Acta Chemica Scandinavica A 30 (1976) 1—7

Hexamethylphosphoramide as Proton Acceptor. Part 1. A Near-infrared Study of Its Heteroassociation with Ordinary and Halogenated Alcohols

RITVA KUOPIO,[a] ANTTI KIVINEN[a] and JUHANI MURTO[b]

[a] Department of Pharmacy, University of Helsinki, Fabianinkatu 35, SF-00170 Helsinki 17, Finland and [b] Department of Physical Chemistry, University of Helsinki, Meritullinkatu 1 C, SF-00170 Helsinki 17, Finland

Values of the formation constants K_{11}, frequency shifts $\Delta\nu$OH and thermodynamic parameters ΔH, ΔG and ΔS have been determined by near-infrared spectrometry for the hydrogen-bonded 1:1 alcohol-base complexes formed between fifteen ordinary or halogenated alcohols and hexamethylphosphoramide and for the phenol-hexamethylphosphoramide complex in carbon tetrachloride solutions.

The pK_a values of the alcohols studied vary from about 19 to about 5, the most acidic alcohols being the two perhalogenated *t*-butyl alcohols. The spectrometric quantities K_{11}, ΔH and $\Delta\nu$OH vary almost linearly with the acidity of the alcohols, although the slopes for ordinary and for halogenated alcohols are slightly different. The complexation entropies for the different alcohol-base pairs are quite similar in magnitude, *i.e.*, the systems are essentially isoentropic. The frequency shifts vary with temperature. The Badger-Bauer relation holds with a few small deviations. In the case of the most acidic alcohols and the phenol there are several hydrogen-bonded OH absorption peaks, probably due to the interaction of νOH(bonded) vibrations with overtones or combinations of lower frequency vibrations.

Hexamethylphosphoramide, $[(CH_3)_2N]_3PO$ (HMPA), is a dipolar, aprotic solvent with excellent solvent properties.[1-4] In addition, HMPA has some interesting biological properties, which are not so widely known as its excellent solvent properties. HMPA has been considered as possibly the most suitable model compound for the study of certain anticancer (cytostatic) drugs and the general mechanism of chemosterilation.[5-8] The acute [9] as well as the chronic [10] toxicity of HMPA seems to be low.

The importance of hydrogen bonding in biological systems is nowadays generally recognized.[11,12] In addition to the carbonyl group, also the P=O group is a very efficient proton acceptor in these systems. The experimental data on the P=O group are still meagre, however. In this paper we wish to report the results obtained for the hydrogen bonding between HMPA and various alcohols and phenol, special attention being directed to the effects of the acidity and steric factors of alcohols and phenol.

EXPERIMENTAL

Chemicals. Hexamethylphosphoramide (zur Synthese, E. Merck AG) was refluxed under vacuum over CaO for about 20 h, decanted and distilled, b.p. 80 °C/2 mmHg. HMPA was stored over molecular sieves 4Å. Hexamethylphosphoramide-d_{18} [octadecadeuteriohexamethylphosphoramide, HMPA-d_{18}, $[(CD_3)_2N]_3PO$ (Uvasol, E. Merck AG)] was used as received. It was stored under nitrogen.

2,2,2-Tribromoethanol (*purum*, Fluka AG) and 1,1,1,3,3,3-hexachloro-2-propanol (Hynes Chemical Research Corp.) were crystallized from hexane. 2,2,2-Trichloroethanol (*purum*, Fluka AG) was distilled under vacuum, b.p. 87 °C/2 mmHg. 1,1,1-Trichloro-2-methyl-2-propanol (Ph. Nordica quality) contained about 5 % water, which was distilled away, after which the alcohol was sublimed at ordinary pressure. All other alcohols were purified as described previously.[13-17] The liquid alcohols were stored over molecular sieves 3A (methanol

Table 1. Spectral data for 1:1 hydrogen-bonded complexes between alcohols or phenol and HMPA in carbon tetrachloride at 25 °C and the pK_a values [16–22] of alcohols and phenol.

