3.62; Cl, 12.71.

***p*-Nitrophenyl Quinoline-8-carboxylate. Method B.** The remaining solid was added to cold acetonitrile and the urea removed by filtration. The acetonitrile was removed under reduced pressure and the solid recrystallized from benzene–hexane; mp 127–128° (lit.[4] mp 127–128°).

***p*-Nitrophenyl Quinoline-6-carboxylate. Method B.** Urea was removed as with the 8 isomer. The product recrystallized from benzene; mp 206–207°. *Anal.* Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.50; H, 3.49; N, 9.58.

2,4-Dinitrophenyl Quinoline-8-carboxylate. Method B. Recrystallized from acetonitrile; mp 140.5–141°. A satisfactory analysis could not be obtained. However, the calculated amount of 2,4-dinitrophenol was released upon hydrolysis of the ester.

(4) A. Williams, E. C. Lucas, and K. T. Douglas, *J. Chem. Soc., Perkin Trans. 2*, 1493 (1972).

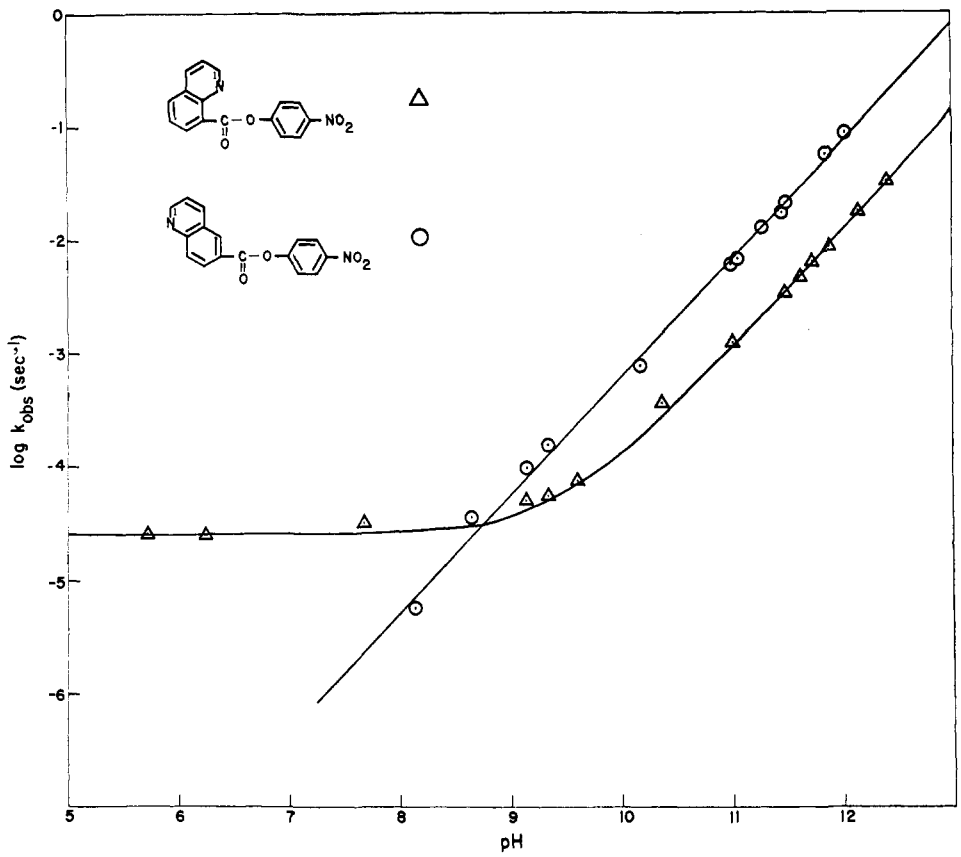


Figure 1. pH–rate profiles for the hydrolysis of p-NO_2-Q-8 and p-NO_2-Q-6. The points are experimental and the lines theoretical, derived from the data in Table I.

2,4-Dinitrophenyl Quinoline-6-carboxylate. Method B. Recrystallized from acetonitrile; mp 152.5–154°. *Anal.* Calcd for $C_{16}H_9N_3O_6$: C, 56.64; H, 2.67; N, 12.39. Found: C, 56.72; H, 2.58; N, 12.34.

***p*-Cyanophenyl Quinoline-8-carboxylate, *p*-Cyanophenyl Quinoline-6-carboxylate, *o*-Nitrophenyl Quinoline-8-carboxylate, *o*-Nitrophenyl Quinoline-6-carboxylate. Method B.** Not submitted for combustion analysis but the calculated amount of phenol was released upon hydrolysis.

Kinetic Measurements. All kinetic determinations were done in a 20% (v/v) acetonitrile–water solution containing 10^{-4} M EDTA and at an ionic strength of 0.5 (KCl) and a temperature of 30°. Fresh doubly glass-distilled water and spectrograde (Matheson Coleman and Bell) acetonitrile were used to make up all kinetic solutions.

The hydrolytic rates were carried out in a radiometer pH-Stat assembly specifically designed for a Cary 15 spectrophotometer.[5] Aminolysis rates were determined on either a Cary 16, Gilford Model 2000, Zeiss PMQII, or a Durrum–Gibson Model 13001 stopped flow spectrophotometer. All spectrophotometers were thermostated at 30°. Readings of pH were determined on a radiometer Type PMH 22 equipped with a PHA 630 scale expander.

The concentration of ester employed in the kinetic studies was about 2×10^{-4} M. Rates were determined by following either the disappearance of ester or appearance of phenolic product: Q-8 at 312 nm, Q-6 at 330 nm, p-CH_3O-Q-8 and p-CH_3O-Q-6 at 265 nm, p-Cl-Q-8 at 320 or 265 nm, p-Cl-Q-6 at 320 or 270 nm, p-NO_2-Q-8 at 295 nm, p-NO_2-Q-6 at 300 or 276 nm, 2,4-diNO_2-Q-8 at 360 or 300 nm, 2,4-diNO_2-Q-6 at 360 or 265 nm, p-CN-Q-8 at 310 nm, p-CN-Q-6 at 276 nm, o-NO_2-Q-8 and o-NO_2-Q-6 at 350 nm.

The amine–amine hydrochloride buffer solutions were prepared just prior to use by addition of standardized KOH or HCl to the amine hydrochloride or free amine. All aminolysis reactions were studied at a pH = pK_a ± 1; thus the amine acted as its own buffer. A minimum of five serially diluted buffer solutions (0.05–0.50 M in total amine) were employed at each pH. The pH's of the serial dilutions agreed within 0.02 pH units.

(5) J. R. Maley and T. C. Bruice, *Anal. Biochem.*, 34, 275 (1970).

