The General Acid Catalyzed Displacement of Amines from *o*-Hydroxylaminobenzamides in Aqueous and Nonaqueous Solvents

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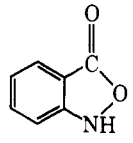
Abstract: The general acid catalyzed displacement of amines from *o*-hydroxylaminobenzamides, with formation of 2,1-benzoxisoxazolin-3-one, occurs readily in water and a wide variety of nonaqueous solvents. This, together with the fact that the *o*-hydroxylaminobenzamides can be obtained simply and quantitatively from the corresponding *o*-nitrobenzamides by reduction, suggests that amines may be conveniently masked as their *o*-nitrobenzoyl derivatives. This has been confirmed for some simple amines in preliminary synthetic studies. Kinetic measurements in both aqueous and nonaqueous solvents show that the *o*-hydroxylamino group strongly promotes the liberation of the amines. In aqueous perchloric acid solutions, for example, the cleavage of *o*-hydroxylamino-*N,N*-dimethylbenzamide occurs some 10^5–10^6 times more rapidly than the hydrolysis of the unsubstituted *N,N*-dimethylbenzamide. The mechanism of the reaction is discussed and, in particular, it is suggested that the relatively rapid reaction in solvents such as carbon tetrachloride and benzene can only be accounted for by a one encounter mechanism.

The liberation of alcohols from esters of *o*-hydroxylaminobenzoic acid, with formation of 2,1-benzisoxazolin-3-one (I), has been shown by kinetic[1] and synthetic studies[2] to be



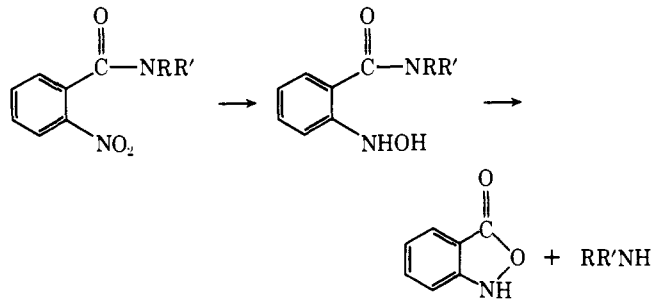
I

rapid and quantitative in basic solution. The corresponding reaction in acid solution, although considerably slower than in alkaline solution, also shows evidence for direct participation of the hydroxylamino group.[1] The hydroxylaminobenzoates can be readily prepared from the corresponding *o*-nitrobenzoates by reduction, and this has led to the proposal[2] of *o*-nitrobenzoate as a protecting group for phenols and alcohols.

An attempt[2] to mask amines as their *o*-nitrobenzoyl derivatives (Scheme I) was, however, less successful. Thus it was reported that the cyclohexylamide of *o*-hydroxylaminobenzoic acid (produced by reduction of the *o*-nitroamide) did not readily liberate cyclohexylamine with base. In an earlier study,[3] Cohen and Gray reported rapid cleavage of *o*-hydroxylamino-*N,N*-dimethylbenzamide in aqueous alkali, although the yield of the amine was not reported (51% of benzisoxazolinone was recovered). Preliminary work in this laboratory also suggests that, in base solution, the reactions of the amides are not as simple as those of the esters.[1,2] However, we have found that the reactions proceed quite rapidly and without complications in acid solutions in both aqueous and nonaqueous solvents.

In the present paper, we report a detailed study of the kinetics of the acid catalyzed liberation of amines from the corresponding *o*-hydroxylaminobenzamides and some preliminary results of a synthetic study on the usefulness of this reaction sequence (Scheme I) for the protection of amines.

Scheme I



Experimental Section

Materials. The nitroamides were prepared according to the procedure of Barton, Coates, and Sammes.[2]

Reduction of Nitrobenzamides. The nitroamide (3 g) in tetrahydrofuran (THF) (30 ml) was added to a solution of ammonium acetate (8 g) in water (30 ml) and the resultant mixture stirred vigorously between −5 and 0°C. Zinc dust (2.5 g) was added over 15 min, maintaining the temperature between −5 and 0°C. In all cases examined, TLC (SiO_2-$CHCl_3$/MeOH 9:1) indicated that the reduction was complete within 15 min of completion of the addition of zinc.

