tained was then purified by steam distillation and crystallization from petroleum ether (bp 30–60°) (3 g, yield 61%, mp 39.5–41.5°).

Anal. Calcd for $C_{13}H_{14}NCl$: C, 71.00; H, 6.37; N, 6.37; Cl, 16.13. Found: C, 70.61; H, 6.49; N, 6.29; Cl, 16.13.

4-Chloro-8-*t*-butylquinoline. *o*-*t*-Butylaniline hydrochloride[15] (41.6 g, 0.22 mole) and sodium oxalacetate (47.2 g) were mixed and stirred at room temperature for 20 hr. The obtained β-carbethoxy-β-anilinoacrylate (65.7 g, yield 92%) was dissolved in 500 ml of Dowtherm and heated under reflux for 1 hr. Most of the solvent was removed by distillation under reduced pressure and 4-hydroxy-3-carbethoxy-8-*t*-butylquinoline (32 g, yield 57%, mp 166–173°) was precipitated by adding petroleum ether to the residue. It was successively converted by conventional procedures into the 4-hydroxy-3-carboxy-8-*t*-butyl (21 g, mp 220° dec), the 4-hydroxy-8-*t*-butyl (12.8 g, mp 248–251°), and the 4-chloro-8-*t*-butyl derivatives. After purification by steam distillation and subsequent crystallization from petroleum ether, the chloro derivative melted at 46.5–47.5°.

Anal. Calcd for $C_{13}H_{14}NCl$: C, 71.00; H, 6.37; N, 6.37. Found: C, 70.99; H, 6.73; N, 6.28.

A previous attempt to synthesize this compound by the procedure used for the 6-*t*-butyl isomer (*i.e.*, condensation with ethyl ethoxymethylenemalonate) gave a much lower yield.

Kinetic Procedure. The procedure used for the kinetic measurements was that described in previous paper.[11,13] For the treatment of the rate data for the reactions subject to autocatalysis, see ref 2. A total of 90 independent kinetic experiments was carried out.

(15) J. B. Shalsmith and A. Mackie, *J. Chem. Soc.*, 2334 (1928).

Table IV. Methoxy and Piperidino Dechlorination of 4-Chloro-6- (and-8-) alkylquinolines (Rate Constants at Diverse Temperatures)

Reagent and solvent	Subst	$k \times 10^6$ 75.2°	99.5°	115.7°
MeO^- in methanol	6-Me	95.7[a]	791[a]	2870
	6-*t*-Bu		799	2820
	8-Me	68.8	559	1910
	8-*t*-Bu		21.9	98.0
Piperidine in piperidine	6-Me		0.617	1.50
	6-*t*-Bu		0.410	1.06
	8-Me		0.894	2.01
	8-*t*-Bu		0.395	0.899
Piperidine in DMSO	6-Me	20.6	84.8	181
	6-*t*-Bu	17.8	69.8	133
	8-Me	24.2	93.6	200
	8-*t*-Bu	5.80	32.5	64.3
Piperidine in MeOH	6-Me		21	50
	6-*t*-Bu		16	38
	8-Me		11	27
	8-*t*-Bu	17[b]	4.8[c]	2.0

[a] See ref 11. [b] At 150°. [c] At 130°.

The activation parameters reported in Tables II and III were determined on the basis of the rate constants at the different temperatures reported in Tables I, III, and IV.

The Kinetics and Mechanism of the Reaction of *p*-Toluenethiol with Chloroquinolines in Methanol Solution[1]

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Contribution from the Departments of Chemistry, University of Rome, Rome, Italy and University of Trieste, Trieste, Italy. *Received January 21, 1967*

Abstract: The noncatalyzed reaction of a chloroquinoline with *p*-toluenethiol in methanol solution is faster than the reaction involving either the aryl sulfide or the chloroquinolinium ion with the nonionized form of the other reactant. All the investigated reactions follow simple second-order kinetics, but the substituent effects are anomalous. These and other facts are interpreted in terms of a complex reaction consisting of a fast acid–base preequilibrium between reactants followed by the substitution proper between aryl sulfide and chloroquinolinium ions. The nucleophilicity of the nonionized thiol with respect to solvent and substrate is also discussed in connection with the mechanism of the reaction in nonpolar aprotic solvents.