Alcohol [a] (Phenol)	K_{11} / M^{-1}	$-\Delta H°$ / kJ mol^{-1}	$\Delta\nu$ / cm^{-1}	pK_a	From literature $-\Delta H°$ / kJ mol^{-1}	From literature $\Delta\nu$ / cm^{-1}	
1 MeOH	39.0	22.8	275	15.09			
2 EtOH	30.5	19.8	271	15.93			
3 i-PrOH	21.2	19.0	263	17.1			
4 *t*-BuOH	16.0	17.6	252	> 19	23.8 [c]		
5 3-MP	9.77	17.2	242				
6 TBE	289	24.9	393	12.70			
7 TCE	406	26.1	396	12.25			
8 TFE	1230	34.2	394	12.39	32.1 [d]	405 [e]	
9 HCP	3960	33.5	> 553 [b]				
10 HFP	23600	37.3	> 519 [b]	9.3	41.4 [f]	540 [f]	
11 TCTB	64.8	21.3	357				
12 TFTB	199	24.8	372				
13 HFTB	4640	31.2	> 502 [b]	9.6			
14 TCHFB	20300	32.5	> 645 [b]	5.1			
15 PFTB	82600	40.5	> 651 [b]	5.4	43.9 [g]	770 [g]	
16 PhOH	1820	29.9	> 464 [b]	9.97	31.8 [c]	450 [h],	460 [i,j]

[a] 3-MP = 3-methyl-3-pentanol, TBE = 1,1,1-tribromoethanol, TCE = 1,1,1-trichloroethanol, TFE = 1,1,1-trifluoroethanol, HCP = 1,1,1,3,3,3-hexachloro-2-propanol, HFP = 1,1,1,3,3,3-hexafluoro-2-propanol, TCTB = 1,1,1-trichloro-2-methyl-2-propanol, $CCl_3(CH_3)_2COH$, TFTB = 1,1,1-trifluoro-2-methyl-2-propanol, $CF_3(CH_3)_2COH$, HFTB = 1,1,1,3,3,3-hexafluoro-2-methyl-2-propanol, $(CF_3)_2CH_3COH$, TCHFB = 2-trichloromethyl-1,1,1,3,3,3-hexafluoro-2-propanol, $CCl_3(CF_3)_2COH$, PFTB = perfluoro-*t*-butyl alcohol, $(CF_3)_3COH$, [b] complex band with several maxima, measured from the first maximum, [c] Ref. 23, [d] Ref. 24, [e] Ref. 25, [f] Ref. 26, [g] Ref. 27, [h] Ref. 28, [i] Ref. 29, [j] Ref. 30.

and ethanol) or 4A (other alcohols and CCl_4). It should be mentioned that the alcohols containing much chlorine are very hygroscopic.

Measurements. The near-infrared spectra were recorded on a Beckman DK-2A spectrophotometer equipped with a thermostated cell holder. The details of the measurements have been published previously.[13,17]

The IR spectra were recorded with a Perkin-Elmer 621 spectrometer at ambient temperature, using 5 mm cells with KBr windows (sealed cells from RIIC). The spectra of the alcohol-HMPA complexes in CCl_4 were scanned against HMPA in CCl_4. HMPA-d_{18} was also used as a proton acceptor to avoid the disturbing influence of the C–H stretching vibrations of HMPA on the hydrogen bonded OH stretching absorption.

Calculations were carried out as previously described.[17]

The $\Delta\nu$OH values are estimated to be accurate within $\pm 3-5$ cm^{-1}, ΔH values within ± 2 kJ mol^{-1} and K_{11} values within 10 %.

The non-SI units used were: 1 M = 1 mol dm^{-3}; 1 mmHg = 133.322 Pa.

RESULTS AND DISCUSSION

The experimental data obtained are presented in Table 1, which also contains the pK_a's of alcohols determined in water. The symbols used for the alcohols are explained in a footnote to Table 1. When the proton donor was an ordinary alcohol, TBE, TCE, TFE, TCTB or TFTB (for which the pK_a's are about 12 or greater), the absorption bands of the bonded νOH vibration were simple in form and the frequency shifts $\Delta\nu$OH were easy to estimate (see Fig. 1). No indication was found of the existence of a double maximum, frequently observed when the bonding occurs at the carbonyl group. This may be related to the fact that P=O groups are more polar than C=O groups. It has been estimated that in HMPA the P=O bond has about 50 % ionic character.[1,2,31,32] We assume that the hydrogen bonding occurs only to the lone pairs of oxygen of HMPA.