***o*-Hydroxylamino-*N,N*-dimethylbenzamide:** prepared by the above procedure in 90% yield; mp 100–101°C; ir ν_{max} ($CHCl_3$) 3560, 3300, 3000, 2930, 1620, 1450–1500, 1395 cm^{-1}, and others; NMR (D_2O) τ 1.9–2.5 (4 H, m), 6.4 (3 H, s) 6.7 (3 H, s); NMR ($CDCl_3$) τ 2.5–3.3 (4 H, m), 7.0 (6 H, s). Anal. ($C_9H_{12}N_2O_2$) C, H, N.

***o*-Hydroxylamino-*N*-methylbenzanilide:** isolated in 84% yield; mp 101–102°C; ir ν_{max} ($CHCl_3$) 3580, 3300, 3000, 1630, 1590, 1490, 1360 cm^{-1}, and others; NMR ($CDCl_3$) τ 2.0–3.5 (4 H, m), 2.85 (5 H, s), and 6.55 (3 H, s). Anal. ($C_{14}H_{14}N_2O_2$) C, H, N.

***o*-Hydroxylamino-*N*-methylbenzamide:** isolated in 89% yield; mp 123°C (ethyl acetate); ir ν_{max} (KBr) 3320, 3020, 2900, 1620, 1596, 1550, 1450–1480, 1395, 1330 cm^{-1}, and others; NMR (Me_2SO-d_6) τ 7.3 (3 H, d, J = 8 Hz), 2.2–3.5 (4 H, m), 1.7 (1 H, broad singlet), 1.5 (1 H, exchanges with D_2O), 0.7 (1 H, exchanges with D_2O). Anal. ($C_8H_{10}N_2O_2$) C, H, N.

***o*-Hydroxylaminobenzanilide:** isolated in 80% yield; mp 119–120°C (ethyl acetate); ir ν_{max} (KBr) 3290, 3190, 1628, 1595, 1535, 1488 cm^{-1}, and others; NMR (Me_2SO-d_6) τ 2.0–3.2 (multiplet). Anal. ($C_{13}H_{12}N_2O_2$) C, H, N.

Recovery of *N*-Methylaniline. The *o*-nitro-*N*-methylbenzanilide (5 g) was reduced with Zn-NH_4OAc under the conditions described above. The THF phase was separated and the aqueous phase extracted with THF. The combined THF extracts were dried over anhydrous $MgSO_4$ and filtered, and the total volume was adjusted to 50 ml. Chloroacetic acid (5 g) was added and the mixture stirred for 3 hr at room temperature. The solution was extracted with saturated Na_2CO_3 solution, dried over anhydrous $MgSO_4$, and evaporated to yield *N*-methylaniline (2.26 g) in quantitative recovery. Microdistillation of the recovered product gave 1.85 g of pure *N*-methylaniline (82% recovery).

Table I. Cleavage of *o*-Hydroxylaminobenzamides in Acid Solution at 25°C

	10^3k_e, sec^{-1}			
[HCl], *M*	*N*-Methylamide	*N,N*-Dimethylamide	Anilide	*N*-Methylanilide
0.002	0.0557	0.389	0.346	0.359
0.005	0.109	0.798	0.700	0.836
0.01	0.218	1.43	1.34	1.59
0.02	0.369	2.73	2.66	2.74
0.04	0.637	5.26	4.81	5.21
0.06	0.859	7.53	6.76	7.49
0.08	1.07	9.75	9.31	10.0
0.1	1.22	12.0	11.1	12.3
$[HClO_4]$, *M*				
0.55	1.92	36.4	19.4	28.5
1.1	1.68	55.4	19.8	32.7
2.2	1.14	70.8	19.2	32.9
3.3	0.80	67.8	16.6	30.1
5.5	0.511	51.1	12.7	25.6

Table II. Catalytic Constants for the Acid Catalyzed Cleavage of *o*-Hydroxylamino-*N,N*-dimethylbenzamide and *o*-Hydroxylamino-*N*-methylbenzanilide at 25°C

	10^4k_e, $dm^3\ mol^{-1}\ sec^{-1}$	
Acid (A)	*N,N*-Dimethylamide	*N*-Methylanilide
(H_2O)	1.4/55.5	0.9/55.5
Formic	12.8	9.8
Chloroacetic	18.5	20.2
H^+	1300	1400

Kinetic Measurements. The reactions were followed by observing the appearance of the product benzisoxazolinone spectrophotometrically at 308 nm with a Gilford 2400 spectrophotometer. All kinetic measurements were made at 25 ± 0.2°C.