Calculations of the pseudo-first-order rate constants and least-squares slopes and intercepts were done using a Hewlett–Packard Model 9820A, an Olivetti–Underwood Programma 101, or the UCSB on-line interface to an IBM 360-75 computer.

pK_a Determinations. The pK_a's of the amines were determined by half-neutralization and the pK_a's of the phenols, phenyl quinoline-8-carboxylate, and phenyl quinoline-6-carboxylate were determined by spectrophotometric titration in the equilibrium titration cell of the Cary 15.[5] Spectrophotometric titration data were fitted to theoretical titration curves employing a computer program written by Dr. David M. E. Reuben of this laboratory. All pK_a determinations were performed in the same solvent and at the same ionic strength and temperature as the kinetic studies.

Results

The observed first-order rate constant for reaction of an ester with a tertiary amine may be described by the addition of an amine term to the hydrolytic expression

$$k_{obsd} = k_{HO^-}[HO^-] + k_{H_2O}[H_2O] + k_n[N] \quad (1)$$

k_{HO^-} represents the specific base catalyzed hydrolysis of the ester, k_{H_2O} the spontaneous hydrolysis, k_n the second-order nucleophilic rate constant for amine attack or the second-order rate constant for tertiary amine catalyzed hydrolysis, and [N] the concentration of tertiary amine present as the free base.

The pH–rate profiles for the hydrolysis of p-NO_2-Q-8 and p-NO_2-Q-6 are given in Figure 1. Similar pH–rate profiles were obtained for the other esters employed in this study. From the profiles values of the hydrolytic rate constants (k_{HO^-} and $k_{H_2O}[H_2O]$) were obtained and are given in Table I. Hydrolysis of the Q-6 esters occurred too slowly below about pH 9 for values of the spontaneous rates of hydrolysis to be obtained.

Plots of log k_{HO^-} *vs.* the Hammett substituent con-

Table I. Hydrolytic Rate Constants for Substituted Phenyl Quinoline-8-carboxylates (Q-8) and Phenyl Quinoline-6-carboxylates (Q-6)[a,b]

Substituent	σ	k_{HO^-}, M^{-1} sec^{-1} Q-8	k_{HO^-}, M^{-1} sec^{-1} Q-6	$k_{H_2O}[H_2O]$, sec^{-1} Q-8
p-CH_3O	−0.27	$6.0 \pm 0.2 \times 10^{-2}$	$3.2 \pm 0.1 \times 10^{-1}$	
H	0.0	$7.4 \pm 0.4 \times 10^{-2}$	$4.0 \pm 0.1 \times 10^{-1}$	
p-Cl	0.227	$1.5 \pm 0.1 \times 10^{-1}$	$9.6 \pm 0.1 \times 10^{-1}$	$4.5 \pm 0.2 \times 10^{-6}$
p-CN	0.66	$3.8 \pm 0.2 \times 10^{-1}$	$9.3 \pm 0.3 \times 10^{-1}$	$1.5 \pm 0.1 \times 10^{-5}$
o-NO_2	0.75	$3.6 \pm 0.2 \times 10^{-1}$	1.7 ± 0.1	$1.4 \pm 0.1 \times 10^{-5}$
p-NO_2	1.00	$7.6 \pm 0.3 \times 10^{-1}$	4.4 ± 0.3	$2.5 \pm 0.2 \times 10^{-5}$
2,4-diNO_2	1.75	4.0 ± 0.2	17.5 ± 0.5	$4.7 \pm 0.4 \times 10^{-6}$

[a] In the calculation of k_{HO^-}, $-\log K_w$ is taken to be 13.83, the value of the ionization constant in pure water at 30° (H. S. Harned and R. A. Robinson, *Trans. Faraday Soc.*, **36**, 973 (1940)). [b] Rate constants are recorded with their average deviations.

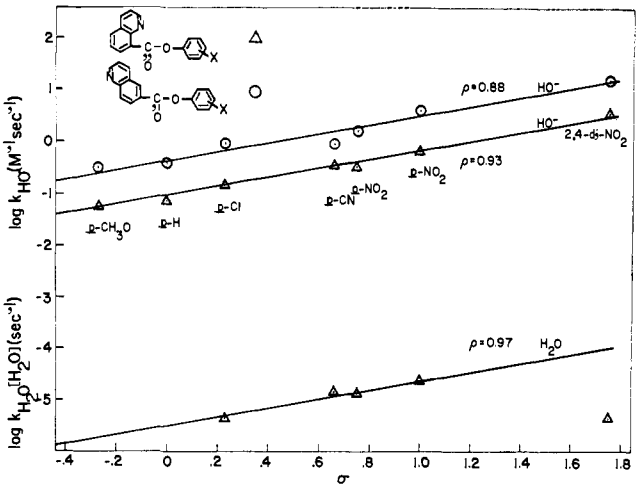


Figure 2. Hammett $\sigma\rho$ plots of the second-order rate constant for hydroxide ion attack and the first-order rate constant for water attack on substituted Q-8 (△) and Q-6 (○) esters.

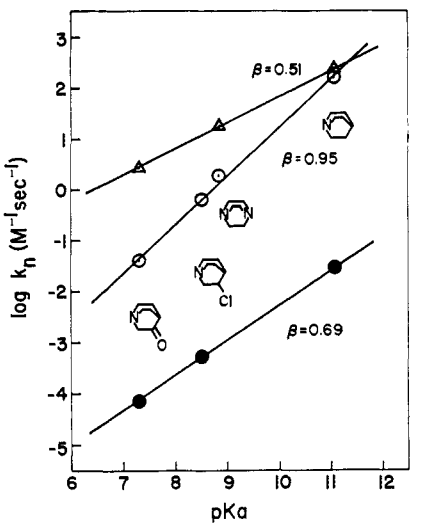


Figure 3. Brønsted plots for the second-order aminolysis rate constant *vs.* the pK_a of the amine nucleophile for the reaction of 2,4-diNO_2-Q-8 (△), 2,4-diNO_2-Q-6 (○), and p-NO_2-Q-6 (●) with several quinuclidine amines.

stant gave ρ's of 0.93 and 0.88 for the substituted Q-8 and Q-6 esters, respectively, and a ρ of 0.97 was obtained for the reaction of the 8 isomers with water (Figure 2). A σ value of 1.0 was employed for the p-NO_2 group as this value has been found to better correlate data for nucleophilic displacement reactions on phenyl esters than the usual σ values of 0.78 and 1.27.[6] The $\Sigma\sigma$ value of 1.75 employed for 2,4-diNO_2 substitution was arrived at by the best fit of the log k_{HO^-} values for 2,4-diNO_2-Q-8 and 2,4-diNO_2-Q-6 to the Hammett plot (Figure 2). It has been reported[7] that for reactions in which the reaction site is not directly attached to the benzene ring, the electronic effect of a substituent in the ortho position is about 0.75 times its effect in the para position. Thus the σ value of the o-NO_2 substituent has been taken to be 0.75. That this is a satisfactory value is evidenced by the fact that the sum of the o-NO_2 and p-NO_2 σ values (0.75 + 1.0 = 1.75) gives the value obtained for the 2,4-diNO_2 substituent as described above. The pK_a values of the various phenolic leaving groups employed in this study and the pK_a's of the quinoline nitrogen of Q-8 and Q-6 are given in Table II. From these pK_a values, ρ for the ionization of phenols in 20% acetonitrile (μ = 0.5, T = 30°) is calculated to be 2.38 with a correlation coefficient of 0.996. (Note that a σ^- value of 1.0 was used for p-CN and 1.27 for o-NO_2 and p-NO_2, and a $\Sigma\sigma$ of 2.54 was used for 2,4-diNO_2, rather than the σ's given in Table II.)[8] The ρ value is comparable to the ρ of 2.13 obtained for the ionization of phenols in water at 25°.[9]