For complexes between the alcohols with pK_a values smaller than 12 or phenol and

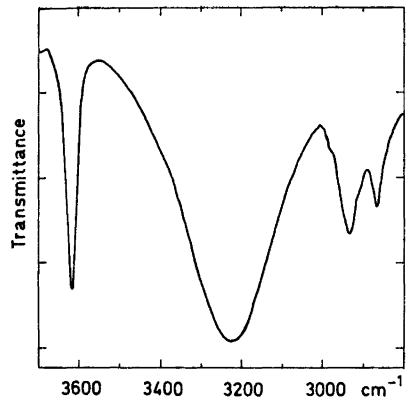

Fig. 1. Illustrative spectrum for the system TFE – HMPA-d_{18}. Solvent CCl_4, temperature ambient, 5 mm cells with KBr windows; concentrations: 0.0153 M TFE + 0.00772 M HMPA-d_{18}, 0.00772 M HMPA-d_{18} in the reference beam.

HMPA, the bonded OH absorption bands consist of several submaxima. Examples are the IR spectra of the HFP – HMPA and PFTB – HMPA complexes shown in Fig. 2. The existence of these submaxima is probably due to the coupling of νOH(bonded) vibrations with combinations or overtones of some other vibration of lower frequency. For the phenol – HMPA complex the substructure of the νOH-(bonded) band can be explained by assuming Fermi resonance between νOH(bonded) vibrations and suitable combination vibrations of the phenol.[33]

The free νOH absorption band of HFP, as of HCP, consists of two maxima (Fig. 2). In both cases the values of $\Delta\nu$OH were estimated from the higher frequency absorption peak.

For complexes with several νOH(bonded) absorption peaks only the lowest limit of $\Delta\nu$OH can be estimated (Table 1).

It has been stated that the values of $\Delta\nu$OH-(bonded) depend on the base concentration and, accordingly, a concentration-independent value should be determined by extrapolation to infinite dilution of the $\Delta\nu$OH values measured at varying concentrations.[34,35] For several alcohol – HMPA pairs the $\Delta\nu$OH's were measured by varying the concentration of HMPA. The small changes observed in $\Delta\nu$OH were within the range of experimental error. The values of $\Delta\nu$OH in Table 1 are unextrapolated values measured at relatively high dilution.

The values obtained in this work (Table 1) are in good accord with those reported in the literature. The only exception is the *t*-BuOH – HMPA system, for which the value of $-\Delta H°$, 23.8 kJ mol^{-1}, reported by Bogachev *et. al.*[23] is remarkably higher than our value. The value of Bogachev *et al.* appears too large when compared with $-\Delta H°$ values for other ordinary alcohols. The discrepancies in the $\Delta\nu$OH values for HFP, PFTB and phenol are explained by the fact that the absorption band of the complex is not simple and the $\Delta\nu$OH values are measured from different points in the spectra.

Acidity of alcohols and spectrometric quantities. Most studies of the influence of the acidity on hydrogen bond strength have been made

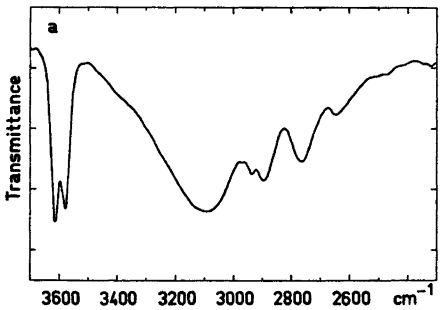

Fig. 2a. Illustrative spectrum for the system HFP – HMPA-d_{18}. Solvent CCl_4, temperature ambient, 5 mm cells with KBr windows; concentrations: 0.0186 M HFP + 0.00566 M HMPA-d_{18}, 0.00566 M HMPA-d_{18} in the reference beam.

