Reactions of Nitroanisoles. Part 6.[1] Reaction of 2,6-Dinitroanisole with Cyclohexylamine in Mixed Solvents. Solvent Evidence for the 'Dimer' Mechanism

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The reaction of 2,6-dinitroanisole with cyclohexylamine in methanol and benzene–methanol was studied at several amine concentrations. Although the reaction rate in methanol is higher than in benzene, addition of small amounts of methanol to the benzene solution diminishes the rate of reaction (which is of third order in amine), reaching a minimum value at nearly 30% methanol, after which the rate increases almost linearly with the methanol content. These and other results, here described, are satisfactorily explained by a previously proposed reaction scheme, in which the dimer of the amine is operating.

It is well established that the solvent considerably modifies chemical equilibria[2] and reactivity.[3] In aromatic nucleophilic substitution (ANS) interactions of the reagents and or the intermediate/s with the solvent molecules may be extensive and complex and some of them have been reckoned in previous solvent studies on ANS.[4-9] When the mechanism of the reaction is a simple two-step process, as originally proposed[10] and nowadays widely accepted,[11] the aprotic solvent effects are well correlated by the Reichardt equation.[12] Although the influence of the solvent on the relative importance of the base-catalysed pathway has long been known[13,14] no systematic study of the solvent effect on base (or amine) catalysis has been carried out.[15] When the reaction is run in protic solvents the detailed mechanisms seem firmly established after the work by Bernasconi *et al.*[16] (although some doubt on the rate-limiting proton-transfer interpretation has recently been cast)[17] but for reactions in aprotic solvents the situation is still unclear[16a] and subject to controversy.[7,9,18]

We have recently reported an unusual third-order amine rate dependence for the reactions of 2,4- and 2,6-dinitroanisole with butylamine and cyclohexylamine in benzene and cyclohexane[19] and of 2,4-dinitrofluorobenzene with *o*-anisidine in benzene.[20] We have interpreted this finding as a result of amine association (dimer, B:B) in the aprotic solvents used [equation (1)]. Since amines are known to associate with protic solvents, it was therefore of critical importance to determine the effect of the addition of defined amounts of a protic solvent to the reaction media.

The present paper reports the effect of adding increasing amounts of methanol (ranging from 4 to 100%, v/v) to the benzene medium of the reaction of 2,6-dinitroanisole (**I**) with cyclohexylamine. The observed effects are consistent with the existence of amine aggregates and their importance in determining the reaction rates.

Results and Discussion

The specific second-order rate coefficients, k_A, for the reaction of (**I**) with cyclohexylamine at several amine concentrations in pure methanol at 45 °C are gathered in Table 1. The reactions were carried out under pseudo-first-order conditions and only one reaction product, *N*-(2,6-dinitrophenyl)cyclohexylamine (**II**), was formed. All runs afforded linear plots of $\ln(A_\infty - A_t)$ *versus* time; k_ψ values were reckoned as the slope calculated by the least-squares method and the second-order rate coefficients, k_A, were obtained by dividing k_ψ by the amine concentration.

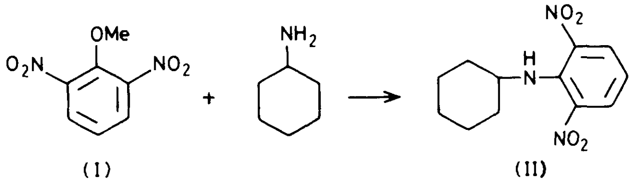


Table 1. Kinetics of the reaction of 2,6-dinitroanisole (I) with cyclohexylamine (CHA) in methanol at 45 °C[a]

[CHA]/M	10^5k_A/l mol^{-1} s^{-1}
0.050	14.7
0.100	27.8
0.150	37.8
0.200	45.9
0.300	51.1
0.350	57.8
0.400	58.2

[a] [(I)] *ca.* 1.7—2.2 × 10^{-4}M.