Table II. pK_a Values[a]

Compd	pK_a	Compd	pK_a
p-Methoxyphenol	10.56	2,4-Dinitrophenol	3.99
Phenol	10.24	Phenyl quinoline-8-carboxylate	4.26
p-Chlorophenol	9.90		
p-Cyanophenol	8.13	Phenyl quinoline-6-carboxylate	3.37
o-Nitrophenol	7.36		
p-Nitrophenol	7.24		

[a] Determined by spectrophotometric titration in 20% acetonitrile (μ = 0.5) at 30°.

Values of k_n obtained from slopes of plots of k_{obsd} *vs.* [N] are given in Tables III and IV for the reaction of tertiary amines with the Q-8 and Q-6 esters, respectively. For three of the esters, values of k_n were determined for their reaction with several quinuclidine amines. The widely varying pK_a's and similar steric requirements of these amines give rise to satisfactory β values obtained from slopes of plots of log k_n *vs.* pK_a (Figure 3). Deuterium solvent kinetic isotope effects are given in Table

(6) T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, **86**, 418 (1964).
(7) M. Charton, *Can. J. Chem.*, **38**, 2493 (1960).
(8) L. P. Hammett, "Physical Organic Chemistry," 1st ed, McGraw-Hill, New York, N. Y., 1940, p 188.
(9) (a) C. M. Judson and M. Kilpatrick, *J. Amer. Chem. Soc.*, **71**, 3115 (1949); (b) H. Kloosterziel and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **71**, 295 (1952); (c) E. E. Sager, M. R. Schooley, A. S. Carr, and S. F. Acree, *J. Res. Nat. Bur. Stand.*, **35**, 521 (1945); (d) R. Näsänen, P. Lumme, and A. L. Mukula, *Acta Chem. Scand.*, **5**, 1199 (1951).

Table III. Second-Order (k_n) Rate Constants and Third-Order General Base (k_{gb}, in Parentheses) Rate Constants for the Aminolysis of Substituted Phenyl Quinoline-8-carboxylates

Amine	pK_a[a]	k_n, M^{-1} sec^{-1}						
		p-CH_3O	H	*p*-Cl	*p*-CN	*o*-NO_2	*p*-NO_2	2,4-diNO_2
Quinuclidine	11.08	3.00×10^{-4}	5.43×10^{-4}	1.39×10^{-3}			1.86×10^{-2}	234
Triethylamine	10.70							1.52×10^{-2}
N-Methylpiperidine	9.97		8.81×10^{-5}	1.98×10^{-4}			1.16×10^{-3}	1.35
Trimethylamine	9.83	5.72×10^{-5}	7.96×10^{-5}	2.24×10^{-4}		1.13×10^{-3}	1.55×10^{-3}	47.3
Triethylenediamine	8.85							37.4
3-Chloroquinuclidine	8.51							
N-Methylmorpholine	7.57							4.48×10^{-2}
3-Quinuclidinone	7.30							2.68
Imidazole	6.92	2.56×10^{-5} (7.27×10^{-5})	3.67×10^{-5}	1.72×10^{-4}			7.26×10^{-3}	1.11
4-Morpholineethanesulfonic acid	6.21							3.78×10^{-5}
2-Dimethylaminoethyl chloride	5.83							6.04×10^{-4}

[a] pK_a's determined by half-neutralization.

Table IV. Second-Order (k_n) Rate Constants and Third-Order General Base (k_{gb}, in Parentheses) Rate Constants for the Aminolysis of Substituted Phenyl Quinoline-6-carboxylates

Amine	k_n, M^{-1} sec^{-1}						
	p-CH_3O	H	*p*-Cl	*p*-CN	*o*-NO_2	*p*-NO_2	2,4-diNO_2
Quinuclidine	4.32×10^{-4}	8.24×10^{-4}	2.24×10^{-3}			2.99×10^{-2}	171
Triethylamine							2.23×10^{-2}
N-Methylpiperidine		1.28×10^{-4}	2.49×10^{-4}			1.89×10^{-3}	1.21×10^{-1}
Trimethylamine	1.08×10^{-4}	9.94×10^{-5}	3.09×10^{-4}		1.30×10^{-3}	2.38×10^{-3}	3.22
Triethylenediamine							1.96
3-Chloroquinuclidine						5.19×10^{-4}	9.92×10^{-1}
N-Methylmorpholine							9.24×10^{-4}
3-Quinuclidinone						7.25×10^{-5}	3.99×10^{-2}
Imidazole	1.55×10^{-5} (6.55×10^{-5})	3.41×10^{-5} (1.01×10^{-4})	1.23×10^{-4} (3.67×10^{-4})			5.42×10^{-3} (1.30×10^{-2})	1.23
4-Morpholineethanesulfonic acid							4.36×10^{-5}
2-Dimethylaminoethyl chloride							7.60×10^{-6}

[a] pK_a values given in Table III.

Table V. Deuterium Solvent Kinetic Isotope Effects for Aminolysis with Trimethylamine[a]

Ester	pK_a^H	pK_a^D [b]	k_n^H [c]	k_n^D [c]	k_n^H/k_n^D
p-Cl-Q-8	9.83	10.53	2.24×10^{-4}	1.36×10^{-4}	1.6
p-Cl-Q-6			3.09×10^{-4}	2.09×10^{-4}	1.5
2,4-diNO_2-Q-8			47.3	61.3	0.8
2,4-diNO_2-Q-6			3.22	3.69	0.9

[a] Determined in 20% acetonitrile, $\mu = 0.5$, $T = 30°$. [b] Determined by half-neutralization employing the electrode correction: pD = pH meter reading + 0.38: T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961). [c] Units in M^{-1} sec^{-1}.

V for the reaction of the *p*-Cl and 2,4-diNO_2 substituted esters with trimethylamine.