Results

Reactions in Aqueous Acid Solutions. The rates of cleavage of the amides of *N*-methylamine, *N,N*-dimethylamine, aniline, and *N*-methylaniline were measured in aqueous hydrochloric or perchloric acid solutions, with acid concentrations varying between 2×10^{-3} and 5.5 *M*. Amide concentrations were ca. 10^{-4} *M*. In all cases, the observed rate law was as shown in eq 1

$$-d[S]/dt = k_e[S] \quad (1)$$

where S represents the amide. At low acid concentrations ($<5 \times 10^{-2}$ *M*), k_e increased almost linearly with acid concentration, and extrapolation to zero acid concentrations gave the following approximate values for the spontaneous (solvent catalyzed) reaction in water (k_0, sec^{-1}).

o-hydroxylamino-*N*-methylbenzamide $= 0.2 \times 10^{-4}$ sec^{-1}
o-hydroxylamino-*N,N*-dimethylbenzamide $= 1.4 \times 10^{-4}$ sec^{-1}
o-hydroxylaminobenzanilide $= 1.1 \times 10^{-4}$ sec^{-1}
o-hydroxylamino-*N*-methylbenzanilide $= 0.9 \times 10^{-4}$ sec^{-1}

Values of k_e for the various reactions in acid solution are listed in Table I.

The reactions of the *N,N*-dimethylamine and *N*-methylaniline compounds were studied in aqueous formate and chloroacetate buffers to check for the presence of general acid catalysis. Ionic strength was maintained at 0.2 by addition of $NaClO_4$. The observed rate law was again of the form shown in eq 1, with k_e being given by eq 2

$$k_e = k_0 + k_{H^+}[H^+] + k_A[A] \quad (2)$$

Table III. Cleavage of *o*-Hydroxylamino-*N,N*-dimethylbenzamide and *o*-Hydroxylamino-*N*-methylbenzanilide in Aqueous Buffers at 25°C

	N,N-Dimethylamide		*N*-Methylanilide	
[Formic acid],[a] *M*	10^4k_e, sec^{-1}	10^4k_e (calcd),[b] sec^{-1}	10^4k_e, sec^{-1}	10^4k_e (calcd),[b] sec^{-1}
0.00		1.90		1.20
0.08	2.96	2.92	2.00	1.98
0.14	3.77	3.69	2.58	2.57
0.20	4.57	4.46	3.11	3.18
[Chloroacetic acid],[a] *M*				
0.00		4.61		4.00
0.08	6.03	6.09	5.47	5.62
0.14	7.24	7.20	6.72	6.83
0.20	8.15	8.31	8.08	8.04

[a] Buffer ratio = 1.0, ionic strength = 0.2 ($NaClO_4$). [b] Calculated from eq 2, using catalytic constants in Table II.

Table IV. Effect of Solvent on the Acetic Acid Catalyzed Cleavage of *o*-Hydroxylamino-*N,N*-dimethylbenzamide at 25°C

Solvent	$[CH_3CO_2H] = 1.0\ M$ 10^3k_e, sec^{-1}
Acetonitrile	0.92
Dioxane	1.00
Ether	1.58
Benzene	3.06
Carbon tetrachloride	2.99
Water	~0.8[a]

[a] Estimated from the results for chloroacetic and formic acids as catalysts (Table II).

where A refers to formic or chloroacetic acid. The catalytic constants for the acids are listed in Table II. Values of k_0 and K_{H^+} obtained in dilute hydrochloric acid solutions are also listed for comparison. In Table III, the observed constants (k_e) for the cleavage reactions in the buffer solutions are given, together with values calculated from eq 2, using the catalytic constants shown in Table II.

Reactions in Nonaqueous Solvents. The rate of displacement of *N,N*-dimethylamine from its *o*-hydroxylaminobenzamide was measured in acetonitrile solutions of acetic, monochloroacetic, dichloroacetic, and trichloroacetic acids. In all cases, the rate law was of the form shown in eq 1. At low acid concentrations, the first-order rate constant was approximately proportional to the acid concentration ($k_e = k_A[A]$) but leveled off at higher acid concentrations (see Figure 1). Values of k_A (obtained from initial slopes of k_e against [A]) for acetic and mono-, di-, and trichloroacetic acids were 2.09×10^{-3}, 4.35×10^{-3}, 15.9×10^{-3}, and 124×10^{-3} $mol^{-1}\ dm^3\ sec^{-1}$, respectively.

