Nuclear Magnetic Resonance Chemical Shifts for Alcoholic and Phenolic Protons in Dimethyl Sulphoxide: Utility as a Structural Parameter

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The n.m.r. spectra of various pyridyl alcohols and phenols were measured in dimethyl or [$^2H_6$]dimethyl sulphoxide. Pyridyl alcohols were classified into three categories on the basis of their n.m.r. behaviour. In cases in which the hydroxy-proton was sufficiently fixed in space through intermolecular hydrogen bonding with the solvent, the n.m.r. signal was a triplet due to coupling with the α-methylene group. The δ_{OH} value was found to be temperature dependent and to vary with change of the structural nature of hydroxy-group. Various types of intra- and intermolecular hydrogen bonding interactions are invoked for the elucidation of n.m.r. patterns. Several *N*-methylated pyridyl alcohols were subjected to n.m.r. investigation, but failed to provide well resolved n.m.r. patterns. The correlation between δ_{OH} and pK_{HA} of the corresponding phosphates proved the reliability of δ_{OH} as a structural parameter for a linear free energy relationship study of phosphate hydrolysis.

CHAPMAN and KING[1] have suggested that the n.m.r. spectra of alcoholic protons in dimethyl sulphoxide (DMSO) provide very useful data for the identification of alcohols. In DMSO solution the strong hydrogen bond of an alcohol to the solvent shifts the hydroxy-resonance downfield and also reduces the rate of proton exchange sufficiently to permit observation of the splitting of the hydroxy-proton signal.[1] We have carried out n.m.r. measurements for various kinds of previously prepared pyridyl alcohols[2-10] and phenols in DMSO or [$^2H_6$]DMSO. The temperature dependence of the n.m.r. spectra has also been investigated.

In addition, we have examined the correlation between the δ_{OH} values for alcohols and the acid dissociation constants for the last dissociating phosphate proton of the corresponding phosphates (K_{HA}). Since both δ_{OH} and pK_{HA} may be efficient structural parameters for a linear free energy relationship (l.f.e.r.) study of phosphate hydrolysis, an examination into their validity and reliability is necessary.

RESULTS AND DISCUSSION

The hydroxy-proton interacts with DMSO in solution by forming a strong hydrogen bond and the interaction inhibits proton exchange.[1,11] It was thus possible to observe clearly resolved triplets due to coupling with the α-methylene group for primary alcohols. The hydroxy-proton resonance in DMSO was almost independent of concentrations below 25 mole %.[1] In fact, the hydroxy-proton of phenol gave a singlet at δ 9·27 with a concentration of 2·76 mole % in our work and one at δ 9·25 with a concentration of 10 mole % as reported by Chapman and King;[1] agreement between the results is sufficient. The n.m.r. behaviour of hydroxy-protons can be classified into three categories. First, the proton resonances shift toward upper field along with some broadening as the temperature increases, the signal being resolved as a triplet. Secondly, as, for example, for 2-pyridyl-ethanol and -propanol, only broad signals are observed at elevated temperatures. Thirdly, the resonances are not clearly resolved even at ordinary temperatures, as in the examples, 3-hydroxy-2-pyridylmethanol, 3-hydroxymethyl-2-pyridone, 2-amino-3-pyridylmethanol, and 6-methyl-2-pyridylmethanol. The hydroxy-proton resonance of quinolin-8-ol was also very broad even at 34 °C. Hydrogen bonding of the hydroxy-proton with the solvent must be disturbed in the last cases for reasons such as desolvation by steric hindrance[8,12] or intramolecular hydrogen bonding.[13] Consequently, hydrogen exchange may occur to some extent and cause line broadening.

Temperature dependences of the δ_{OH} values are listed in Tables 1 and 2 and are illustrated in Figure 1. For quinolin-8-ol and 6-methyl-2-pyridylmethanol, a sharp fall in the temperature dependence curve was observed. In the case of 3-hydroxy-2-pyridylmethanol the temperature effect on the δ_{OH} value was very small and only a sharp singlet (2H) was observed without any line broadening despite the existence of two hydroxy-protons in the molecule. This may suggest that strong intramolecular hydrogen bonding between the 3-hydroxy and 2-hydroxymethyl groups is present and mutual rapid hydrogen exchange occurs. A similar phenomenon was observed in the n.m.r. spectra of ethanolamine. On the other hand, the spectra of ethanolamine hydrochloride gave separate hydroxy- and amino-proton signals with some broadening. The appearance of these two signals can be ascribed to the fixing of the hydrogen bond in the molecule as $H_2\overset{+}{N}{-}H\cdots OH$.

