K was varied systematically from 0.7 to 1.2. The method of McLachlan[9] was used to correct for spin polarization of the paired π electrons.

Results

Table V lists some of the spin densities calculated by this procedure along with "experimental" spin densities (Q = 25 G/electron).

Values of K between 1.00 and 1.10 give predicted spin densities in close agreement with experiment for all compounds studied. The value K = 1.05 predicts spin densities whose average deviation from the experimental results is 0.0074, corresponding to 0.19 G for all positions of these three compounds. The largest deviation, 0.0247 (0.62 G), is for the *meta* position of the diphenyl sulfone anion radical.

Conclusions

The spin density distributions in sulfone-containing aromatic anion radicals can be adequately explained by an inductive model for the sulfone residue. The inductive effect of the sulfone group was represented by assigning the Hückel coulomb integral of the α carbon atom the value $\alpha = \alpha_C + (1.05 \pm 0.05)\beta_{CC}$ in this work.

While it is not necessary to postulate d orbital interactions to explain the esr spectra of these systems, these calculations do not demonstrate that d orbital conjugation is not important in sulfone-containing aromatic systems. Since d orbital conjugation does affect calculated spin distributions in much the same way as do inductive effects, it is impossible to separate these two effects on the basis of simple calculations.

These results are similar to results obtained for systems containing divalent sulfur. It is not necessary to postulate any sulfur d orbital participation to explain the esr spectra of thioxanthone,[8] dibenzothiophene,[11] and 2,1,3-benzothiodiazole.[12]

Acknowledgment. The authors wish to thank Dr. Richard Brockmeier, Department of Physics, Hope College, for assistance in operating the IBM 1130 computer.

(11) R. Gerdil and E. A. C. Lucken, *J. Am. Chem. Soc.*, 87, 213 (1965).
(12) E. T. Strom and G. A. Russel, *ibid.*, 87, 3326 (1965).

Pyridine-Induced Solvent Shifts in the Nuclear Magnetic Resonance Spectra of Hydroxylic Compounds[1]

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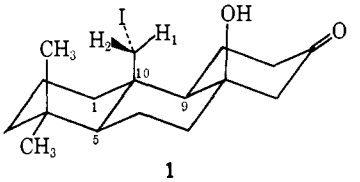
Abstract: Proton chemical shifts for a wide variety of structurally different compounds containing the hydroxyl function have been measured in deuteriochloroform and pyridine-d_5. The solvent shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$) observed are rationalized in terms of specific solute–solvent complexes between pyridine molecules and the polar hydroxyl function in the solute molecules. It is found that in saturated cyclic systems, protons occupying positions 1,3-diaxial, vicinal, or geminal to a hydroxyl function are deshielded. In phenolic systems, protons *ortho* to a hydroxyl function experience much larger deshielding effects than protons in the *meta* or *para* positions. Pyridine-induced solvent shifts can therefore be extremely useful in establishing both the location and stereochemical nature of protons situated in the vicinity of hydroxyl functions.

Pyridine has for some time now been recognized as a useful solvent for the nmr analysis of molecules containing polar functional groups for solubility reasons as well as for increased spectral simplification relative to chloroform or carbon tetrachloride.[3–5] Because of the ability of aromatic systems like pyridine to coordinate at electron-deficient sites within a solute molecule, protons situated in the vicinity of a polar functional group invariably experience large screening effects as a result of the large anisotropy in the magnetic susceptibility of the aromatic system.[6] The correlation of chemical shifts induced in benzene and pyridine (relative to chloroform) with specific structural features in a variety of carbonyl-containing compounds is well known, and the potential of this technique for use in structural analysis has been amply demonstrated.[7]

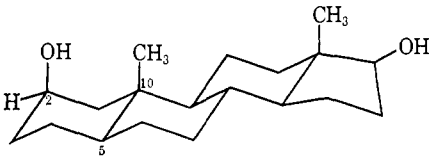
We wish to report a further extension of the use of pyridine to the study of polar molecules containing the