In Figure 4 is given the Hammett plot obtained from reaction of the Q-8 and Q-6 esters with trimethylamine. The large positive deviation evidenced by the two 2,4-diNO_2 substituted esters occurs with all tertiary amines. These esters have been ignored, for reasons which will become evident, in the calculation of the ρ values of Table VI. To show that the positive deviation exhibited by the 2,4-diNO_2 substituted esters is not due to a poor choice of σ, in the insert to Figure 4 the same data are plotted against the pK_a of the leaving group. Addition of *p*-nitrophenol (10 times that of [ester] employed) to the reaction medium had no effect on the

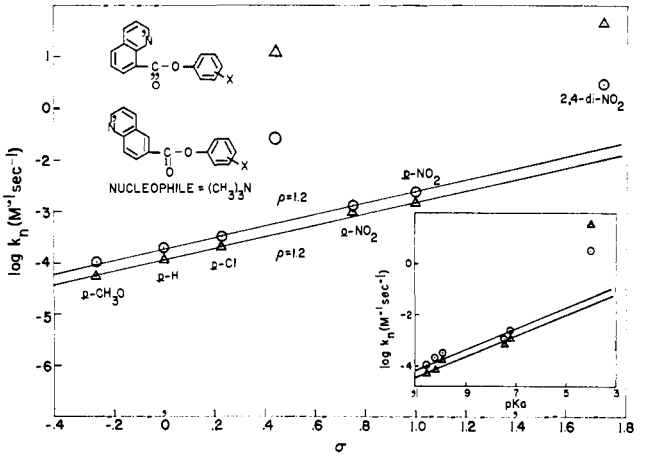


Figure 4. Hammett $\sigma\rho$ plots of the second-order rate constant for reaction of trimethylamine with substituted Q-8 (△) and Q-6 (○) esters. The insert contains the same data plotted against the pK_a of the leaving group.

rate of aminolysis of *p*-NO_2-Q-8 or *p*-NO_2-Q-6 with tertiary amines contrary to the results obtained with acetate esters.[10]

Discussion

Hydrolysis. The near identity of the Hammett

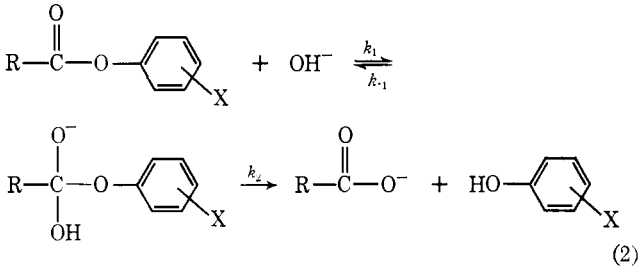
(10) W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 90, 2622 (1968).

Table VI. Hammett ρ Values Obtained from Reaction of Various Nucleophiles with a Series of Substituted Phenyl Quinoline-8- and -6-carboxylates[a]

Nucleophile	log k_n *vs.* σ		log k_{gb} *vs.* σ
	ρ_{Q-8}	ρ_{Q-6}	ρ_{Q-6}
Hydroxide ion	0.93 (0.995)[b]	0.88 (0.991)[b]	
Water	0.97 (0.984)[c]		
Quinuclidine	1.4 (0.997)[d]	1.5 (0.998)[d]	
N-Methylpiperidine	1.1 (0.995)[d]	1.2 (1.00)[d]	
Trimethylamine	1.2 (0.989)[d]	1.2 (0.980)[d]	
Imidazole	2.3 (0.993)[e]	2.4 (0.993)[e]	1.9 (0.991)[d]

[a] Correlation coefficients given in parentheses. [b] Calculated for p-CH_3O, H, p-Cl, p-CN, o-NO_2, p-NO_2, and 2,4-diNO_2. [c] Calculated for p-Cl, p-CN, o-NO_2, and p-NO_2. [d] Calculated for p-CH_3O, H, p-Cl, p-CN, and p-NO_2 (o-NO_2 included in those cases where data for that ester had been obtained). [e] Calculated for p-CH_3O, H, p-Cl, p-NO_2, and 2,4-diNO_2.

ρ values for hydroxide ion attack on the Q-8 and Q-6 esters (Figure 2) indicates that all the esters of this study follow the same mechanism in their reaction with hydroxide ion. The values of k_{HO^-} for the Q-6 esters are 5–6 times greater than those for the Q-8 esters (Table I). Electronically the Q-6 and Q-8 esters should be similar since MO calculations of the π-electron densities of the quinoline ring system indicate that the 6 position is the one which most resembles the 8 position (0.989 and 1.003 charge distributions, respectively).[11] Thus the five- to sixfold difference in reactivity may be attributed to steric factors and/or to the slight nonidentity of the electron density at the 6 and 8 positions. With 6- and 8-acetoxyquinoline, where steric differences should be less than in the esters of the present study, the reactivity of the 6 isomer toward hydroxide ion is about three times greater than that of the 8 isomer.[2b] The ρ values of 0.93 and 0.88 may be compared with the ρ of 0.8 obtained for nucleophilic attack of hydroxide ion on a series of substituted phenyl acetates.[12] The rate-limiting step is presumably attack on the carbonyl carbon (k_1 of eq 2) to form a tetrahedral intermediate



(2)

with essentially no phenoxide bond breaking occurring. In the case of carboxyl nucleophilic attack upon phenyl esters where it has been suggested that bond breaking to the leaving phenoxide is of critical importance in the transition state,[13] considerably larger ρ values ($\sim$2.2) are obtained.[13a,14]

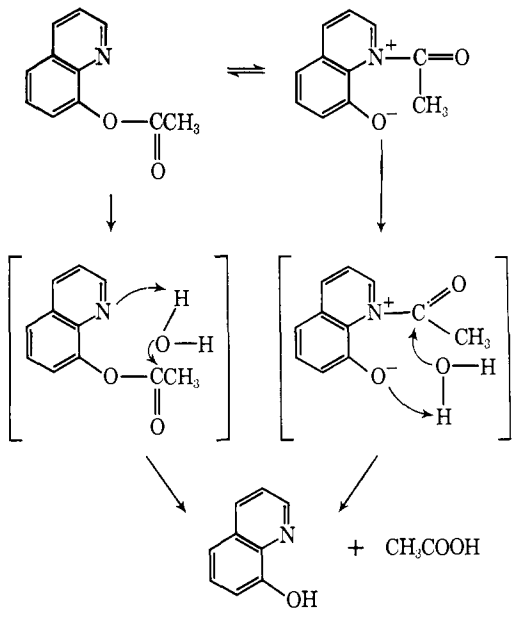
Although the Q-6 esters are five- to sixfold more reactive than the Q-8 esters toward hydroxide ion, the Q-8 esters show a greater reactivity toward water. The spontaneous rates of hydrolysis are given in Table I. The 6 isomers hydrolyzed too slowly for their spontaneous rates of hydrolysis to be determined. The ρ value for water attack on the substituted Q-8 esters is 0.97 with the 2,4-diNO_2 substituted ester exhibiting a significant negative deviation (Figure 2). The reason for this negative deviation is not clear. Presumably it is not due to steric hindrance since no deviation is shown by the o-NO_2 substituted ester. Examination of Figure 1 shows that the spontaneous rate of hydrolysis is experimentally at least 10^2-fold greater for the 8 isomer. The second-order nucleophilic rate constants (k_n) have been determined for the reaction of several primary and secondary amines with all substituted Q-8 and Q-6 esters of this study, and plots of log k_n (Q-8) *vs.* log k_n (Q-6) are linear.[15] If it is assumed that water falls on the line with primary and secondary amines as it did in a similar plot for 8- and 6-acetoxyquinoline,[9] the observed rate of water attack on p-Cl-Q-6 and p-NO_2-Q-6 can be calculated to be about 4×10^{-10} and 2×10^{-9}, respectively. With this assumption the 8 isomer is about 10,000 times more reactive toward water than is the 6 isomer. If the relative steric requirements are those noted for hydroxide attack, the rate enhancement will approach 2 to 5 $\times$ 10^4-fold. The similar ρ values for hydroxide ion and water attack on the substituted Q-8 esters indicate a similar sensitivity of k_{HO^-} and k_{H_2O} to electronic and steric effects. In a study[16] of a large number of α-substituted o-nitrophenyl esters the relationship between k_{HO^-} and k_{H_2O} has been found to be log k_{HO^-} = 0.84 log k_{H_2O} + 8.0. Using the four Q-8 esters for which the values of both k_{HO^-} and k_{H_2O} are known (excluding the 2,4-diNO_2 substituted ester), the relationship is log k_{HO^-} = 0.87 log k_{H_2O} + 3.8. The values of the slopes for the two studies are in good agreement. The differences in the intercepts of 4.2 log units agree with the above calculations indicating that the Q-8 esters hydrolyze more than 10,000 times faster than the usual difference in the reactivity of hydroxide ion and water with substituted phenyl esters would predict.