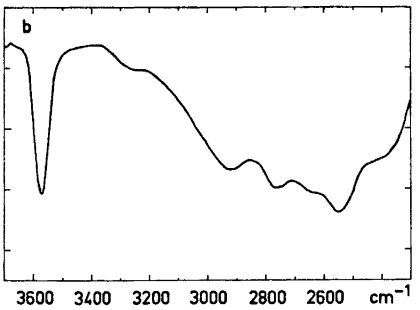

Fig. 2b. Illustrative spectrum for the system PFTB – HMPA-d_{18}. Solvent CCl_4, temperature ambient, 5 mm cells with KBr windows; concentrations: 0.0119 M PFTB + 0.00566 M HMPA-d_{18}, 0.00566 M HMPA-d_{18} in the reference beam.

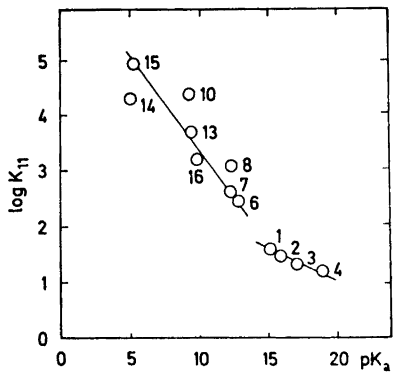

Fig. 3. The plot of log K_{11} against pK_a of the alcohol for the alcohol–HMPA systems at 25 °C.

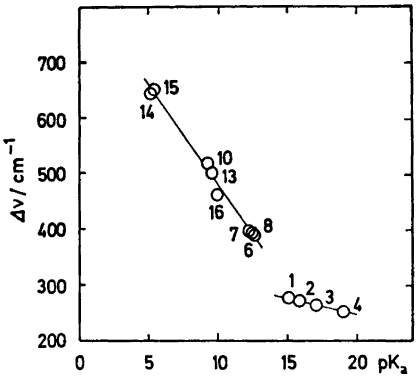

Fig. 4. The plot of $\Delta\nu$ against pK_a of the alcohol for the alcohol–HMPA systems at 25 °C.

with substituted phenols, for which the pK_a's can vary considerably. The pK_a values of ordinary alcohols vary only a few pK_a units and only recently have papers been published on more acidic alcohols. The influence of the acidity on the intermolecular (and intramolecular) hydrogen bonding has recently been reviewed by Rochester.[36] The Brønsted acidity can best be introduced in terms of the water acidity, pK_a, of the alcohols. Table 1 reveals that the more acidic an alcohol is, the more marked is the tendency to hydrogen bond. This usually leads to increased values of the spectrometric parameters K_{11}, $-\Delta H°$ and $\Delta\nu$OH.[20,37] In Figs. 3 and 4, K_{11} and $\Delta\nu$OH are plotted against the pK_a of the alcohols, and it can be seen that the dependence is linear in both cases. This is also true in the case of $-\Delta H°$. The slight scatter of a few points of K_{11} (and also of $-\Delta H°$) may be due to experimental inaccuracy inherent in the determination of these quantities. It seems, however, that the slopes for the ordinary alcohols differ somewhat from those for the halogenated alcohols. The situation is analogous to that found by Dierckx *et al.*[38] in their study on the influence of the acidity of proton donor on $\Delta\nu$OH values. They, too, obtained different slopes for phenols and for ordinary alcohols.

Our studies on the heteroassociation of substituted phenols with HMPA are in progress; preliminary results indicate that the behaviour of halogenated alcohols resembles more closely that of the phenols than that of the ordinary alcohols.

On the basis of the values of Figs. 3 and 4 we decided that the influence of steric effects on the hydrogen bonding is negligible.

Relations between spectrometric quantities. It has been stated that the value of $\Delta\nu$X–H is a better measure of the strength of a hydrogen bond than is K_{11} or ΔH.[39] This is true because, in the hydrogen-bonded system Z–X–H···Y–Z′, $\Delta\nu$X–H measures energetic changes in the formation of the hydrogen bond H···Y, while ΔH is a measure of the energies of different interactions between Z–X–H and Y–Z′. Also, recent force field calculations on hydrogen-bonded complexes indicate that $\Delta\nu$X–H is a good measure of the complex strength.[40] It is not therefore surprising that the Badger-Bauer relation, *i.e.* the linear dependence between ΔH and $\Delta\nu$OH, does not always hold. The experimental results obtained in this work and reproduced in Fig. 5 show the Badger-Bauer relation to be approximately valid.