(1) D. D., B. L. M., and E. W. gratefully acknowledge the support of Eli Lilly and Co. for that portion of this work carried out at Indiana University.
(2) (a) Lilly Research Laboratories; (b) Department of Chemistry, Indiana University.
(3) G. Slomp and F. MacKellar, *J. Amer. Chem. Soc.*, **82**, 999 (1960).
(4) S. M. Kupchan, W. S. Johnson, and S. Rajagapolan, *Tetrahedron*, 7, 47, (1959); O. L. Chapman, H. G. Smith and R. W. King, *J. Amer. Chem. Soc.*, **85**, 803 (1963).
(5) J. R. Hanson, *J. Chem. Soc.*, 5036 (1965); K. Tori and K. Aono, *Ann. Rept. Shionogi Res. Lab.*, **14**, 136 (1964); K. Tori and E. Kondo, *Steroids*, **4**, 713 (1964); H. Minato and M. Ishikawa, *J. Chem. Soc., C*, 423 (1967).
(6) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956); J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 180–183.
(7) N. S. Bhacca and D. H. Williams, "Application of N.M.R. Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 7; J. Ronayne and D. H. Williams, *J. Chem. Soc., B*, 540 (1967), and references cited therein.

hydroxyl function. In studies carried out over the past few years on a variety of structurally different, natural and synthetic compounds containing the hydroxyl function, we have, on several occasions, been compelled to analyze the nmr spectra of some of these compounds in pyridine because of solubility difficulties in other solvents. Unexpectedly large chemical shifts observed in this solvent, for two examples in particular, stimulated our interest to examine in greater detail the generality of this phenomenon. Compounds **1** and **2** subsequently responsible for initiating the present investigation are shown.



1



2

A rather dramatic chemical shift difference between the two iodomethyl protons of **1** was noted in pyridine solution.[8] The nmr spectrum of the compound reveals the presence of two low-field one-proton doublets (J = 11 Hz) at δ 5.17 and 3.73 which are assigned to protons H_1 and H_2, respectively. The enormous chemical shift difference between these two protons ($\delta_1 - \delta_2$ = 1.44 ppm) can only be rationalized if the C(10) iodomethyl group assumes the conformation illustrated in Figure 1, *i.e.*, the conformation in which nonbonded interactions between the bulky iodine atom and the β-axial substituents in rings A and B are minimal. In this conformation, H_1 is situated considerably closer to the C(9) β-axial hydroxyl function than is H_2 and will, as a result, experience a greater deshielding effect from highly anisotropic pyridine molecules coordinated to the polar hydroxyl function.[9-11]

5α-Androstane-2β,17β-diol (**2**) also provides an interesting example since the C-19 methyl protons in this compound resonate at considerably lower field (0.30 ppm) than the value anticipated for these protons from calculations employing Zürcher's additivity tables.[12,13] Since the Zürcher empirical shift coefficients are derived from the nmr spectra of compounds taken in chloroform, the excess shift observed for the C-19 methyl protons of **2** must therefore be attributed to a pyridine solvent shift contribution.

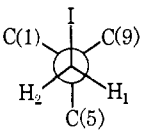


Figure 1. Preferred conformation of the C(10) iodomethyl group in **1**.

The previous two examples (**1** and **2**) provide a clear indication of the potential utility of pyridine-induced shifts for the identification of salient structural features in the vicinity of a hydroxyl function, a 1,3-diaxial relationship[5] being indicated in these examples between hydroxyl function and proton(s) under consideration. Because of these observations, a more thorough investigation of pyridine-induced solvent shifts was undertaken with the specific intention of determining other solvent shift–structure relationships. The results of this study are discussed on the following pages.

Results and Discussion

In Tables I and II are reported the Δ values ($\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$) for the different protons and methyl groups present in the various alcohols and phenols analyzed in this study. It is evident from the data presented in these tables that definite relationships do exist between the chemical shift values induced in pyridine (Δ values) and the location and orientation of solute protons in the vicinity of the hydroxyl function. The various relationships which evolve from this study are summarized as follows.

(1) 1,3-Diaxial Deshielding. Individual protons or methyl groups occupying positions 1,3-diaxial to a hydroxyl function experience deshielding effects of the order of 0.20–0.40 ppm in pyridine relative to chloroform. The generality of this observation in the compounds analyzed is verified by the Δ values recorded in Table III and strongly confirms the validity of previous isolated observations of this effect.[5]

(2) Vicinal Deshielding. Protons and methyl groups vicinally situated to a hydroxyl function are deshielded. The extent of the deshielding seems to be dependent upon the magnitude of the dihedral angle θ, subtended between the proton (or methyl group) and the hydroxyl function. Table IV, which correlates dihedral angles with the Δ values observed, clearly illustrates this angular dependence.