In the study of 8- and 6-acetoxyquinoline,[2] the 8 isomer was found to be 500 times more reactive than the 6 isomer toward water. This was attributed to intramolecular general base catalysis by the quinoline nitrogen although O $\rightarrow$ N transfer of the acetoxy group followed by intramolecular general base catalysis by the phenoxide ion could not be ruled out (Scheme I). Since in the case of IV no O $\rightarrow$ N transfer is possible, the observed rate enhancement can only be due to intramolecular general base catalysis by the quinoline nitrogen. These results suggest that the same mechanism should be favored for spontaneous hydrolysis of 8-acetoxyquinoline.

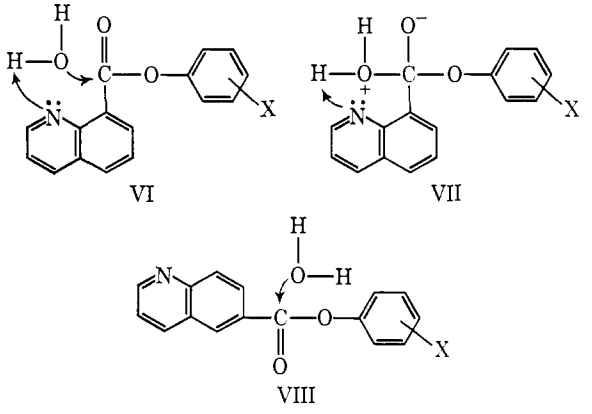
The observed intramolecular general base catalysis by the quinoline nitrogen may be concerted with nucleophilic attack (VI) or follow nucleophilic attack (VII). For the 6 isomer, intramolecular catalysis is not possible (VIII). The ρ value of 0.97 obtained for spontaneous hydrolysis of the substituted Q-8 esters (Figure 2) indicates that nucleophilic attack is rate limiting; thus the observed intramolecular catalysis must be concerted with nucleophilic attack (VI). A ρ

(11) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).
(12) T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, **82**, 3067 (1960).
(13) (a) E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, **82**, 5328 (1960); (b) R. Goitein and T. C. Bruice, *J. Phys. Chem.*, **76**, 432 (1972).
(14) T. C. Bruice and A. Turner, *J. Amer. Chem. Soc.*, **92**, 3422 (1970).
(15) P. Y. Bruice and T. C. Bruice, *J. Amer. Chem. Soc.*, **96**, 5533 (1974).
(16) B. Holmquist and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 2982 (1969).

Scheme I



value of 0.96 was obtained for spontaneous hydrolysis of 4- and 5-substituted aspirin anions which are subject to rate-limiting nucleophilic attack.[1] Hydrolysis reactions involving rate-determining breakdown of the tetrahedral intermediate are characterized by much larger ρ values. The tertiary amine catalyzed hydrolysis of phenyl acetates evidences of ρ of 2.5 and the corresponding intramolecular amine catalyzed hydrolysis of phenyl γ-(*N*,*N*-dimethylamino)butyrates and phenyl δ-(*N*,*N*-dimethylamino)valerates both give ρ's of 2.2.[3]

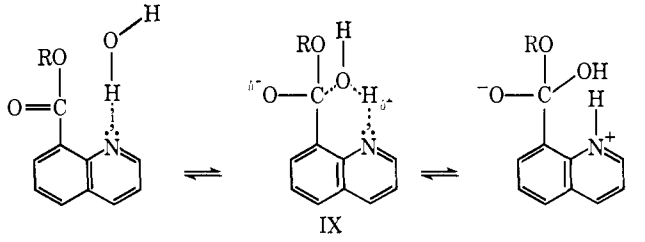


VI VII VIII

In a comparison of the ability of quinoline-8-carboxylate and α-naphthoate to bind to an antibody specific to *p*-azobenzoate ion it was found that quinoline-8-carboxylate behaves like α-naphthoate with a large substituent on the position occupied by the ring nitrogen.[17] This was attributed to water of hydration. Positioning of a water molecule at the site of nucleophilic attack (IX) would be in accord with concerted proton transfer.

From the rate constants determined for the spontaneous hydrolysis of *p*-Cl-Q-8 at 29.7 and 70.3° (4.5×10^{-6} and 1.50×10^{-4} sec^{-1}, respectively), $T\Delta S_{25}^{\ddagger}$ is calculated to be -7.9 kcal mol^{-1} ($\Delta S_{25}^{\ddagger} = -26.5$ eu). The $T\Delta S^{\ddagger}$ value is similar to those obtained for other intramolecular hydrolysis reactions[1,2b] and is in agreement with the empirical rule of Bruice and Benkovic which states that an average value of $-T\Delta S^{\ddagger}$ for a