An intramolecular hydrogen bond between the

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pyridine nitrogen atom and the hydroxy-proton must be considered for the 2-pyridyl alcohols.[13] In order to examine the anchimeric effect of the pyridine nitrogen atom on the n.m.r. behaviour through such hydrogen bonding interactions, several kinds of *N*-methylated pyridyl alcohols were prepared and their hydroxy-proton resonances were measured under the same conditions as those adopted for the free pyridyl alcohols. Results are listed in Table 3. Contrary to expectation, the quarternization of the pyridine nitrogen atom resulted only in the downfield shift of the hydroxy-proton resonance and line broadening became larger. A counter-anion of these quaternary compounds catalyses the protons exchange through ion pair interaction and consequently broadening of the hydroxy-proton line increases for these cases. 3-Hydroxy-2-hydroxymethyl-1-methylpyridinium iodide was the exception and gave a sharp singlet for the reason given above for the corresponding non-methylated compound.

TABLE 1

N.m.r. chemical shifts for alcoholic hydroxy-protons in DMSO or [$^2H_6$]DMSO

Alcohol	δ_{OH} (p.p.m.) 33·5 °C	55·5 °C	87·5 °C	Multiplicity [a]	Classification [g]
2-Pyridylpropanol	4·46	4·37	4·13	t	2
2-Pyridylethanol	4·59	4·52	4·28	t	2
2-Pyridylmethanol	5·33	5·24	5·06	t	1
3-Pyridylmethanol	5·25	5·19	5·00	t	1
4-Pyridylmethanol	5·38 [d]	5·27 [c]	5·08	br,s	3
6-Methyl-2-pyridylmethanol	5·27	5·11	4·76	br,s	3
3-Hydroxy-2-pyridylmethanol	7·14 [d]	7·11 [c]	7·09	s	3
2-Chloro-3-pyridylmethanol	5·49	5·43	5·21	t	1
2-Amino-3-pyridylmethanol	5·04	4·81		br,s	3
3-Hydroxymethyl-2-pyridone	4·91	4·85	4·64	br,s	3
Trichloroethanol	6·77 [d]	6·65 [e]	6·48 [f]	t	2
Ethanolamine	2·85		2·62	s	3
Ethanol [b]	4·35			t	
Methanol [b]	4·08			q	
Isopropanol [b]	4·35			d	
Benzyl alcohol [b]	5·16			t	

[a] q = Quartet, t = triplet, d = doublet, s = singlet, br = broad. Multiplicity cited here was at 34 °C. [b] Quoted from ref. 1, at 30 °C. [c] At 58·0 °C. [d] At 36·0 °C. [e] At 60·0 °C. [f] At 90·0 °C. [g] Types of n.m.r. behaviour mentioned in the text.

TABLE 2

N.m.r. chemical shifts for phenolic hydroxy-protons in DMSO

Phenol	δ_{OH} (p.p.m.) 34·0 °C	86·5 °C
Pyridin-3-ol [a]	9·78	9·55
Quinolin-8-ol [b]	9·72	5·62
Phenol	9·27	9·00
o-Nitrophenol	10·87	10·20
m-Nitrophenol	10·38	10·10
p-Nitrophenol	10·98	10·52
m-Methylphenol	9·13	8·84
p-Methylphenol	8·98	8·71

[a] δ 9·70 at 55·5 °C. [b] δ 7·51 at 55·5 °C.