In compounds 5α-androstan-1α-ol (**4**) and 5α-androstan-17α-ol (**12**), where the dihedral angle between hydroxyl function and methyl protons is large (θ = *ca.* 180 and 160°, respectively), the Δ values observed are small, −0.03 and −0.05 ppm, respectively. As θ decreases in magnitude, however, the Δ values increase. Thus for a dihedral angle of 85° as in 2-*endo*-hydroxybornane (**38**), a deshielding effect of 0.13 ppm is noted while in compounds **3**, **22**, **23**, and **35**, where the dihedral angle subtended by a methyl group or proton and a hydroxyl function is approximately 60°, shifts of 0.20–0.27 ppm to lower field are noted.

(3) Geminal Deshielding. Protons or methyl groups situated on a carbon atom bearing a hydroxyl function are deshielded by 0.15–0.25 ppm in pyridine relative to

(8) E. Wenkert and B. L. Mylari, *J. Amer. Chem. Soc.*, **89**, 174 (1967).

(9) It is recognized that other screening parameters such as (a) magnetic[10] and electric[11] field effects of the hydroxyl function itself and (b) van der Waals deshielding effects resulting from the proximity of H_1 to the C(9) hydroxyl function also contribute to the chemical shift difference between H_1 and H_2. However, these screening parameters alone are not sufficient to account for the total shift difference observed between H_1 and H_2 in pyridine.

(10) H. M. McConnell, *J. Chem. Phys.*, 27, 226 (1957).

(11) A. D. Buckingham, *Can. J. Chem.*, 38, 300 (1960).

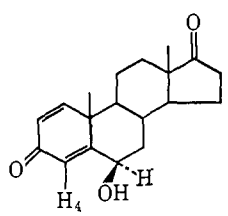
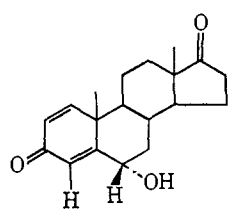
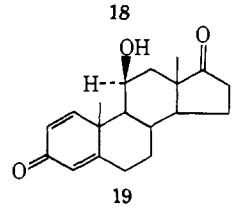
(12) From Zürcher's tables[13] of empirical chemical shifts, the following shift value is calculated for the C-19 protons in 5α-androstane-2β,17β-diol (2).

$$\delta_{(5\alpha\text{-androstane-}2\beta,17\beta\text{-diol}}{}^{C\text{-}19} = \delta_{5\alpha\text{-androstane}}{}^{C\text{-}19} + \delta_{2\beta\text{-OH}}{}^{C\text{-}19} + \delta_{17\beta\text{-OH}}{}^{C\text{-}19}$$
$$= 47.5 + 15.0 + 0.0$$
$$= 62.5 \text{ Hz}$$

The observed shift for the C-19 protons in pyridine is 80 cps from TMS.

(13) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

Table I. Pyridine-Induced Solvent Shifts (Δ^a Values) Observed for Different Protons in Compounds Studied