Almost a four-fold increase in the rate coefficient, k_A, is observed for an eight-fold increase in the amine concentration. When k_A is plotted against the cyclohexylamine concentration (not shown) a downward curve is obtained with the typical shape observed for base catalysis.[11] The practically nil intercept suggests that uncatalysed decomposition of the zwitterionic intermediate is negligible. In principle, the catalyst may be either the amine or the methoxide ion from solvolysis of cyclohexylamine.[21] Since in the reaction of 2,4-dinitroanisole with cyclohexylamine in methanol[22] no base catalysis is observed, and, as the catalytic effect increases with methanol concentration, it is reasonable to assume that the catalytic effect shown in Table 1 is mainly due to the methoxide ion. This conclusion is also in agreement with previous findings of methoxide catalysis in the reaction of 2,4-dinitroanisole with piperidine in methanol.[23] Since the pK_a of cyclohexylamine in methanol[21] is smaller than that of piperidine[24] it is reasonable to assume weaker base-catalytic power for cyclohexylamine.

Table 2 gathers the specific second-order rate coefficients for the reaction of (**I**) with cyclohexylamine in benzene–methanol at different amine concentrations at 45 °C. In all cases the main reaction product is (**II**) and only in the slowest reaction was the formation of 2,6-dinitrophenol, arising from a parallel S_N2 breakdown of (**I**), detected. Although this side-reaction is not very important it has been taken into account to compute the ANS coefficients, k_A.

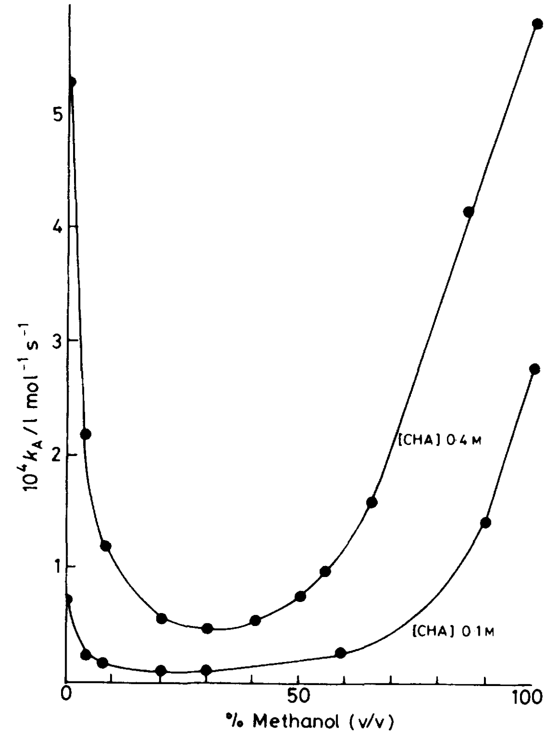


Figure 1. Reaction of 2,6-dinitroanisole with cyclohexylamine (CHA) in benzene–methanol mixtures at 45 °C

Table 2. Kinetics of the reaction of 2,6-dinitroanisole (**I**) with cyclohexylamine (CHA) in benzene–methanol mixtures at 45 °C[a]

[CHA]/M	% Methanol[b]	$10^5 k_A$/l mol^{-1} s^{-1}
0.400	0	52.7[c]
	4	21.6
	8	11.9
	20	5.4[d]
	30	4.8[d]
	40	5.4[d]
	50	7.7
	55.4	10.4
	65.4	16.3
	85.4	41.7
0.100	0	7.8[c]
	4	2.3[d]
	8	1.7[d]
	20	1.0[d]
	30	1.0[d]
	59	2.8[d]
	89	14.3
0.150	4	3.9[d]
0.200	4	6.1[d]
0.500	4	32.6
0.200	30	2.0[d]
0.500	30	6.6[d]

[a] [(I)] *ca.* 1.7—2.2 × 10^{-4}M. [b] v/v. [c] From ref. 19. [d] k_{S_N2} *ca.* 0.2 × 10^{-5} l mol^{-1} s^{-1}

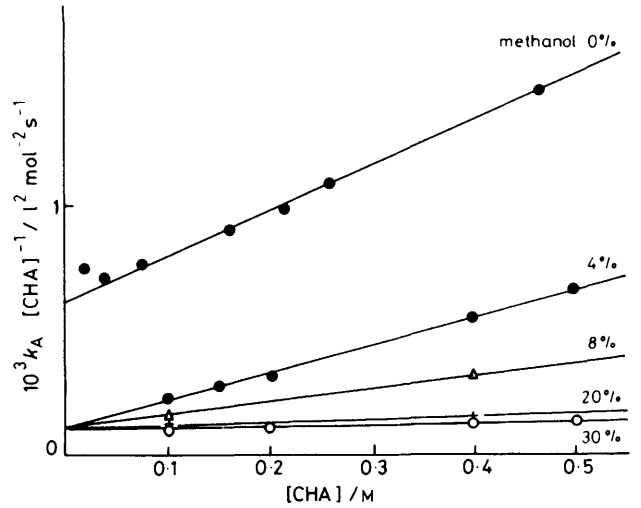


Figure 2. Reaction of 2,6-dinitroanisole with cyclohexylamine (CHA) in benzene–methanol mixtures at 45 °C