The effect of several solvents of varying polarity on the acetic acid catalyzed reaction was also investigated. Table IV lists values of k_e obtained in the various solvents. A relatively fast reaction was also found in tetrahydrofuran, but the observed spectral changes were not consistent with the production of benzisoxazolinone. The reaction was not investigated further.

Discussion

The effectiveness of the *o*-hydroxylamino group in promoting the liberation of amines from their *o*-hydroxylaminobenzamides in aqueous acid solution may be seen from the results in Tables I–III. Thus in 1 *M* $HClO_4$, the cleavage of the *N,N*-dimethylamide ($t_{1/2} \sim 12$ sec) occurs some

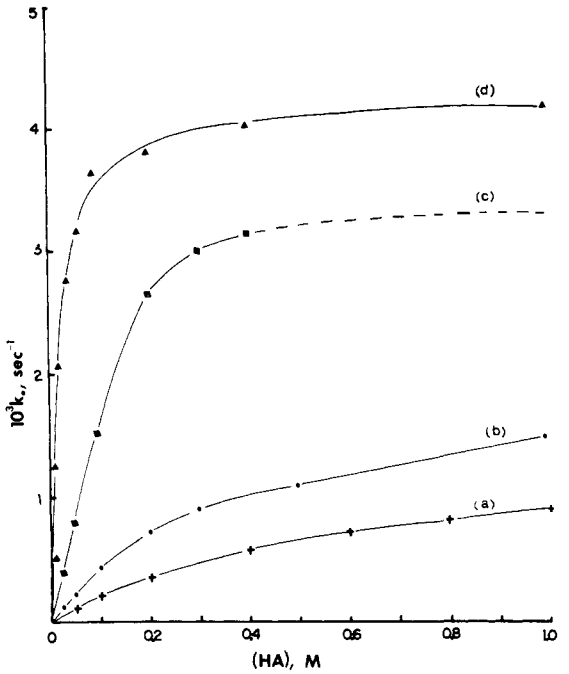


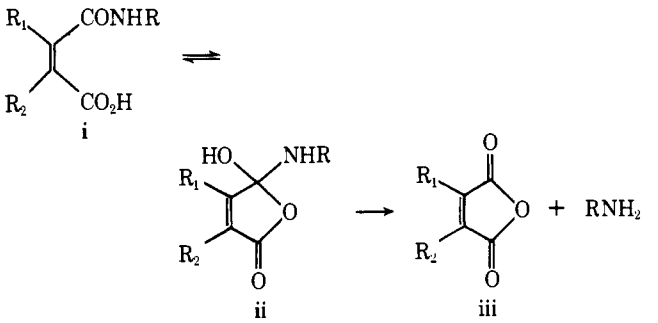
Figure 1. Carboxylic acid catalysis of the displacement of *N,N*-dimethylamine from *o*-hydroxylamino-*N,N*-dimethylbenzamide in acetonitrile: (a) acetic acid; (b) chloroacetic acid; (c) dichloroacetic acid; (d) trichloroacetic acid.

10^5–10^6 times more rapidly than the hydrolysis of the unsubstituted *N,N*-dimethylbenzamides[4] and ca. 10^2 times more rapidly than that of the *o*-carboxy derivative (phthalamic acid).[5] The lower reactivity of the *N*-methylamide parallels behavior observed earlier in the hydrolysis of benzamides[4,6] and acetamides[7] (for both of these series of amides, the order of reactivity toward hydrolysis is amide > *N,N*-dimethylamide > *N*-methylamide). This difference in reactivity has not been satisfactorily explained, and indeed no such difference exists for the corresponding anilides (Table I).