A normal linear relationship between δ_{OH} and pK_a is observed for ordinary phenols as shown in Figure 2. Quinolin-8-ol deviated upward from the straight line. The δ_{OH}–temperature correlation curve falls sharply relative to others on increasing the temperature as seen in Figure 1, and n.m.r. line broadening for the hydroxy-proton signal is observed even at ordinary temperatures. These facts suggest that a strong intramolecular hydrogen bond prevents acid dissociation as well as the intermolecular hydrogen bond between the hydroxy-group of quinolin-8-ol and DMSO. For compounds with a strong intramolecular hydrogen bond, therefore, the δ_{OH} value

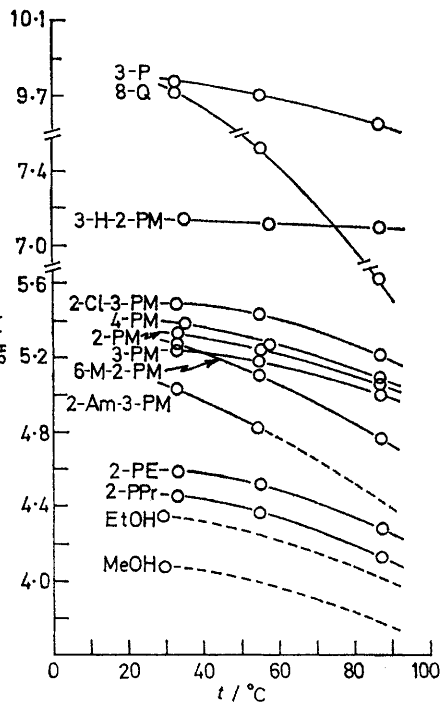

FIGURE 1 Temperature dependence of the hydroxy-proton resonances in DMSO. Broken lines indicate extrapolation. Abbreviations: 3-P, pyridin-3-ol; 8-Q, quinolin-8-ol; 3-H-2-PM, 3-hydroxy-2-pyridylmethanol; 2-Cl-3-PM, 2-chloro-3-pyridylmethanol; 4-PM, 4-pyridylmethanol; 2-PM, 2-pyridylmethanol; 3-PM, 3-pyridylmethanol; 6-M-2-PM, 6-methyl-2-pyridylmethanol; 2-Am-3-PM, 2-amino-3-pyridylmethanol; 2-PE, 2-pyridylethanol; 2-PPr, 2-pyridylpropanol

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[13] L. P. Kuhn, R. A. Wires, W. Ruoff, and H. Kwart, *J. Amer. Chem. Soc.*, 1969, **91**, 4790.

does not always provide reliable information on the electronic character.

Independently of this work, we have extensively investigated the hydrolyses of pyridylalkyl phosphates prepared from the alcohols examined here.[4-10,12] For simple alkyl phosphates, three ionic species must be considered due to the acid dissociation of the phosphate group as in Scheme 1 of the following paper, among which the monoanionic form is the most reactive toward hydrolysis.

TABLE 3

N.m.r. chemical shifts for hydroxy-protons of quarternized pyridyl alcohols in DMSO or [$^2H_6$]DMSO

	δ_{OH}(p.p.m.)					
	34·0 °C			88·0 °C		
Alcohol	Free	$\overset{+}{N}$Me	$\Delta\delta_{OH}$ [a]	Free	$\overset{+}{N}$Me	$\Delta\delta_{OH}$ [a]
2-Pyridylmethanol	5·33	6·17 [b]	−0·84	5·06	5·90	−0·84
3-Pyridylmethanol	5·25	5·75 [b]	−0·50	5·00	5·54	−0·54
4-Pyridylmethanol	5·38	5·78 [c]	−0·40	5·08	5·24	−0·16
6-Methyl-2-pyridylmethanol	5·27	6·17 [c]	−0·90	4·76	5·90	−1·14
3-Hydroxy-2-pyridylmethanol	7·14	8·42 [d]	−1·28	7·09	7·84	−0·75

[a] $\Delta\delta_{OH} = \delta_{OH}(\text{free}) - \delta_{OH}(\overset{+}{N}\text{Me})$. [b] Triplet. [c] Broad singlet. [d] Sharp singlet.