In the literature there is found a large amount of information concerning the nucleophilic reactions of organic sulfide ions in preparative as well as kinetic work. The reactions of thiols in the presence of strong bases clearly belong to this class. However, in a number of cases, the intervention of the sulfide anions is less obvious or, even, unlikely. As belonging to this group, we may mention the acid-catalyzed addition reactions to double bonds[2,3] and the substitution reactions with chloroquinolines in nonpolar, aprotic solvents (toluene).[4,5] The latter reactions exhibit complex kinetics and involve a slow, initial process followed by autocatalytic phenomena.

In the course of related work on the reactivity of aza-activated substrates we have recently discovered[6] that *p*-toluenethiol reacts quite rapidly with 4-chloroquinoline in methanol solution. In principle, protic solvents and reagents may interact with aza-activated substrates in a specific way.[7] Several aspects of the influence of specific solvation due to hydroxylic solvent–substrate interaction have been described in the preceding papers.[7–9] From such work it appears that piperidine, being only weakly protic, does not give rise

(1) Nucleophilic Heteroaromatic Substitution. XXVIII. Work carried out under a CNR (Rome) research contract at the Universities of Rome (G. I.) and Trieste (P. L. and G. M.) on the basis of a conjoint program. Presented by G. I. at the Gordon Conference on the Chemistry of Heterocyclic Compounds (New Hampton, N. H., July 4–8, 1966).

(2) E. Campaigne in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Oxford, 1961, p 134 ff.

(3) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 72.

(4) G. Illuminati and L. Santucci, *Gazz. Chim. Ital.*, **83**, 1106 (1953).

(5) G. Grassini and G. Illuminati, *ibid.*, **86**, 437 (1956).

(6) G. Illuminati and G. Marino, *Tetrahedron Letters*, 1055 (1963).

(7) G. Illuminati, G. Marino, and G. Sleiter, *J. Am. Chem. Soc.*, **89**, 3510 (1967).

(8) F. Genel, G. Illuminati, and G. Marino, *ibid.*, **89**, 3516 (1967).

(9) M. Calligaris, G. Illuminati, and G. Marino, *ibid.*, **89**, 3518 (1967).

to any preliminary detectable interaction with the aza group of the N-heteroaromatic substrate; however, the more highly protic reagent *p*-toluenethiol may do so. It seemed therefore of interest to investigate in some detail the kinetics of the reaction of this reagent with a number of N-heteroaryl chlorides in methanol solution.

Results

Table I reports the observed kinetic data for the reaction of 2-chloro- and 4-chloroquinoline with *p*-toluenethiol in methanol. In contrast with the expectations,[4,5] neither substrate reacts by an autocatalytic course, and the reaction rates in both cases are fairly large. The reactions follow second-order kinetics because the second-order diagrams were found to be linear in the investigated ranges and the observed rate constants independent of the initial reactant concentrations. The reactions proceeded to completion; the reaction products were isolated and identified as the expected 2- and 4-*p*-tolylthioquinolines.

Table I. Kinetic Data for the Reaction of Some 2- and 4-Chloroquinoline Derivatives with *p*-Toluenethiol in Methanol

Substituent	k_{obsd}, l. mole^{-1} sec^{-1}	k/k_0[a]
	2-Chloroquinolines	
H[b]	7.46×10^{-4}	1
4-CH_3O	7.14×10^{-4}	0.95
7-Cl	6.20×10^{-4}	0.83
	4-Chloroquinolines	
H[c]	8.61×10^{-2} [d]	1
2-CH_3O	2.00×10^{-4}	0.0023
7-NO_2	3.22×10^{-2}	0.37
7-Cl	3.38×10^{-3} [e]	0.42[c,e]

[a] Rate relative to the parent compound, at 30° unless stated otherwise. [b] E_a, 12.11 kcal/mole; $\Delta S^{\ddagger}$, −34.9 eu (at 30°). These parameters were determined on the basis of the rate constants at 30° (see table), at 40° (1.51×10^{-3}), and at 50° (2.57×10^{-3}). [c] E_a, 9.38 kcal/mole; $\Delta S^{\ddagger}$, −34.2 eu (at −10°). These parameters were determined on the basis of the rate constants at −10° (8.03×10^{-3}), at 0° (1.57×10^{-2}), and at 10° (2.87×10^{-2}). [d] Calculated from the Arrhenius equation on the basis of the rate data reported in footnote *c*. [e] At −10°.