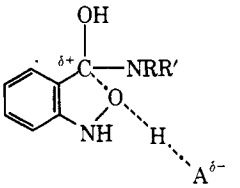
Of considerably more importance from a synthetic point of view, however, and perhaps of more interest mechanistically, is the ease with which the general acid catalyzed cleavage occurs in a variety of nonaqueous solvents (Table IV and Figure 1). Thus with 1 *M* acetic acid as catalyst, half-lives for the cleavage of 25°C vary from 12 min in acetonitrile to 4 min in benzene. In the Experimental Section, illustrative conditions are given for the almost quantitative recovery of *N*-methylaniline from its *o*-nitrobenzanilide, and similar results were achieved for *N,N*-diphenylamine. The reaction is particularly convenient for the catalyzing acid, and the other product (benzisoxazolinone, pK_a = 7.63[1]) can be simply removed by washing with Na_2CO_3 solution. It is clear from the results in Table IV that a wide variety of solvents can be used, thus reducing any problems concerning solubility of the amides. The recovery of amines containing other functional groups sensitive to acid and base hydrolysis is currently under investigation.

Resolution of the mechanism of the cleavage reaction is not a simple problem. Kirby and coworkers[8] have recently discussed the intramolecular catalyzed hydrolysis of substituted maleamic acids according to Scheme II (giving the anhydride iii which is rapidly hydrolyzed to the dicarboxylic acid). With $R_1 = R_2 = i$-Pr, the reactions exhibit general acid catalysis, this being attributed to catalysis of the breakdown of the tetrahedral intermediate (ii), with preequilibrium cyclization of i to ii. For the cleavage of the *o*-hydroxylaminobenzamides in aqueous acid solution, a sequence analogous to conversions i → iii of Scheme II could be written and again the observed catalysis could result from assistance in the breakdown of the tetrahedral intermediate to give products. An alternative hypothesis for this reaction (and the hydrolysis of maleamic acids) is that the formation of the tetrahedral intermediate is general acid catalyzed, with the rate-determining step being a reaction between the protonated substrate (formed in a rapid preequilibrium step) and the anion of the catalyzing acid (i.e., via II for the *o*-hydroxylamino derivatives). It is difficult to

Scheme II

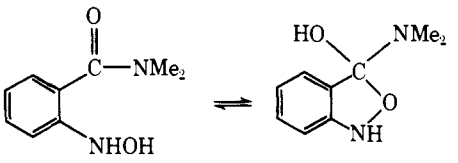


i ii iii



II

distinguish between these possibilities. However, it is possible to set an upper limit to the rate (in the absence of added acid) of any reversible or preequilibrium cyclization of *N,N*-dimethyl-*o*-hydroxylaminobenzamide to give a tetrahedral intermediate (III ⇌ IV) by noting that the NMR

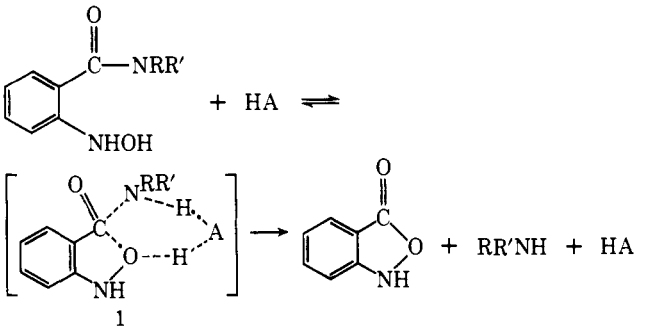


III IV

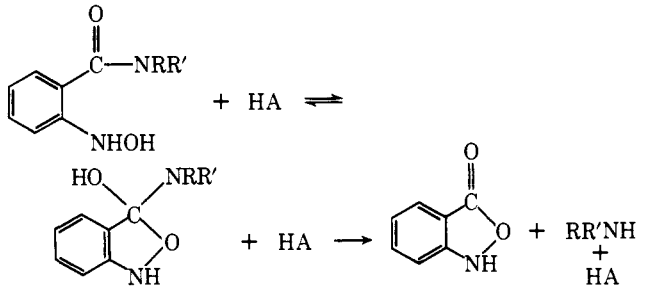
spectrum of the amide in D_2O shows the two *N*-methyl groups to be nonequivalent (see Experimental Section). This may be attributed to restricted rotation about the C–N bond of the amide[9,10] and, as reversible cyclization of the amide (III ⇌ IV), would provide a mechanism for rotation about the C–N bond; the absence of even any observable broadening of the two *N*-methyl singlets of III puts a limit of ca. 1 sec^{-1} for this exchange process (this being estimated[11] from the chemical shift difference of the two methyl signals). In view of the fact that rate constants for the overall cleavage reaction in aqueous acid solution as high as 0.7 sec^{-1} were observed (Table I), it seems unlikely that this reaction involves an uncatalyzed preequilibrium cyclization to a tetrahedral intermediate as has been suggested for the corresponding reactions of maleamic acids (Scheme II).[8] NMR studies on *N,N*-dimethylmaleamic acids might provide additional evidence relevant to the mechanism of their hydrolyses.