The thermodynamic quantities for different alcohol–HMPA complexes are listed in Table 2. In many equilibrium and kinetic systems, ΔH is quite often found to be a linear function of ΔS. This relation is also common in the case of hydrogen-bonded systems. Thus Pimentel and McClellan[11] have discussed the significance of the ΔH *vs.* ΔS relation, and refer to cases in which the linearity of the enthalpy-entropy relation holds. The explanation given by Pimentel and McClellan[41] for hydrogen-bonded

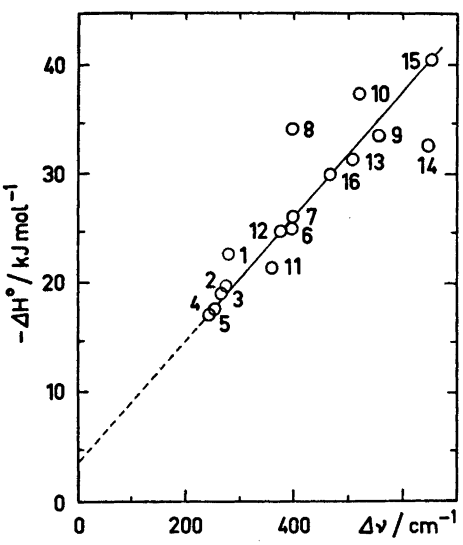

Fig. 5. The plot of $-\Delta H°$ against $\Delta\nu$ for the alcohol – HMPA systems at 25 °C.

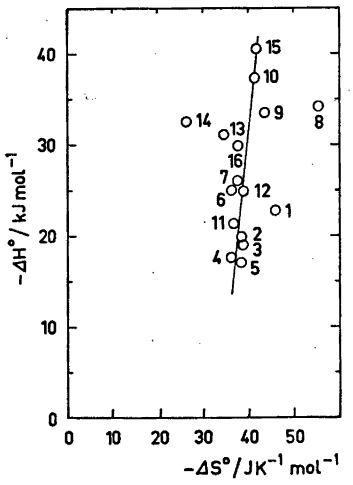

Fig. 6. The plot of $-\Delta H°$ against $-\Delta S°$ for the alcohol – HMPA systems at 25 °C.

systems, that "a higher value of $-\Delta H$ implies stronger bonding, with a more restricted configuration in the polymer, hence greater order leading to a larger value of $-\Delta S$", is widely cited.

In Fig. 6, $\Delta H°$ is expressed as a function of $\Delta S°$. We can see that the correlation, instead of being linear, illustrates rather the isoentropic case, *i.e.* ΔS values are roughly constant. There are only a few other systems, with substituted phenols as proton donors, where isoentropicity is also observed.[42–44]

Table 2. Thermodynamic quantities for 1:1 hydrogen-bonded complexes between alcohols or phenol and HMPA in carbon tetrachloride at 25 °C.

Alcohol (Phenol)	$-\Delta H°$ kJ mol^{-1}	$-\Delta G°$ kJ mol^{-1}	$-\Delta S°$ JK^{-1} mol^{-1}
MeOH	22.8	9.08	46.0
EtOH	19.8	8.45	38.2
i-PrOH	19.0	7.57	38.6
t-BuOH	17.6	6.86	36.2
3-MP	17.2	5.65	38.6
TBE	24.9	14.1	36.4
TCE	26.1	14.9	37.6
TFE	34.2	17.6	55.3
HCP	33.5	20.5	43.5
HFP	37.3	25.0	41.4
TCTB	21.3	10.3	36.8
TFTB	24.8	13.1	39.0
HFTB	31.2	20.9	34.6
TCHFB	32.5	24.6	26.4
PFTB	40.5	28.1	41.7
PhOH	29.9	18.6	37.7

At present, the experimental data are too meagre and to some extent too uncertain to allow us to decide whether there is any fundamental difference between those hydrogen-bonded acid-base systems that are isoentropic and those that are not. We expect, however, that the increase in order is of the same order of magnitude for most 1:1 hydrogen-bonded complexes when the geometries of the complexes are nearly the same, namely "linear" or open type configuration. This would favour isoentropicity. On the other hand, the stiffness of the complex, which increases with increasing hydrogen-bond strength, also affects the entropy term.