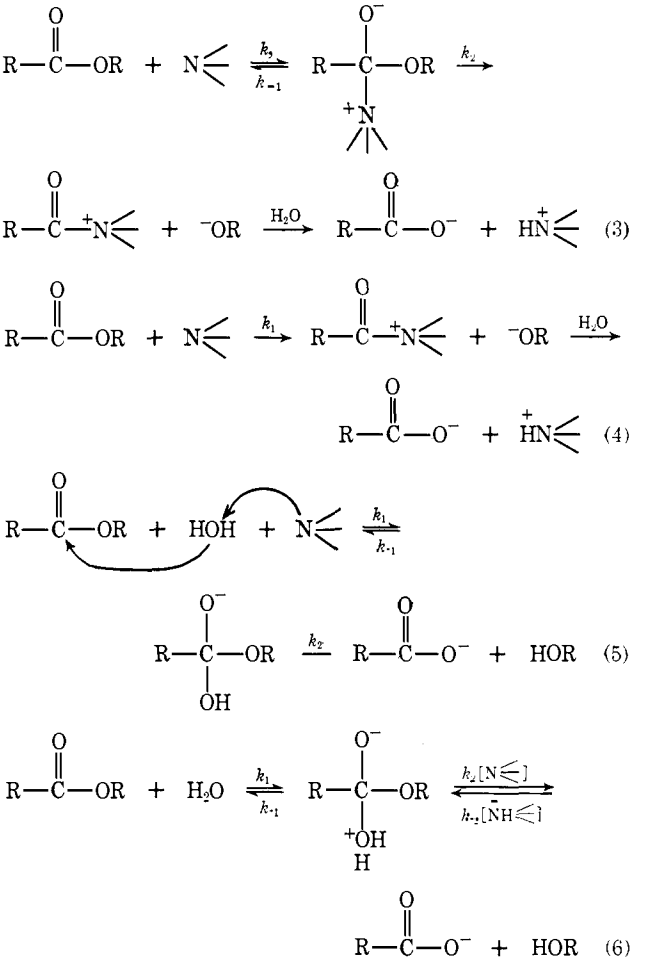
(17) D. Pressman and M. Siegel, *J. Amer. Chem. Soc.*, 79, 994 (1957).



IX

displacement reaction may be obtained by multiplying the order by 4 to 6 kcal mol^{-1}.[6]

Aminolysis with Tertiary Amines. There are several possible mechanisms by which an ester might react with a tertiary amine: (i) nucleophilic attack to form a tetrahedral intermediate followed by expulsion of phenoxide ion (eq 3); (ii) direct nucleophilic displacement of phenoxide ion by the tertiary amine (eq 4); (iii) tertiary amine general base catalyzed attack of water (eq 5); (iv) attack of water followed by tertiary amine general base catalyzed breakdown of the tetrahedral intermediate (eq 6).



(3)

(4)

(5)

(6)

The Hammett $\sigma\rho$ plot for the reaction of trimethylamine with a series of Q-8 and Q-6 esters is given in Figure 4. All the tertiary amines employed in this study, with the exception of imidazole, give similar Hammett plots with values of ρ falling in the range 1.1–1.5 (Table VI). (The unusual reactivity of imidazole will be considered in a separate section.) The marked positive deviation of the 2,4-diNO_2 substituted esters evidenced in Figure 4 is typical of these esters with tertiary amines. The similarity of ρ values for the Q-8 and Q-6 esters indicates that not only is the mech-

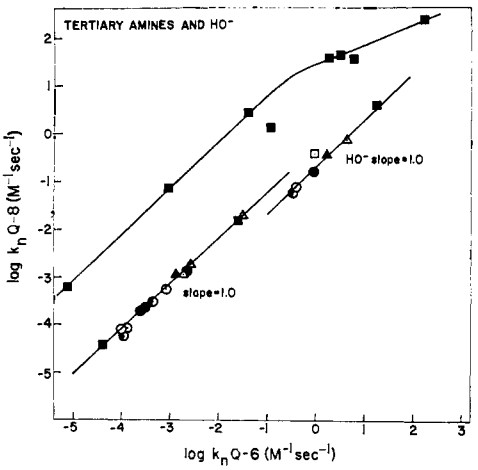


Figure 5. A plot of the log of the second-order rate constants for reaction of tertiary amines and hydroxide ion with substituted Q-8 esters *vs.* the same function for substituted Q-6 esters; ◐, *p*-CH_3O; ●, H; ○, *p*-Cl; ⊡, *p*-CN; ▲, *o*-NO_2; △, *p*-NO_2; ■, 2,4-diNO_2.

anism the same within a series of substituted esters (except for the 2,4-diNO_2 substituted esters) but it is also the same for the Q-8 and Q-6 isomers. The similarity in the dependence upon electronic effects is also evidenced by the slope of 1.0 obtained when log k_n Q-8 is plotted against log k_n Q-6 for reaction with tertiary amines (Figure 5). Intramolecular complexing between the electron-withdrawing 2,4-dinitrophenyl group and the quinoline ring can be ruled out as being responsible for the unusual reactivity of the 2,4-diNO_2 substituted esters since these esters do not show any deviation in their reaction with hydroxide ion (Figure 2). Since the observed deviation from the Hammett $\sigma\rho$ plot is positive, a change in mechanism rather than a change in rate-limiting step is occurring. It is evident that the change in mechanism results from the low pK_a (good leaving ability) of 2,4-dinitrophenol and not from the introduction of an ortho substituent since the *o*-NO_2 substituted esters fall on the Hammett plot with the less reactive esters (Figure 4).

The following observations would suggest that the 2,4-diNO_2 substituted esters undergo nucleophilic attack by tertiary amines (eq 3 or 4), whereas with the less reactive esters tertiary amines act as general bases (eq 5 or 6). (i) A β value of 0.95 was obtained for the reaction of 2,4-diNO_2-Q-6 with a series of quinuclidine amines (Figure 3). This is similar to the β of 1.05 determined for nucleophilic attack of primary amines on phenyl acetates.[18] On the other hand, the *p*-NO_2-Q-6 ester gave a β of 0.69 with the quinuclidine amines. Values of β are expected to be smaller for general base catalyzed water attack than for nucleophilic attack. The reason for the low value of β obtained for nucleophilic attack on 2,4-diNO_2-Q-8 will be considered below. (ii) The reaction of trimethylamine with *p*-Cl-Q-8 and *p*-Cl-Q-6 is characterized by deuterium solvent kinetic isotope effects of 1.6 and 1.5 (Table V), respectively, suggesting that proton transfer may be partially rate limiting. The deuterium solvent kinetic isotope effects for the reaction of trimethylamine with 2,4-diNO_2-Q-8 and 2,4-diNO_2-Q-6 are 0.8 and 0.9, respectively, indicating that proton abstraction is not involved in the mechanism. (iii) It can be approximately interpolated from Hammett plots such as that given in Figure 4 that the ρ values for the reaction of tertiary amines with the 2,4-diNO_2 substituted esters are considerably greater than 2.0 indicating a substantial amount of bond breaking to the phenoxide group in the transition state. The ρ values, ranging from 1.1 to 1.5 for the reaction of tertiary amines with the less reactive esters (Table VI) suggest lack of bond breaking to the phenoxide group in the transition state and indicate that the tertiary amine catalyzes attack of water (eq 5) rather than decomposition of the tetrahedral intermediate (eq 6). The ρ values are similar to the ρ obtained for intramolecular general base catalyzed hydrolysis of the Q-8 esters where proton removal is associated with the attack step. Tertiary amine catalyzed hydrolysis reactions involving rate-determining breakdown of the tetrahedral intermediate are associated with considerably larger ρ values.[3] (iv) In Figure 5 it can be seen that the points for tertiary amines reacting with the 2,4-diNO_2 substituted esters do not fall with the points for tertiary amines reacting with the other esters, with two exceptions. The points for the reaction of triethylamine and 4-morpholineethanesulfonic acid with the 2,4-diNO_2 substituted esters do fall with the less reactive esters. These two amines are the most sterically hindered of the tertiary amines studied. This observation suggests that when there is a sufficient amount of steric hindrance the 2,4-diNO_2 substituted esters react by the same mechanism as the less reactive esters. Thus when steric hindrance prevents an amine from reacting directly with a 2,4-diNO_2 substituted ester as a nucleophile, it reacts as a general base catalyst in the removal of a proton from water, a mechanism less subject to the steric requirements of the tertiary amine. To summarize, the β values, deuterium solvent kinetic isotope effects, and Hammett plots require that the mechanism for reaction of a tertiary amine with the 2,4-diNO_2 substituted esters be different than that for reaction with the less reactive esters, yet with tertiary amines with sufficient steric hindrance all the esters of this study react *via* the same mechanism. The only reasonable explanation for these observations is that, unless prevented by steric hindrance, tertiary amines react with the 2,4-diNO_2 substituted esters as nucleophiles whereas with less reactive esters and when nucleophilic attack is prevented by steric hindrance tertiary amines act as general base catalysts for the attack of water.