Compound	Resonance	Δ
5α-Androstan-1β-ol (**3**)	H-19	−0.22
	H-18	−0.02
	H-1	−0.17
5α-Androstan-1α-ol (**4**)	H-19	−0.03
	H-18	−0.01
	H-1	−0.17
5α-Androstan-2β-ol (**5**)	H-19	−0.30
	H-18	+0.01
	H-2	−0.24
5α-Androstan-2α-ol (**6**)	H-19	0.00
	H-18	+0.02
	H-2	−0.23
5α-Androstan-3β-ol (**7**)	H-19	−0.01
	H-18	+0.01
	H-3	−0.25
5α-Androstan-3α-ol (**8**)	H-19	−0.03
	H-18	0.00
	H-3	−0.21
5α-Androstan-4β-ol (**9**)	H-19	−0.31
	H-18	0.00
	H-4	−0.20
5α-Androstan-4α-ol (**10**)	H-19	−0.02
	H-18	0.00
	H-4	−0.19
5α(14α)-Androstan-17β-ol (**11**)	H-19	0.00
	H-18	−0.24
	H-17	−0.26
5α(14α)-Androstan-17α-ol (**12**)	H-19	0.00
	H-18	−0.05
	H-17	−0.26
5α(14α)-Androstan-16β-ol (**13**)	H-19	0.00
	H-18	−0.21
	H-16	−0.23
5α(14α)-Androstan-16α-ol (**14**)	H-19	+0.02
	H-18	−0.02
	H-16	−0.23
5α(14α)-Androstan-15β-ol (**15**)	H-19	+0.02
	H-18	−0.27
	H-15	−0.20
5α(14α)-Androstan-15α-ol (**16**)	H-19	−0.01
	H-18	−0.03
	H-15	−0.20
 **17**	H-19	−0.39
	H-6	−0.18
	H-4	−0.20
 **18**	H-19	−0.10
	H-6	−0.25
	H-4	−0.31
 **19**	H-19	−0.33
	H-18	−0.31
	H-11	−0.22

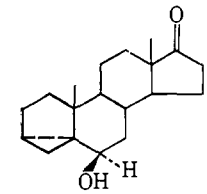
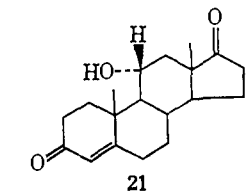
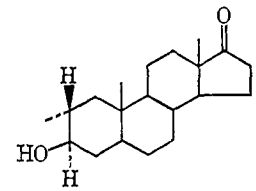
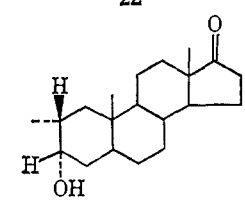
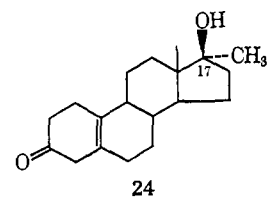
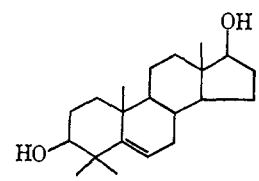
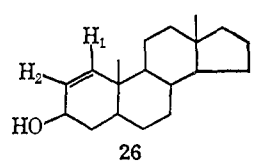
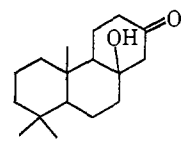
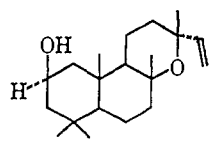
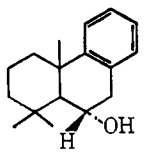
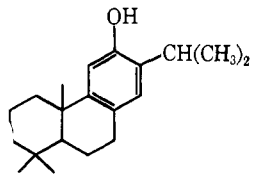
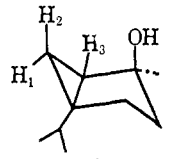
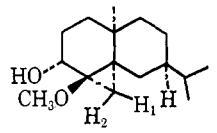
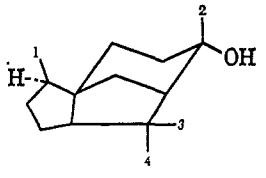
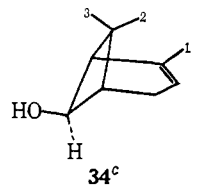
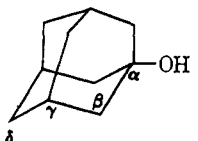
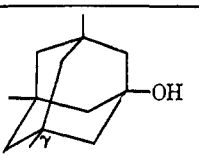
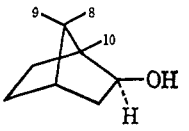
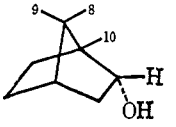
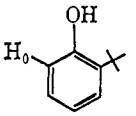
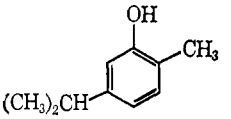
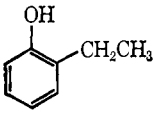
Compound	Resonance	Δ
 **20**	H-19	−0.27
	H-18	+0.01
	H-6	−0.20
 **21**	H-19	−0.21
	H-18	−0.08
 **22**[b]	H-19	−0.01
	2α-CH_3	−0.27
	H-3	−0.19
 **23**[b]	H-19	−0.02
	2α-CH_3	−0.22
	H-3	−0.20
 **24**	H-18	−0.19
	17α-CH_3	−0.20
 **25**	H-19	−0.04
	H-18	−0.23
	4β-CH_3, 4α-CH_3	−0.25 to −0.34
 **26**	H-1	−0.01
	H-2	−0.45
 **27**	10-CH_3	−0.20
	4β-CH_3	0.00
	4α-CH_3	0.00
 **28**	8-CH_3	0.00
	10-CH_3	−0.20
	4β-CH_3	−0.20
	4α-CH_3	0.00