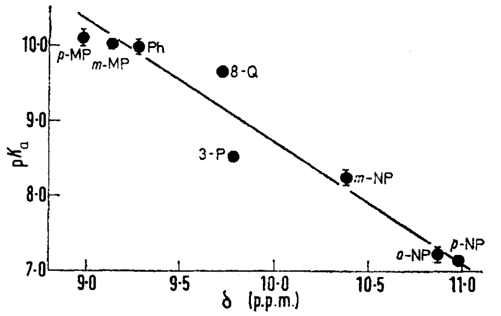

FIGURE 2 Linear relationship between hydroxy-proton resonances (at 34 °C) and acid dissociation constants (at 25 °C) for phenols. Abbreviations: *p*-MP, *p*-methylphenol; *m*-MP, *m*-methylphenol; Ph, phenol; *m*-NP, *m*-nitrophenol; *o*-NP, *o*-nitrophenol; *p*-NP, *p*-nitrophenol; others as in Figure 1

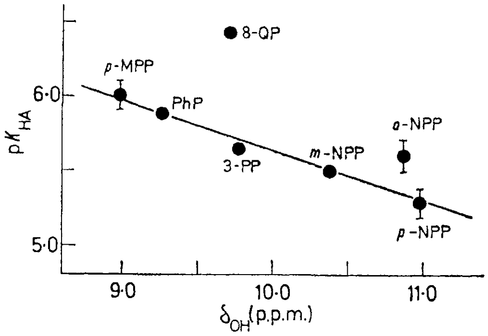

FIGURE 3 Correlation between acid dissociation constants for the last dissociating proton of aryl phosphates (pK_{HA} at 25 °C) and n.m.r. chemical shifts for phenolic protons (δ_{OH} at 34 °C). Abbreviations: *p*-MPP, *p*-methylphenyl phosphate; PhP, phenyl phosphate; 8-QP, 8-quinolyl phosphate; 3-PP, 3-pyridyl phosphate; *m*-NPP, *m*-nitrophenyl phosphate; *o*-NPP, *o*-nitrophenyl phosphate; *p*-NPP, *p*-nitrophenyl phosphate

In the cases of pyridylalkyl phosphates having an additional basic heteroatom in their alcohol groups, another ionic species has to be taken into consideration as shown in Scheme 2 of the following paper. Through our previous investigations, we predicted that the acid dissociation constant for the second phosphate proton (K_{HA} in Schemes 1 and 2 of the following paper) was closely related to the geometrical structure and the electronic nature of the alcohol function.[14] Thus, we investigated whether a linear relationship existed between the pK_{AH} value of the phosphates and the δ_{OH} value of the corresponding alcohols. Acid dissociation constants [2-10] are cited in Tables 4 and 5 of the following paper. Figures 3 and 4 show that a good correlation exists for both alkyl and aryl phosphates. These results suggest that a long range inductive effect takes place with internal transmission through the C–C bond,[15] as well as through the P–O–C ester bond, on the terminal phosphate group. A similar long range effect has been shown to occur in the

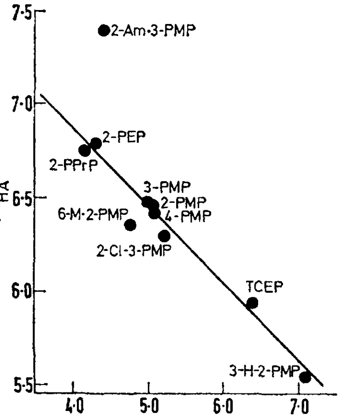

FIGURE 4 Linear relationship between acid dissociation constants for the last dissociating proton of alkyl phosphates (pK_{HA} at 80 °C) and n.m.r. chemical shifts for alcoholic protons (δ_{OH} at 88 °C). Abbreviations: 2-Am-3-PMP, 2-amino-3-pyridylmethyl phosphate; 2-PEP, 2-pyridylethyl phosphate; 2-PPrP, 2-pyridylpropyl phosphate; 3-PMP, 3-pyridylmethyl phosphate; 2-PMP, 2-pyridylmethyl phosphate; 4-PMP, 4-pyridylmethyl phosphate; 6-M-2-PMP, 6-methyl-2-pyridylmethyl phosphate; 2-Cl-3-PMP, 2-chloro-3-pyridylmethyl phosphate; TCEP, trichloroethyl phosphate; 3-H-2-PMP, 3-hydroxy-2-pyridylmethyl phosphate

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[14] Y. Murakami and J. Sunamoto, following paper.