As Figure 1 shows, although the reaction in pure methanol is slightly faster than in benzene, addition of a small amount of methanol to benzene produces an important decrease in the reaction rate which reaches a minimum at nearly 30% methanol. For mixtures richer in methanol the reaction rate begins to increase, and does so sharply at higher methanol content.

We interpret this effect as a result of competition between self-association of the cyclohexylamine and the amine–methanol aggregates. It is known that amines in alcoholic solutions are associated with the solvent through R–OH ··· NHR$_2$ bonds, where the alcohol acts as a proton donor,[25] while in non-polar aprotic solvents self-association of the amine molecules is a well established phenomenon.[26]

In pure benzene, we observed third-order dependence of k_A on the amine concentration[19] which can be interpreted as derived from a mechanism where the dimer of the cyclohexylamine (B:B) acts as nucleophile forming an intermediate complex SB$_2$ [equation (1) where S stands for the substrate and P for the product]. From this mechanism the kinetic equation (2) can be derived, where K is the approximate amine dimerization constant ($K = [\mathrm{B{:}B}]/[\mathrm{B}]_0^{\,2}$). Usually, in the reactions of amines with nitroanisoles the second step is rate determining, the inequality $k_{-1} \gg (k_2 + k_3[\mathrm{B}])$ holds, and equation (2) can be further simplified to (3).

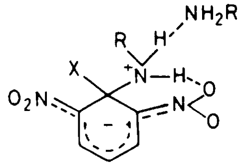
$$\mathrm{S} + \mathrm{B{:}B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\mathrm{SB}_2] \xrightarrow[k_3[\mathrm{B}]]{k_2} \mathrm{P} \qquad (1)$$

$$k_A = \frac{k_1k_2K[\mathrm{B}] + k_1k_3K[\mathrm{B}]^2}{k_{-1} + k_2 + k_3[\mathrm{B}]} \qquad (2)$$

$$\frac{k_A}{[\mathrm{B}]} = \frac{k_1k_2K}{k_{-1}} + \frac{k_1k_3K}{k_{-1}}[\mathrm{B}] \qquad (3)$$

This equation fits the present results which show third-order dependence on the amine concentration for the rate of reaction in benzene and in mixed benzene–methanol solvents of low methanol contents (Figure 2).

Although we first wrote a cyclic structure[19b] for intermediate SB$_2$ according to the original Capon & Rees proposal[27] it is probable that structure (**III**) is a better representation for this



(III)

intermediate since aliphatic amines are known to form non-cyclic trimers.[28] This has been demonstrated for butylamine, among other aliphatic amines, and it is reasonable to assume that the same will be true for cyclohexylamine too. Additional conceptual difficulties inherent to the cyclic intermediate have been previously recognized[7a] and similar cyclic intermediates have been also precluded in aminolysis of esters.[29]

Structure (**III**) circumvents these difficulties and makes clearer the role of the third molecule of amine: because of the inability of non-polar aprotic solvents to stabilize ionic species the third molecule of amine should form a homoconjugated acid BH^+B by proton transfer from intermediate (**III**) and the electrophilically catalysed departure of the nucleofugue could be, at least partially, due to BH^+B. A rather similar treatment of the electrophilic catalysis step has recently been proposed by Hirst *et al.*[18] to explain their and Bernasconi and Zollinger's[30] anomalous results in benzene, as an alternative explanation of a 'medium effect'.

Catalysis by the dimer of the amine has been also recently proposed by Nagy *et al.*[31] to explain the rate constants of the reaction of tetrachloro-*N*-n-butylphthalimide with n-butylamine in a quantitative evaluation of solute–solvent interactions.