The double-scale enthalpy equation. Among many multiparameter equations for correlating acid-base behaviour the empirical double-scale enthalpy equation $-\Delta H = E_A E_B + C_A C_B$ proposed by Drago and Wayland [45] is perhaps the most useful in predicting the enthalpies of hydrogen-bond formation. Parameters E_A and E_B are interpreted as the susceptibility of the acid and base, respectively, to undergo electrostatic interaction; C_A and C_B are interpreted as the susceptibility of the acid and the base,

Table 3. The parameters E_A and C_A of alcohols and phenol, and experimental and calculated (see text) enthalpy values of the HMPA-proton donor systems. The E_B and C_B values of HMPA are 1.52 and 3.55, respectively.[47]

Alcohol (Phenol)	E_A	C_A	$-\Delta H°_{calc}$ / kJ mol^{-1}	$-\Delta H°_{exp}$ / kJ mol^{-1}
t-BuOH	2.04	0.300	17.4	17.6
TFE	3.88	0.451	31.4	34.2
HFP	5.93	0.623	46.9	37.3
PFTB	7.34	0.731	57.5	40.5
PhOH	4.33	0.442	34.1	29.9

respectively, to form a covalent bond.[45–48] Table 3 shows the experimental enthalpy values together with values calculated from the double-scale enthalpy equation using the parameters E_A and C_B (indicated in Table 3), which give the $-\Delta H$ values in the units of kcal mol^{-1}. It has been estimated that the difference between measured and calculated values should be less than 4 kJ mol^{-1} [45,46] (*cf.* also Ref. 44). In the present study the agreement is excellent for the *t*-BuOH–HMPA system and satisfactory for the TFE–HMPA and PhOH–HMPA systems. The marked difference between measured and calculated enthalpy values for HFP–HMPA and PFTB–HMPA systems may be attributed partly to the steric hindrance and partly to the high acidity, *i.e.*, strong hydrogen bonds of these alcohols. It has also been stated that because of the intramolecular hydrogen bonding in HFP and PFTB, one should add 4.6 kJ mol^{-1} and 4.2 kJ mol^{-1}, respectively, to the calculated negative enthalpy value.[47]

The values obtained in this study imply that the hydrogen bonding of halogenated alcohols resembles more closely the bonding of phenol than that of the ordinary alcohols. Work is in progress to obtain more information on the complexing of substituted phenols with HMPA.

REFERENCES

1. Normant, H. *Angew. Chem. 79* (1967) 1029.
2. Normant, H. *Russ. Chem. Rev. 39* (1970) 457.
3. Robert, L. *Properties and use of hexamethylphosphorotriamide*, Pierrefitte–Auby, Paris 1970.
4. Cox, B. G. and Parker, A. J. *J. Amer. Chem. Soc. 95* (1973) 408, and the references cited.
5. Chang, S. C., Terry, P. H. and Bořcovec, A. B. *Science 144* (1964) 57.
6. Bulyginskaya, M. A. and Vronskikh, M. D. *Russ. Chem. Rev. 39* (1970) 964, and the references cited.
7. Koshy, T. and Chandra, K. R. *J. Sci. Ind. Res. 31* (1972) 515.
8. Bořcovec, A. B. *Insect Chemosterilants*, Interscience, New York 1966.
9. Gaines, T. B. *Toxicol. Appl. Pharmacol. 14* (1969) 515.
10. Kimbrough, R. D. and Gaines, T. B. *Bull. Environ. Contam. Toxicol. 10* (1973) 225.
11. Pimentel, G. C. and McClellan, A. L. *Annu. Rev. Phys. Chem. 22* (1971) 347, and the references cited.
12. Vinogradov, S. N. and Linnell, R. H. *Hydrogen Bonding*, Van Nostrand-Reinhold, New York 1971, Chapter 9.
13. Kivinen, A. and Murto, J. *Suom. Kemistilehti B 40* (1967) 6.
14. Kivinen, A., Murto, J., Korppi-Tommola, J. and Kuopio, R. *Acta Chem. Scand. 26* (1972) 904.
15. Murto, J., Kivinen, A., Kajander, K., Hyömäki, J. and Korppi-Tommola, J. *Acta Chem. Scand. 27* (1973) 96.
16. Murto, J., Kivinen, A., Korppi-Tommola, J., Viitala, R. and Hyömäki, J. *Acta Chem. Scand. 27* (1973) 107.
17. Kivinen, A., Murto, J. and Kilpi, L. *Suom. Kemistilehti B 40* (1967) 301.
18. Murto, J. In Patai, S., Ed., *The chemistry of the hydroxyl group*, Wiley, London 1971, Chapter 20.
19. Filler, R. and Schure, R. M. *J. Org. Chem. 32* (1967) 1217 .
20. Zeegers-Huyskens, Th. *Spectrochim. Acta A 23* (1967) 855.
21. Nikiforov, G. A. and Ershov, V. V. *Russ. Chem. Rev. 39* (1970) 644.
22. Takahashi, S., Cohen, L. A., Miller, H. K. and Peake, E. G. *J. Org. Chem. 36* (1971) 1205.
23. Bogachev, Yu. S., Vasianina, L. K., Shapetko, N. N. and Yakushin, F. S. *Dokl. Akad. Nauk SSSR 206* (1972) 1142.
24. Sherry, A. D. and Purcell, K. F. *J. Phys. Chem. 74* (1970) 3535.
25. Sherry, A. D. Ph. D. *Thesis*, Kansas State University, 1971; *Diss. Abstr. B 32* (1971) 3288.
26. Purcell, K. F., Stikeleather, J. A. and Brunk, S. D. *J. Amer. Chem. Soc. 91* (1969) 4019.
27. Sherry, A. D. and Purcell, K. F. *J. Amer. Chem. Soc. 94* (1972) 1853.
28. Gramstad, T. *Spectrochim. Acta 20* (1964) 729.