The kinetic influence of some typical substituents, such as MeO, Cl, and NO_2, has also been considered, and the related rate data are also collected in Table I. The results are not as would be anticipated for a normal nucleophilic substitution reaction, since in both series the electron-withdrawing groups Cl and NO_2 exert a deactivating, rather than an activating, effect.

A number of experiments have been devised to test the reactivity of the reactants or of species related to them for additional information regarding the reaction mechanism. They are summarized in Table II.

Discussion

There are a number of interesting points emerging from the present investigation on the reaction of a chloroquinoline with *p*-toluenethiol in methanol solution. (a) The reaction rates (unsubstituted 2- and 4-chloro isomers) are greater than those of the corresponding reactions with *p*-tolyl sulfide ion (Table II, entries 1, 2, 6, and 7); (b) the reaction rate (4-chloro isomer) is greater than that of the N-methyl-4-chloroquinolinium ion (Table II, entries 2 and 3); and (c) the substituent effects are anomalous (Table I).

Table II. Reactivity Data for the Action of *p*-Toluenethiol and Related Reagents on Some N-Heteroaryl and Aryl Chlorides

No.	Substrate	Exptl conditions[a]	k_{obsd}, l. mole^{-1} sec^{-1}
	Reactions with *p*-Toluenethiol		
1	2-Chloroquinoline	MeOH, 30°	7.46×10^{-4}
2	4-Chloroquinoline	MeOH, 30°	8.61×10^{-2}
3	1-Methyl-4-chloroquinolinium iodide	MeOH, 30°	4.66×10^{-3}
4		Toluene, 75°, 60 hr	No reaction
5	2,4-Dinitrochlorobenzene	MeOH, 75°, 48 hr	No reaction
	Reactions with Sodium *p*-Tolyl Sulfide		
6	2-Chloroquinoline	MeOH, 86.5°	1.68×10^{-4}
7	4-Chloroquinoline	MeOH, 86.5°	1.60×10^{-3}
8	1-Methyl-4-chloroquinolinium iodide	MeOH, −10°, 30 sec	90% reaction
	Reactions with Methyl *p*-Tolyl Sulfide		
9	2-Chloroquinoline	MeOH, 100°, 8 hr	No reaction
10		Xylene, 140°, 72 hr	No reaction
11	1-Methyl-4-chloroquinolinium iodide	MeOH, 115°, 24 hr	No reaction

[a] Solvent, temperature (°C), and, where necessary, time, in the stated order.

Points a and b show that each of the two conceivably most reactive species of reactants, *i.e.*, the organic sulfide anion and the cationic chloroquinolinium ion, is not sufficiently reactive to account alone for the rate of the reaction under investigation.

Furthermore, some of the other data (Table II, entries 4, 5, 9, 10, and 11) show that the reaction of the N-methyl-4-chloroquinolinium ion does not involve the thiol with its "intact" S–H bond. Dicovalent sulfur does not seem to be a nucleophilic atom capable of reacting with the present substrates as can be deduced from the failure of methyl *p*-tolyl sulfide to displace the halogen from either 2-chloroquinoline or the N-methyl-4-chloroquinolinium ion. The nucleophilicity of a thiol may increase on H bonding with the solvent. In aromatic solvents interaction with the π electrons of the benzene ring is possible[10] but again is unable to produce sufficiently reactive species toward heteroaromatic substrates. Thus, no reaction was obtained by the action of *p*-toluenethiol on N-methyl-4-chloroquinolinium iodide in toluene solution. However, stronger H-bonding interaction and some ionization occur in methanol solution,[10] by the following equilibria.

$$\text{ArS–H} + \text{MeOH} \rightleftharpoons \text{ArS–H}\cdots\text{OHMe}$$

$$\text{ArS–H}\cdots\text{OHMe} \rightleftharpoons \text{ArS}^-\cdots\text{H–OHMe}^+$$

Thus, the reaction of the N-methyl-4-chloroquinolinium ion in methanol solution involves nucleophilic species ranging from the H-bonded thiol to the H-bonded sulfide ion. The reactivity of the thiol in these conditions is still far smaller than that expected for the reagent existing completely in the anionic form, as is shown by the inertness of 2,4-dinitrochlorobenzene, which is known to be a highly activated substrate toward organic sulfides.[11]

(10) J. G. David and H. E. Hallam, *Trans. Faraday Soc.*, **60**, 2031 (1964); *Spectrochim. Acta*, **21**, 841 (1965).