Table I (*Continued*)

Compound	Resonance	Δ
 **29**	10-CH_3	−0.07
	4β-CH_3	−0.08
	4α-CH_3	−0.20
 **30**	4β-CH_3	0.00
	4α-CH_3	0.00
	10-CH_3	−0.02
	i-Pr	−0.40
 **31**[b]	H-1	−0.03
	H-2	−0.20
	H-3	0.00
 **32**	H-1	−0.09
	H-2	−0.30
 **33**	1-CH_3	0.00
	2-CH_3	−0.19
	3-CH_3	−0.12
	4-CH_3	0.00
 **34**[c]	1-CH_3	+0.01
	2-CH_3	−0.07
	3-CH_3	−0.25
 **35**[d]	β-H	−0.25
	γ-H	0.00
	δ-H	+0.06

Compound	Resonance	Δ
 **36**[d]	γ-CH_3	0.00
 **37**	8-CH_3	−0.26
	9-CH_3	−0.02
	10-CH_3	−0.18
 **38**	8-CH_3	−0.01
	9-CH_3	−0.01
	10-CH_3	−0.13
 **39**	*o*-H	−0.47
	t-Butyl	−0.31
 **40**	*o*-CH_3	−0.20
	i-Pr	0.00
 **41**	$-CH_2-$	−0.33
	CH_3	−0.13

[a] $\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$ (in parts per million). The Δ values recorded in Table I are solvent shifts induced by the hydroxyl function only. Correction has been made for solvent shifts resulting from the presence of other functional groups in the solute molecule. This is conveniently accomplished by subtracting the observed Δ values for any molecule shown in Table I from the observed Δ values for the corresponding system in which the OH function is absent. [b] These compounds were kindly supplied by Dr. L. H. Knox, Syntex Laboratories. [c] These compounds were kindly supplied by Dr. W. F. Erman, Procter and Gamble Co. [d] These compounds were kindly supplied by Dr. K. Gerzon, The Lilly Research Laboratories.

chloroform. These shifts are verified by the Δ values tabulated for the tertiary methine protons in the steroidal derivatives studied (see compounds **3**–**19** and **24**, Table I).

(4) *ortho*, *meta*, *para* **Deshielding (Phenolic Systems).** In phenolic systems protons and alkyl groups substituted *ortho* to a hydroxyl function have larger Δ values than protons or alkyl groups located *meta* or *para*. The magnitude of these shifts are summarized in Table II. Table V which is derived from the results tabulated in Table II lists the range of shifts observed for protons and methyl groups situated *ortho*, *meta*, or *para* to an OH function. Analysis of the results tabulated in Table V indicates that pyridine-induced solvent shifts may be extremely useful in determining the pattern of alkyl substitution in phenolic systems.

It is convenient at this point to consider a comparison of the nmr spectra of a few appropriate examples taken

Table II. Pyridine-Induced Solvent Shifts[a] for Proton Resonances of Methyl-Substituted Phenols