29. Chen, T. and Morgan, L. O. *J. Phys. Chem. 76* (1972) 1973.
30. Gramstad, T. and Storesund, H. J. *Spectrochim. Acta A 26* (1970) 426.
31. Bell, J. V., Heisler, J., Tannenbaum, H. and Goldenson, J. *J. Amer. Chem. Soc. 76* (1954) 5185.
32. Larson, L. *Sv. Kem. Tidskr. 71* (1959) 336.
33. Kivinen, A., Murto, J. and Kuopio, R. *Finn. Chem. Lett.* (1974) 211.
34. Baitinger, W. F., Schleyer, P. von R., Murty, T. S. S. R. and Robinson, L. *Tetrahedron 20* (1964) 1635.
35. Joris, L. and Schleyer, P. von R. *Tetrahedron 24* (1968) 5991.
36. Rochester, C. H. In Patai, S., Ed., *The chemistry of the hydroxyl group*, Wiley, London 1971, Chapter 7.
37. Singh, S., Murthy, A. S. N. and Rao, C. N. R. *Trans. Faraday Soc. 62* (1966) 1056.
38. Dierckx, A.-M., Huyskens, P. and Zeegers-Huyskens, Th. *J. Chim. Phys. Physicochim. Biol. 62* (1965) 336.
39. Lutskii, A. E. *Zh. Strukt. Khim. 13* (1972) 534.
40. Cummings, D. L. and Wood, J. L. *J. Mol. Struct. 20* (1974) 1.
41. Pimentel, G. C. and McClellan, A. L. *The Hydrogen Bond*, Freeman, San Francisco 1960, pp. 220–221.
42. Ghersetti, S. and Lusa, A. *Spectrochim. Acta 21* (1965) 1067.
43. Stymne, B., Stymne, H. and Wettermark, G. *J. Amer. Chem. Soc. 95* (1973) 3490.
44. Arnett, E. M., Mitchell, E. J. and Murty, T. S. S. R. *J. Amer. Chem. Soc. 96* (1974) 3875.
45. Drago, R. S. and Wayland, B. B. *J. Amer. Chem. Soc. 87* (1965) 3571.
46. Drago, R. S., Vogel, G. C. and Needham, T. E. *J. Amer. Chem. Soc. 93* (1971) 6014.
47. Guidry, R. M. and Drago, R. S. *J. Amer. Chem. Soc. 95* (1973) 759.
48. Drago, R. S. *J. Chem. Educ. 51* (1974) 300, and the references cited.

Received June 4, 1975.