(11) J. F. Bunnett and W. D. Merritt, *J. Am. Chem. Soc.*, **79**, 5967 (1957).

In view of the exceedingly high speed of the reaction of organic sulfide ions with cationized N-heteroaryl halides (see Table II, entry 8, and work by Miller[12,13]), the *simultaneous* presence of these species, even in minute concentrations, may be assumed to be responsible for the observed rate of the reaction of the chloroquinoline with a thiol in alcohol. To account for all the observations, we propose a reaction mechanism consisting of a fast preequilibrium 1 followed by a slow substitution reaction 2 where Q is a quinoline residue

$$\text{ArS–H(solv)} + \text{Q–Cl(solv)} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{ArS(solv)}^- + \text{HQ–Cl(solv)}^+ \quad (1)$$

$$\text{ArS(solv)}^- + \text{HQ–Cl(solv)}^+ \xrightarrow{k_2} \text{HQ–SAr(solv)}^+ + \text{Cl(solv)}^- \quad (2)$$

and solvation is indicated to emphasize its essential role in connection with eq 1. If the steady-state treatment is applied, and neglecting the solvation signs, eq 3 is obtained which, on the reasonable assumption

$$\text{rate} = \frac{k_1 k_2}{k_{-1} + k_2}[\text{ArSH}][\text{QCl}] \quad (3)$$

that preequilibrium 1 is quickly established and $k_{-1} >> k_2$, yields eq 4 with $K = k_1/k_{-1}$. This rate equation is

$$\text{rate} = k_2 K[\text{ArSH}][\text{QCl}] \quad (4)$$

in accord with the observed second-order kinetics if we set $k_{obsd} = k_2 K$.

Going to point c, the puzzling effects of the structure on the rate may be now easily explained if we consider that the substituents are expected to exert opposite effects on K and k_2 values; then, the over-all effects on the rate depend on the interplay of these values whatever the polar effect of the substituent may be. Similarly, the higher reactivity of 4-chloroquinoline as compared to the 2-chloro isomer, involving a rate factor of 115, can be ascribed to the greater basicity of 4-chloroquinoline,[14] *i.e.*, to a higher K value for this isomer, despite the reverse order predicted for the k_2 values, on the basis of analogy with similar reactions[12,13] of N-methylchloropyridinium cations.

Although autocatalysis is expected for nucleophilic N-heteroaromatic substitutions with neutral reagents,[15] absence of this effect is also consistent with the proposed mechanism. Both active species are actually charged (eq 4), and any strong acid eventually formed in the course of the reaction cannot have any rate-enhancing influence on the already cationized substrate species.

The preparative implications of the present results are obvious. In contrast with a standard procedure consisting of the use of strong bases to produce the aryl sulfide ion, the best way to perform replacement of a chloro with an arylthio group at a reactive position of the quinoline ring is simply to mix the reactants in methanol solution or, even, with no solvent at all.[16]

We may now compare the present results concerning the reaction in methanol to those obtained previously in toluene solution.[4,5] As mentioned in the introductory section, in the latter solvent the reaction is slow at the start and eventually becomes faster by autocatalysis. The different kinetic course is in agreement with the view that the reaction mechanism is not the same in the two solvents, the one in toluene probably involving the essentially nonionized thiol. However, the present work suggests that for the reaction of a nonionized thiol to occur with substrates of type under investigation, some S–H bond loosening by H-bond interaction with the medium is to be assumed. In toluene solution such an interaction is possible in two ways, with the lone pair of the aza group of the substrate[17] and with the π electrons of the benzene ring of the solvent.[10,18]

Experimental Section

Materials. *p*-Toluenethiol (E.K.) was crystallized twice from petroleum ether (bp 30–50°), mp 43.5–44.0°. Commercial reagent-grade methyl *p*-tolyl sulfide was used without any further purification after a purity check by vapor phase chromatography.