Although our present kinetic results do not allow distinction between $S + B{:}B \rightleftharpoons [SB_2] \xrightarrow{+B} P$ and $S + B \rightleftharpoons [SB]^* \xrightarrow{+B:B} P$ and even with a third sequence $S + B \rightleftharpoons [SB] \overset{+B}{\rightleftharpoons} [SBB] \xrightarrow{+B} P$ nor give information about the structures of intermediates and transition states involved, we prefer the first sequence for the following reasons.

(1) In some reactions of 2,4-dinitroanisole in aprotic solvents[19] a 'plateau' is observed at high amine concentrations in the plot of $k_A/[B]$ *versus* [B]. This behaviour can be explained by the first sequence but not by the last two.

(2) To our knowledge no specific study of the structure of the cyclohexylamine–methanol aggregate in benzene has been done; as a model one can use the 1:1 hydrate formed by cyclohexylamine in water–benzene and Gregory *et al.*[32] have shown that no hydrates of polymeric amines are present in significant amounts. The difference between the observed and computed dipole moment of the complex (0.4 D)[32b] was ascribed to charge separation as previously proposed by several authors for complexes between an amine and a proton donor.[33,34] The dielectric measurements are also consistent with the inferred geometry and charge distribution of cyclohexylamine–water complex.[32]

In addition, it is known that $R{-}OH \cdots NHR_2$ interactions are stronger than those of the type $NH \cdots N$,[25,35,36] in agreement with *ab initio* theoretical calculations carried out on $NH_3 \cdots NH_3$[37] and $CH_3OH \cdots NH_3$[38] complexes. Finally, Sinsheimer *et al.*[39] have demonstrated that in dilute solution (*e.g.* 0.16% cyclohexylamine) amine–amine hydrogen bonding is vulnerable to solvent hydrogen-bonding even with aprotic solvents such as acetonitrile and nitromethane.

From all the above considerations it is reasonable to assume that the amine–amine dimer concentration will diminish when methanol is added to a benzene solution of the amine. It has been shown that the $ROH \cdots NHR_2$ association depresses the nucleophilicity of the reagent because of the reduced charge density on the nitrogen atom.[38] Then, if the dimer mechanism depicted in equation (1) is operating, a diminution in the reaction rate is expected on addition of methanol to the aprotic solvent as observed in Figure 1.

(3) It can be observed in Figure 2 that linearization of the amine profiles could be achieved when k_A divided by [cyclohexylamine] was plotted against the [amine], showing that the third-order rate dependence is also observed in low-methanol-content media. The slope and intercept decreases with the increase in methanol content are easily understood as a decrease in the concentration of the dimer of the amine and satisfactorily explained by equation (3). The diminution in the slope is due to a continuous diminution in the self-association constant of the amine *K* (by competition with amine–solvent interactions) to be practically nil at 30% methanol. Since the importance of the dimer decreases with continuous methanol additions the intercept diminishes to reach an almost constant value which measures the rate of monomer attack which is the only operative mechanism for methanol contents near 30% or higher [equation (4)].

$$S + B \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} [SB] \xrightarrow{k_5[B]} P \qquad (4)$$

The increase in rate for a methanol content >30% is explained by equation (5), where the second-order term in base also includes the new base present in the media (CH_3O^-). As shown before, its concentration at the amine concentrations used is not negligible and methoxide is an effective base catalyst.

$$k_A = \frac{k_4 k_5 [B]}{k_{-4} + k_5 [B]} \qquad (5)$$

(4) If base-catalysed breakdown of intermediate SB were the only rate-determining step, the rate should increase from the beginning of the addition of methanol when a greater catalyst, the methoxide ion, replaces the amine molecules, as found in the reaction of 2,4-dinitrofluorobenzene with piperidine in benzene for which addition of methanol produces an increase in the rate.[40] In contrast, in the reaction of 2,4-dinitrochlorobenzene (which is not piperidine catalysed) the rate is continuously slowed down by small additions of methanol and this diminution was referred to hydrogen-bond associate formation between methanol and piperidine.[40]

Finally, it would be worth mentioning that the mechanism depicted in equation (1) should be only observable for ANS on a poor nucleofugue and in aprotic solvents of low polarity.