If a tertiary amine reacts with an ester *via* nucleophilic attack as in eq 3, one would expect breakdown of the zwitterionic tetrahedral intermediate (k_2) to be rate limiting since $k_{-1} \gg k_2$. On the other hand, if the tertiary amine acts as a general base in its catalysis of hydrolysis as in eq 5, one would expect water attack (k_1) to be rate limiting since the anionic tetrahedral intermediate is very unstable and $k_2 \gg k_{-1}$. (Similar reasoning may be used to explain why hydroxide ion attack upon esters is associated with rate-limiting nucleophilic attack while carboxyl nucleophilic attack is associated with rate-limiting breakdown of the tetrahedral intermediate.) Thus a change from rate-limiting breakdown of the tetrahedral intermediate to rate-limiting nucleophilic attack may be associated with a change from a mechanism in which the tertiary amine acts as a nucleophile to one in which the tertiary amine

(18) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, 89, 2106 (1967).

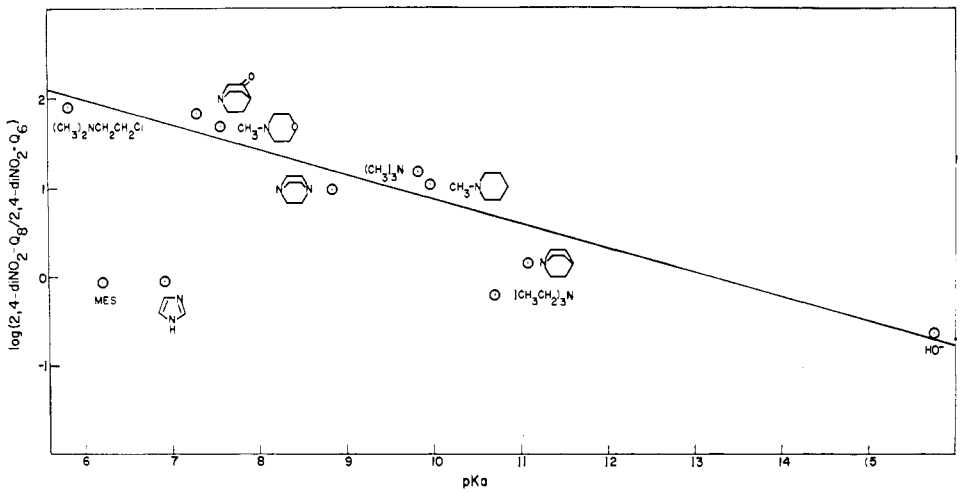


Figure 6. A plot of the log of the ratio of the second-order rate constant for reaction of a tertiary amine with 2,4-diNO$_2$-Q-8 to that for reaction with 2,4-diNO$_2$-Q-6 *vs.* the pK_a of the tertiary amine. The log of the ratio of the second-order rate constants for hydroxide ion is also included.

acts as a general base. Trimethylamine has been proposed to react with phenyl acetates *via* nucleophilic attack with rate-limiting breakdown of the tetrahedral intermediate (ρ = 2.5).[3] Trimethylamine reacts with the quinoline esters *via* rate-limiting general base catalysis of water attack (ρ = 1.2). Thus the apparent change in mechanism must be the result of the difference in acyl function. Phenyl acetates are generally more reactive than either phenyl quinoline-8- or -6-carboxylates. The present study has clearly established that in a given series of esters a change from tertiary amine general base to nucleophilic catalysis occurs with increasing reactivity.

The reactions of hydroxide ion with all esters, tertiary amines with all esters except the 2,4-diNO$_2$ substituted esters, and tertiary amines with the 2,4-diNO$_2$ substituted esters are defined in Figure 5 by three different lines of approximately unit slope suggesting that three different mechanisms are involved. Reaction with hydroxide ion occurs *via* rate-limiting attack with little or no phenoxide departure in the transition state (eq 2). Tertiary amines react with esters other than the 2,4-diNO$_2$ substituted derivatives *via* general base catalyzed attack of water (eq 5). Mechanisms which would account for the identical rates of aminolysis in water and deuterium oxide and the relatively large values of ρ and β_{nuc} exhibited by the 2,4-diNO$_2$ substituted esters in their reaction with tertiary amines are nucleophilic attack to form a tetrahedral intermediate with breakdown of that intermediate rate limiting (eq 3) or direct nucleophilic displacement of phenoxide ion (eq 4). Tertiary amines react more rapidly with 2,4-diNO$_2$-Q-8 than they do with the 6 isomer (Tables III and IV), and the lower the pK_a of the amine the slower the rate of reaction but the greater the acceleration of the rate of 8 isomer as compared to that of the 6 (Figure 6); *i.e.*, k_n^{Q-8}/k_n^{Q-6} is 1.4 for quinuclidine with a pK_a of 11.08 and 79 for dimethylaminoethyl chloride with a pK_a of 5.83. (Note that the three amines that show marked deviations from the line in Figure 6 are triethylamine, 4-morpholineethanesulfonic acid, and imidazole which are postulated herein to react with 2,4-diNO$_2$ substituted esters by a mechanism other than that followed by other tertiary amines.) That the rate of aminolysis of the 8 isomer becomes greater compared to the 6 isomer as the pK_a of the attacking amine is decreased requires that amine bond formation is not complete in the transition state, for if it were the rate ratio would not depend on the pK_a of the amine. Thus the mechanism for the reaction of tertiary amines with 2,4-diNO$_2$ substituted esters is either direct nucleophilic displacement (eq 4) or the mechanism given in eq 2 with k_{-1} and k_2 very large so that the fleeting existence of the tetrahedral intermediate would cause the reaction to have essentially the characteristics of an S$_N$2 displacement.