The chloroquinolines examined in the present work were obtained as described in previous studies.[19–21] N-Methyl-4-chloroquinolinium iodide, mp 209–210° dec, was prepared by the action of methyl iodide on 4-chloroquinoline.[22]

Reactions of N-Heteroaryl and Aryl Chlorides with *p*-Toluenethiol and Methyl *p*-Tolyl Sulfide. a. Equimolecular amounts of chloroquinoline and *p*-toluenethiol were mixed in methanolic solution and allowed to stand for 4–6 hr at room temperature. The solvent was removed by evaporation, and the *p*-tolylthioquinoline hydrochloride was obtained in quantitative yield. The hydrochloride was then treated with a sodium hydroxide solution, and the free quinoline base was extracted with ether. The expected *p*-tolylthioquinolines were obtained in high yield (over 85%); 4 isomer, mp 88–89°;[5] 2 isomer, mp 66–67°.[16]

b. Equimolecular amounts (0.004 mole) of 4-chloro-1-methylquinolinium iodide and *p*-toluenethiol were dissolved in 50 ml of methanol and allowed to stand at room temperature for 6 days. The halide salt of the product thus obtained was then converted into the nitrate by addition of a solution containing the required amount of silver nitrate (0.008 mole) in methanol. The precipitate of silver halide was separated by filtration, and the filtrate was evaporated off, yielding a yellow crystalline residue melting at 160–165°. After crystallization from methanol, the melting point was 165–167° dec.

Anal. Calcd for $C_{17}H_{16}N_2O_3S$: N, 8.53. Found: N, 8.59.

c. In the attempted reactions of *p*-toluenethiol with N-methyl-4-chloroquinolinium iodide in toluene and with 2,4-dinitrochlorobenzene in methanol (Table II, entries 4 and 5), analyses were carried out for both the chloride ion and the thiol. Neither chloride ion was detected nor decrease in the thiol concentration observed within experimental error.

d. In the attempted reactions of methyl *p*-tolyl sulfide with 2-chloroquinoline in methanol and toluene and with N-methyl-4-chloroquinolinium iodide in methanol (Table II, entries 9, 10, and 11), chloride ion analyses resulted in no detectable amounts of released chloride ion in all cases. Since 4-chloroquinoline is a substrate of intermediate reactivity between the above ones, it was concluded that no reaction with the sulfide could be reasonably assumed in this case.

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(19) G. Illuminati and G. Marino, *J. Am. Chem. Soc.*, **80**, 1421 (1958).
(20) M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron*, **19**, 345 (1963).
(21) M. L. Belli, M. Forchiassin, G. Illuminati, P. Linda, G. Marino, and E. Zinato, *Ric. Sci.*, [2A] **33** 530 (1963).
(22) E. Campaigne, R. E. Cline, and C. E. Kaslow, *J. Org. Chem.*, **15**, 600 (1950).

Table III. Typical Kinetic Data for the Reaction of 4-Chloroquinoline with *p*-Toluenethiol in Methanol[a]

Time, sec	NH_4CNS, ml	Reaction, %	$1/(a - x)$
0	4.84	0	34.42
130	4.72	9.92	38.21
275	4.62	18.18	42.07
405	4.53	25.62	46.28
555	4.45	32.23	50.79
747	4.37	38.84	56.27
1030	4.28	46.28	64.06
1450	4.20	52.89	73.10
2322	4.04	66.11	101.70

[a] Reaction solution, 0.0329 *M* in both reactants; temperature, 10°; resulting $k_{obsd} = 2.87 \times 10^{-2}$, k in l. mole^{-1} sec^{-1}.

Kinetic Procedures. The reaction mixtures were prepared by weighing out a calculated amount of the substrate in a 25-ml volumetric flask, then adding about 15 ml of the solvent, a known volume of a standard solution of the thiol, and finally solvent to the mark. After shaking, the flask was immersed into a constant-temperature bath. Samples (2 ml) of the solution were withdrawn at appropriate time intervals and quenched in a separatory funnel containing ether and water. The ether layer was separated and washed with another 20 ml of water. The aqueous layers were combined, acidified with 6 *N* nitric acid, and analyzed for the chloride ion by the Volhard method. The extraction with ether was necessary in order to eliminate the sulfur compounds which interfere with the silver nitrate reagent. Data for a typical experiment are reported in Table III.