[15] C. K. Ingold, ‘Structure and Mechanism,’ Cornell University Press, Ithaca, 2nd edn., 1969.

acetolyses of some steroids.[16] The linear correlations (1) and (2) are thus established. Consequently, the δ_{OH} value is a useful structural parameter in the l.f.e.r. study of ester hydrolyses.[14]

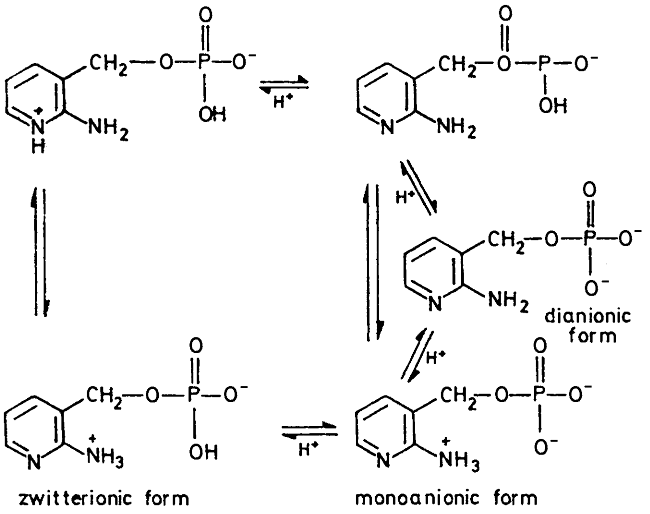
For the aryl phosphates:

$$pK_{HA} \text{ (at 25 °C)} = 8{\cdot}39 - 0{\cdot}27\delta_{OH} \text{ (at 34 °C)} \qquad (1)$$
$$r = -0{\cdot}913$$

For the alkyl phosphates:

$$pK_{HA} \text{ (at 80 °C)} = 8{\cdot}38 - 0{\cdot}39\delta_{OH} \text{ (at 88 °C)} \qquad (2)$$
$$r = -0{\cdot}976$$

Several compounds were found to deviate from the linear relationship of pK_{HA} *vs.* δ_{OH}, positively or negatively. For all the anomalous compounds unusual hydrolytic behaviour has been observed. These include a large increase in the entropy of activation for the monoanion hydrolysis of 8-quinolyl phosphate,[6] a decrease in solvation in the monoanion and zwitterion hydrolyses of 6-methyl-2-pyridylmethyl phosphate,[8] and promotion of the γ-elimination of the chlorine atom during the phosphate hydrolysis of 2-chloro-3-pyridylmethyl phosphate.[10] A large rate enhancement was also observed in the hydrolyses of both species, the monoanion and zwitterion forms, for 2-amino-3-pyridylmethyl phosphate.[17] Since the phosphate is a tetrabasic acid, the acid dissociation processes became somewhat complex as shown in the Scheme. Thus, an assignment of a discrete structure to the monoanionic form is rather difficult with the information available at present. Nevertheless, a large rate enhancement was certainly observed, for which the participation of the neighbouring group is responsible.[17]



SCHEME

EXPERIMENTAL

Materials.—Most of the pyridyl alcohols used in this work were those previously used for phosphorylation studies.[2-4, 7, 8] 2-Pyridyl-ethanol and -propanol were commercial and were purified in the usual manner.[8] Pyridin-3-ol and quinolin-8-ol were those used previously.[3] Other alcohols and phenols were GR grades obtained from Nakarai Chemical Co. Ltd or Wako Pure Chemical Ind. Ltd. and were purified if necessary. *N*-Methylated pyridyl alcohols were obtained from the corresponding pyridyl alcohols by treatment with methyl iodide as usual.[18]

DMSO (GR grade; Wako Pure Chemical Ind. Ltd.) was distilled under reduced pressure and the distillate with b.p. 74·2 °C at 14 mmHg was collected under anyhdrous conditions. It was stored over Linde molecular sieves 4A and used without further purification. [$^2H_6$]DMSO (>99·5%) was obtained from Merck and used without any further treatment.

N.m.r. Spectra.—All the n.m.r. spectra were measured with a Varian A-60 spectrometer in DMSO or [$^2H_6$]DMSO with tetramethylsilane as internal standard for 0·40M solutions of the alcohols. The probe temperature was calibrated by means of the ethylene glycol signal at 34, 56, and 87 °C.

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[16] K. Takeda, H. Tanida, and K. Horiki, *J. Org. Chem.*, 1966, **31**, 734.

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[18] G. F. Duffin, *Adv. Heterocyclic Chem.*, 1964, **3**, 2 and references cited therein.