A recent paper by Banjoko and Ezeani[41] describes the reactions of 2,4,6-trinitrophenyl phenyl ether with several substituted anilines in benzene. Their kinetic observations were rather similar to the ones described here and in preceding papers.[19,20] The reactions are third order in nucleophile and the energies of activation are either negligible or negative. Nevertheless, the mechanism they proposed does not explain the present and previous results.[19,20] Conversely, the dimer mechanism explains Banjoko's results, and the changes in the energy of activation and the substituent effects are easily understood upon taking into account the equilibrium $2\,B \rightleftharpoons B{:}B$.

Conclusions.—This and recently published papers provide evidence for the existence of a 'dimer' of the nucleophile in ANS

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* SB represents the classical zwitterionic intermediate.

by amines in aprotic, low-polarity solvents. The incidence of the dimer on the formation or breakdown of the zwitterionic intermediate formed in the first step should explain the third-order rate dependence observed for several reactions in aprotic solvents. Rate-determining departure of the nucleofugue should be a prerequisite for the observation of the dimer mechanism.

Experimental

Materials—Anhydrous methanol was prepared by Lund and Bjerrum's method.[42] Benzene, cyclohexylamine, and 2,6-dinitrophenol were purified as previously described.[19b] 2,6-Dinitroanisole, m.p. 117—118 °C, and *N*-(2,6-dinitrophenyl)-cyclohexylamine, m.p. 77.5—78 °C, were prepared as already reported.[19b]

Kinetic Procedures.—The reactions were studied spectrophotometrically at 426 nm in a Beckman DU 2 spectrophotometer. In the reactions in mixed solvents the methanol content (v/v) is referred to the final volume of the reaction mixtures. In all the cases pseudo-first-order kinetics were observed. In mixed solvents, 4—59% methanol (see Table 2), a parallel demethylation reaction takes place yielding 2,6-dinitrophenol. The ratio of dinitrophenol to **(II)**, *R*, was determined by measuring the optical density of the reaction mixtures at 'infinity' time in benzene and in quenching solution (ethanol–HCl; 9 : 1, v/v). Only in the zone of minimum values of k_A, and for low amine concentration [B], has the ratio *R* a moderate value (at [B] 0.1M, *R* 0.16 and at [B] 0.2M, *R* 0.10; in 20—30% methanol); for all other runs of Table 2 the S_N2 reaction is negligible ($R \leqslant 0.05$). The reported second-order rate coefficients, k_A, were calculated by the least-squares method as previously described.[19]