In the case of the reactions of the N-methyl-4-chloroquinolinium iodide, it was not possible to use the above-described procedure because of the high solubility of that compound in water; accordingly, the reactions were followed by an iodometric analysis of the unreacted thiol. Since color change in these conditions was not satisfactory by standard chemical methods, the titration end point was determined by an amperometric technique ("dead-stop method").

The Hydration of Acetaldehyde. I. Equilibrium Thermodynamic Parameters

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Abstract: The molar extinction coefficient for the $n \rightarrow \pi^*$ absorption band of unhydrated acetaldehyde in aqueous solution has been measured directly, allowing spectrophotometric data to be used in the calculation of the value of the equilibrium constant for the hydration of acetaldehyde without making any assumption about the temperature dependence of $\Delta H°$ for that reaction. A combination of spectrophotometric and calorimetric data lead to the results for the hydration of acetaldehyde in pure water as solvent at 25°, $\Delta H° = -5.62 \pm 0.14$ kcal/mole and $\Delta S° = -18.7 \pm 0.5$ cal/mole deg (for a unit mole fraction standard state for water), while the corresponding average value of $\Delta C_p°$ over the temperature range 0–25° is -10 ± 5 cal/mole deg. The equilibrium constant is given equally precisely within experimental error by the two equations: $\log K_h = (1212.7/T) - 4.0412$ (which assumes $\Delta C_p° = 0$) and $\log K_h = (543.2/T) - 5.0330 \log T + 10.6594$ (which assumes $\Delta C_p° = -10$ cal/mole deg). The quoted uncertainties are 90% confidence limits.

The values of the thermodynamic parameters, particularly of $\Delta S°$ and $\Delta C_p°$, for the equilibrium addition of water to substrates in aqueous solution are of interest as bases for the interpretation of the corresponding activation parameters for hydrolysis reactions. For example, Kohnstam[1] has proposed that for solvolyses of alkyl halides and related compounds in mixed acetone–water solvents, the ratio, $\Delta C_p^{\ddagger}/\Delta S^{\ddagger}$, should be independent of the substrate for solvolysis *via* an SN1 mechanism and should have a lower value for solvolysis by way of an SN2 mechanism. The rationale for this mechanistic criterion is that both parameters are negative and that for SN1 solvolysis both are controlled by the increase in electrostatic solvation accompanying formation of the polar activated complex, while in SN2 solvolysis covalent binding of a solvent molecule will lower $\Delta S^{\ddagger}$ much more than $\Delta C_p^{\ddagger}$. That covalent binding of water does result in an entropy decrease of *ca.* 10–30 cal/mole deg seems well established,[2] but the absence of a similar large effect on the heat capacity is without experimental support (except that of Kohnstam's activation parameters) and seems based on the assumption that the value of $\Delta C_p°$ for covalently binding water will not differ by a large factor from that predicted for the loss of translational freedom arising from the combination of two mass points in the gas phase ($-5R/2$).

In view of the well-known large increases in heat capacity accompanying the solution of nonionic solutes in water[3–5] and of the changes in heat capacity which occur when substituents capable of hydrogen bonding to solvent are introduced,[6] this assumption would seem to be *a priori* a risky one. In fact, the only experimentally observed value of $\Delta C_p°$ for a simple covalent hydration appears to be that for the hydration of carbon dioxide, $CO_2 + H_2O \rightleftarrows H_2CO_3$, for which $\Delta C_p°$ is

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(2) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, 1, 1 (1963).

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(5) R. L. Bohon and W. F. Claussen, *J. Am. Chem. Soc.*, 73, 1571 (1951).

(6) Compare, for example, $\Delta C_p° = -1$ cal/mole deg for ionization of ethanolammonium ion and $\Delta C_p° = +8$ cal/mole deg for methylammonium ion: ref 7, p 452.

(7) J. T. Edsall and J. Wyman, "Biophysical Chemistry," Vol. 1, Academic Press Inc., New York, N. Y., 1958, pp 550–590.