It is noticeable that the rates of cleavage of each of the *o*-hydroxylaminoamides pass through a maximum with increasing concentration of perchloric acid. This can be readily explained qualitatively in terms of competing equilibrium protonation of the amide group and the hydroxylamino group (it has been shown that RN^+H_2OH, where R is an

Scheme III



Scheme IV



o-ethylbenzoate group, has $pK_a = 0.6$).[1] Any quantitative interpretation is difficult, however, because of the high ionic strengths of the solutions in regions where maximum rates are observed.

The magnitudes of the acetic acid catalyzed reactions in the various nonaqueous solvents (Table IV) call for special comment. Since both the catalyst and substrates are uncharged, any mechanism involving the transfer of a proton will involve considerable change separation and would be expected to be considerably retarded in low dielectric, nonpolar solvents. For example, the equilibrium constant for the reaction $C_6H_5NH_2^+$ $CH_3CO_2H \rightleftharpoons C_6H_5NH_3^+ + CH_3CO_2^-$ is smaller by a factor of 10^{12} in acetonitrile than in water,[12] acetic acid having a pK_a of 22.4 in acetonitrile,[13] and the effect would be even larger in solvents such as benzene and carbon tetrachloride. It can be shown in fact that any mechanisms involving preequilibrium proton transfer from HA, followed by a rate-determining reaction between A^- and the protonated substrate (SH^+), can be ruled out as they would require impossibly high rates of reaction between A^- and SH^+ (similar problems concerning the mechanism of the acid catalyzed hydration of aldehydes and ketones have recently been extensively discussed).[14] This suggests that the reactions must occur via a one encounter mechanism such as shown in Scheme III. The transition state 1 depicted in Scheme III should not be taken to imply that the various proton transfer and bond making and breaking steps occur synchronously as these may occur in a stepwise fashion (involving a series of ion pairs). It is also possible that the reaction occurs in two steps via a tetrahedral intermediate as in Scheme IV, with catalysis of both the formation and breakdown of the tetrahedral intermediate occurring by a one encounter mechanism.

Finally, the results in Figure 1 show that, as expected, the effectiveness of the carboxylic acids as catalysts increases with increasing strength of the acid. However, both the relative rates in solutions of the various acids and the variation of rate with acid concentration for a given acid catalyst will be severely affected by H-bonded association of the acids, dimerization constants for acetic acid, for example, being much higher than those for trichloroacetic acid.[15]

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References and Notes

(1) B. G. Cox, D. McL. A. Grieve, and A. E. A. Porter, *J. Chem. Soc., Perkin Trans. 2*, submitted for publication.
(2) D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 599 (1973).
(3) T. Cohen and W. F. Gray, *J. Org. Chem.*, **37**, 741 (1972).
(4) C. A. Bunton, S. J. Farber, A. J. G. Millbank, C. J. O'Connor, and T. A. Turney, *J. Chem. Soc., Perkin Trans. 2*, 1869 (1972).
(5) M. L. Bender, Y.-L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).
(6) C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, **93**, 6578 (1971).
(7) P. D. Bolton, *Aust. J. Chem.*, **19**, 1013 (1966).
(8) M. F. Aldersley, A. J. Kirby, P. W. Lancaster, R. S. McDonald, and C. R. Smith, *J. Chem. Soc., Perkin Tran. 2*, 1487, 1495 (1974).
(9) G. Fraenkel and C. Franconi, *J. Am. Chem. Soc.*, **82**, 4478 (1960).
(10) B. G. Cox, *J. Chem. Soc. B*, 1780 (1970).
(11) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, N.Y., 1959, Chapter 10.
(12) B. G. Cox, *Annu. Rep. Prog. Chem. Sect. A*, **70**, 249 (1973).
(13) M. K. Chantooni and I. M. Kolthoff, *J. Phys. Chem.*, **77**, 527 (1973).
(14) R. P. Bell and J. E. Critchelow, *Proc. R. Soc. London, Ser. A*, **325**, 33 (1971), and references therein.
(15) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond", Freeman and Co., London, 1960.