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References

1 Part 5, N. S. Nudelman and D. Palleros, *J. Chem. Soc., Perkin Trans. 2*, to be submitted.
2 J. Hine, 'Structural Effects on Equilibria in Organic Chemistry,' Wiley, New York, 1975.
3 (*a*) C. Reichardt, 'Solvent Effects in Organic Chemistry,' Verlag Chemie, Weinheim, 1979; (*b*) E. S. Amis, 'Solvent Effects on Reaction Rates and Mechanisms,' Academic Press, New York, 1965.
4 J. F. Bunnett and R. J. Morath, *J. Am. Chem. Soc.*, 1955, **77**, 5051.
5 (*a*) N. S. Nudelman and J. A. Brieux, *An. Asoc. Quim. Arg.*, 1970, **58**, 207; (*b*) N. S. Nudelman and J. A. Brieux, *ibid.*, p. 217.
6 J. Kavalek and V. Sterba, *Collect Czech. Chem. Commun.*, 1973, **38**, 884.
7 (*a*) D. Ayediran, T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1977, 597; (*b*) D. Ayediran, T. O. Bamkole, J. Hirst, and I. Onyido, *ibid.*, p. 1580.
8 H. W. Lee and I. Lee, *J. Korean Chem. Soc.*, 1978, **22**, 7, 221.
9 (*a*) O. Banjoko and P. Otiono, *J. Chem. Soc., Perkin Trans. 2*, 1981, 339; (*b*) O. Banjoko and K. Ur-Rahman, *ibid.*, p. 1105.
10 J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.
11 For recent reviews see: (*a*) N. S. Nudelman, *An. Acad. Nac. Cs. Ex. Fis. Nat., Buenos Aires*, 1980, **32**, 109; (*b*) C. F. Bernasconi, MTP International Rev. Sci. Aromatic Compounds, Org. Chem. Series One, ed. H. Zollinger, Butterworths, London, 1973, vol. 3, p. 330.
12 P. M. Mancini, R. D. Martinez, L. R. Vottero, and N. S. Nudelman, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1133.
13 N. S. Nudelman, T. H. Suárez, and J. A. Brieux, *Chem. Ind. (London)*, 1964, 1754.
14 J. F. Bunnett and C. F. Bernasconi, (*a*) *J. Am. Chem. Soc.*, 1965, **87**, 5209; (*b*) *J. Org. Chem.*, 1970, **35**, 70.
15 R. D. Martinez, P. M. E. Mancini, L. R. Vottero, and N. S. Nudelman, forthcoming paper.
16 (*a*) C. F. Bernasconi, R. H. de Rossi, and P. Schmid, *J. Am. Chem. Soc.*, 1977, **99**, 4090; (*b*) C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, *ibid.*, 1976, **98**, 845.
17 J. F. Bunnett and A. V. Cartaño, *J. Am. Chem. Soc.*, 1981, **103**, 4861.
18 T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1982, 889.
19 (*a*) N. S. Nudelman and D. Palleros, *Acta Sudamer. Quim.*, 1981, **1**, 125; (*b*) N. S. Nudelman and D. Palleros, *J. Org. Chem.*, in the press.
20 N. S. Nudelman and D. Palleros, *J. Org. Chem.*, in the press.
21 N. S. Nudelman, *An. Asoc. Quim. Arg.*, 1978, **66**, 89.
22 N. S. Nudelman and D. Garrido, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1256.
23 J. F. Bunnett and R. H. Garst, *J. Org. Chem.*, 1968, **33**, 2320.
24 I. M. Kolthoff and L. S. Guss, *J. Am. Chem. Soc.*, 1939, **61**, 330.
25 F. Ratkonics and T. Salamon, *Acta Chim. Acad. Sci. Hung.*, 1977, **94**, 93.
26 (*a*) S. D. Prahan and H. B. Mathews, *Proc. Indian Acad. Sci., Sect. A*, 1978, **87**, 23; (*b*) J. A. Pople, H. J. Berstein, and W. G. Schneider, 'High Resolution NMR,' McGraw-Hill, New York, 1969; (*c*) G. Pannetier and L. Abello, *Bull. Soc. Chim. Fr.*, 1966, 1645; (*d*) M. Ker, B. Servais, L. Abello, and G. Pannetier, *ibid.*, 1968, 2763; (*e*) J. L. Mateos, R. Cetina, and O. Chao, *Chem. Commun.*, 1965, 519.
27 B. Capon and C. W. Rees, *Annu. Rep. Prog. Chem.*, 1963, **60**, 278.
28 J. C. Schug and W. M. Chang, *J. Phys. Chem.*, 1971, **75**, 938.
29 F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824.
30 C. F. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, 1966, **49**, 2570.
31 O. B. Nagy, M. wa Muanda, and J. B. Nagy, *J. Phys. Chem.*, 1979, **83**, 1961.
32 (*a*) M. D. Gregory, S. D. Christian, and H. E. Affsprung, *J. Phys. Chem.*, 1967, **71**, 2283; (*b*) M. D. Gregory, H. E. Affsprung, and S. D. Christian, *ibid.*, 1968, **72**, 1748.
33 T. Zeegers-Huyskens, *Spectrochim. Acta*, 1965, **21**, 221.
34 G. C. Pimentel and C. H. Sederholm, *J. Chem. Phys.*, 1956, **24**, 639.
35 M. K. D. Choudhury and H. B. Mathur, *Indian J. Chem., Sect. A*, 1976, **14**, 735.
36 G. Pimentel and A. McClellan, 'The Hydrogen Bond,' Freeman, New York, 1960, p. 360.
37 P. A. Kollman and L. C. Allen, *J. Am. Chem. Soc.*, 1971, **93**, 4991.
38 J. E. del Bene, *J. Am. Chem. Soc.*, 1973, **95**, 5460.
39 J. E. Sinsheimer and A. M. Keuhnelian, *Anal. Chem.*, 1974, **46**, 89.
40 C. F. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, 1966, **49**, 103.
41 O. Banjoko and C. Ezeani, *J. Chem. Soc., Perkin Trans. 2*, 1982, 1356.
42 A. I. Vogel, 'Practical Organic Chemistry,' Longman, London, 1972.

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