Molecular models show that (i) in the 8 isomer the quinoline nitrogen is very close to the oxygen of the leaving group suggesting the probability of charge repulsion between the electrons on nitrogen and the unshared electrons of oxygen; (ii) as a tertiary amine approaches the 8 isomer, the quinoline nitrogen is in a position to partially stabilize the developing positive charge on the entering amino nitrogen; and (iii) the alkyl groups of the attacking amine can experience lyophobic interactions with the quinoline ring of the 8 isomer. Lyophobic interactions leading to stabilization of transition states in nucleophilic displacement reactions on ester bonds have been proposed previously.[19] However, molecular models indicate that lyophobic interactions are possible to the same extent with the 6 isomer as with the 8. In addition, lengthening of the ester side chain from acetate to octanoate was found to have approximately the same effect on k_{HO^-} for *O*-acyl 6-hydroxyquinolines as for the 8 isomers.[20] Thus the above mentioned electronic effects (i and ii) are likely responsible for the greater rate of aminolysis of 2,4-diNO$_2$-Q-8 as compared to 2,4-diNO$_2$-Q-6 with tertiary amines. The lower the pK_a of the attacking amine the greater the degree of amine bond formation and phenoxide bond breaking and the greater the partial positive charge on the amine nitrogen in the transition state. Thus with tertiary amines of low pK_a there is the possibility of greater stabilization of the transition state of the 8 isomer by the electron pair on the quinoline nitrogen as

(19) (a) C. Gitler and A. Ochoa-Solano, *J. Amer. Chem. Soc.*, 90, 5004 (1968); (b) C. A. Blyth and J. R. Knowles, *J. Amer. Chem. Soc.*, 93, 3017 (1971).

(20) T. Maugh II and T. C. Bruice, *J. Amer. Chem. Soc.*, 93, 6584 (1971).

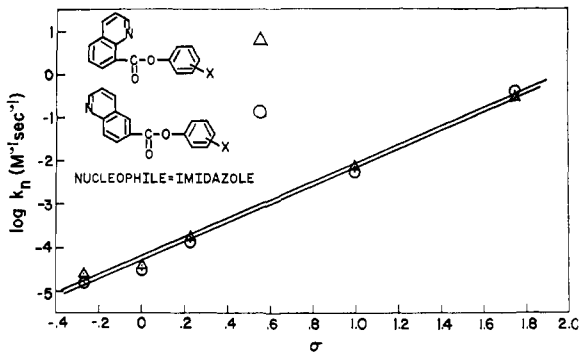


Figure 7. Hammett $\sigma\rho$ plots of the second-order rate constant for reaction of imidazole with substituted Q-8 (△) and Q-6 (○) esters.

well as less charge repulsion between the electrons of the quinoline nitrogen and those of the oxygen of the leaving group. Since these electronic effects are not possible for the 6 isomer, as the pK_a of the tertiary amine is decreased the ratio of the rate of aminolysis of the 8 isomer as compared to the 6 isomer markedly increases. Following this line of reasoning, the rate of aminolysis of the 8 isomer should be less sensitive to the pK_a of the amine since a decrease in basicity is partially compensated by an increase in electrostatic stabilization. Thus β_{nuc} for 2,4-diNO_2-Q-8 is 0.51 as compared to a β_{nuc} of 0.95 for 2,4-diNO_2-Q-6 (Figure 3), although both esters presumably react with amines *via* a nucleophilic mechanism.

Tertiary amines have been found to catalyze the hydrolysis of highly reactive acyl compounds (*e.g.*, acetic anhydride) *via* intermediate formation of an acylated amine thereby implicating the tertiary amine as a nucleophile.[4] The intermediate formed by nucleophilic displacement is very reactive toward water since it is not able to stabilize itself by proton loss. Tertiary amines catalyze the hydrolysis of less reactive esters by acting as general bases. Thus it is not surprising that in the series of quinoline esters investigated a change in mechanism is observed when the pK_a of the conjugate acid of the leaving group is changed from 7.24 (*p*-nitrophenol) to 3.99 (2,4-dinitrophenol).

Aminolysis with Imidazole. The Hammett $\sigma\rho$ plot for imidazole (Figure 7), unlike those for other tertiary amines (Figure 4), is linear providing no evidence for a change in rate-limiting step. It is apparent from the presence of an [imidazole]^2 term in the rate equation that imidazole reacts directly with the esters as a nucleophile as would be predicted on the basis of previous studies[21] which have established intermediate formation of acetylimidazole in the imidazole catalyzed hydrolysis of *p*-nitrophenyl acetate and other activated acyl compounds. The ρ values are comparable to those obtained for the reaction of primary and secondary amines with the substituted Q-8 and Q-6 esters[15] and would suggest that loss of phenoxide from the tetrahedral intermediate is at least partially rate limiting.

The ratios of k_n^{Q-8}/k_n^{Q-6} for aminolysis with imidazole are significantly larger than the ratios obtained for aminolysis with tertiary amines where steric factors account for reactivity differences and much smaller than the ratios obtained for aminolysis with primary and secondary amines where proton slide catalysis enhances the reactivity of the 8 isomers.[15] The small rate enhancement observed for reaction of imidazole with the 8 isomers as compared to the 6 isomers may well be due to electrostatic stabilization of the tetrahedral intermediate by the quinoline nitrogen lone pair.

General base catalysis by imidazole of imidazole catalyzed hydrolysis, as evidenced by the presence of an [imidazole]^2 term in the rate equation, has been observed with *p*-methoxy- and *p*-methylphenyl acetate but not with phenyl, *p*-chlorophenyl, or *p*-nitrophenyl acetate.[6,22] In the present study, *p*-CH_3O-Q-6, Q-6, *p*-Cl-Q-6, and *p*-NO_2-Q-6 exhibit an [imidazole]^2 term (Table IV) associated with a ρ of 1.9 (Table VI). Only the least reactive 8 isomer, *p*-CH_3O-Q-8, exhibits general base catalysis by imidazole (Table III). Thus it is apparent that the acyl group of the ester is an important factor in determining how good the leaving group must become before general base catalysis is no longer detectable. The fact that intermolecular general base catalysis by imidazole is more prevalent with the 6 isomers and the bimolecular rates greater with the 8 isomers gives support to the suggestion that electrostatic stabilization *via* the quinoline nitrogen is possible for the Q-8 esters; the value of k_n is thereby sufficiently increased to make k_{gb} undetectable.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

(21) (a) M. L. Bender and B. W. Turnquest, *J. Amer. Chem. Soc.*, **79**, 1663 (1957); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, p 46; (c) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 67.

(22) J. F. Kirsch and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 833 (1964).