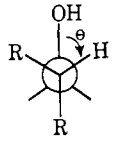
No.	Compound	Resonance					
		o-H	*m*-H	*p*-H	*o*-CH_3	*m*-CH_3	*p*-CH_3
42	*o*-Cresol	−0.38			−0.22		
43	*m*-Cresol	−0.39	−0.13	−0.02		+0.03	
44	*p*-Cresol	−0.37	−0.10				+0.03
45	2,6-Dimethylphenol		−0.16	−0.13	−0.23		
46	3,5-Dimethylphenol	−0.43		−0.01		−0.01	
47	2,4-Dimethylphenol	−0.40	−0.15		−0.24		−0.01
48	3,4-Dimethylphenol	−0.48	−0.09			+0.02	+0.02
49	2,5-Dimethylphenol	−0.45	−0.17	−0.06	−0.25	+0.01	
50	2,4,6-Trimethylphenol		−0.11		−0.25		−0.05
51	3,4,5-Trimethylphenol	−0.45				+0.02	+0.05
52	2,3,5-Trimethylphenol	−0.48		−0.03	−0.26	−0.03	
53	2,4,5-Trimethylphenol	−0.45	−0.13		−0.29	+0.02	+0.02
54	2,3,6-Trimethylphenol		−0.15	−0.12	−0.23	−0.01	
55	2,3,5,6-Tetramethylphenol			−0.07	−0.25	−0.03	

[a] Δ values are given in parts per million.

Table III. Δ Values Observed for Protons Situated 1,3-Diaxial to a Hydroxyl Function

No.	1,3-Diaxial interaction between	Δ, ppm
5	2β-OH and C-19	−0.30
9	4β-OH and C-19	−0.31
13	16β-OH and C-18	−0.21
15	15β-OH and C-18	−0.27
17	6β-OH and C-19	−0.39
18	6α-OH and H-4	−0.31
19	11β-OH and C-19	−0.33
19	11β-OH and C-18	−0.31
27	8β-OH and 10-CH_3	−0.20
28	2β-OH and 4β-CH_3	−0.20
28	2β-OH and 10-CH_3	−0.20
29	6α-OH and 4α-CH_3	−0.20
31	OH and H-2	−0.20
32	OH and H-2	−0.30
34	2-*exo*-OH and 3-CH_3	−0.25
37	2-*exo*-OH and 8-CH_3	−0.26

Table IV. Correlation of Dihedral Angles θ[a] (deg) with Observed Values



Compd	OH location[b]	Resonance	θ	Δ, ppm
4	1α	C-19	180	−0.03
12	17α	C-18	160	−0.05
38	2-*endo*	10-CH_3	85	−0.13
3	1β	C-19	60	−0.20
22	3β (eq)	2α-CH_3	60	−0.27
23	3α (ax)	2α-CH_3	60	−0.22
35		β-CH_2	60	−0.25

[a] Dihedral angles were measured on Dreiding models with the aid of a protractor. [b] Eq = equatorial; ax = axial.

Table V. Range of Δ Values Observed for Protons and Methyl Groups in Phenols

Proton	Δ, ppm	
o-H	−0.37 to −0.48	
m-H	−0.09 to −0.16	Partial
p-H	−0.02 to −0.13	overlap
o-CH_3	−0.22 to −0.29	
m-CH_3	+0.03 to −0.03	Partial
p-CH_3	+0.05 to −0.05	overlap

in deuteriochloroform and pyridine-d_5. Figure 2 illustrates clearly the advantage of this comparison in compounds **25**, **44**, and **26**.

Analysis of the methyl region in the nmr spectra of **25** in the two different solvents indicates the utility of shifts induced in pyridine for identifying methyl groups vicinal to a hydroxyl function. The C-19 methyl group which is neither 1,3-diaxial, vicinal, or geminal to a hydroxyl group is only slightly shifted in pyridine (Δ = −0.05 ppm), whereas the 4α and 4β and C-18 methyl groups experience strong deshielding effects indicative of their vicinal and angular proximity to a hydroxyl function (see Table IV).

The protons in **44** and **26** also illustrate marked chemical shift dependency on the nature of the solvent employed. This is dramatically illustrated in Figure 2 (upper) which shows the signal patterns that arise from the two magnetically nonequivalent aromatic and olefinic protons in **44** and **26**, respectively. Well-defined AB-type spectra are observed in deuteriochloroform, while completely collapsed singlets result in pyridine-d_5. These simplified resonance patterns which arise in pyridine-d_5 are a result of solvent-induced chemical shift equivalence[14] of the A and B protons due to the formation of solute–solvent complexes. Although the generality of this phenomenon is not known for compounds other than for **44** and **26**, it may be possible to utilize this effect in structure elucidation work for identifying the presence of allylic alcohols.

Having formulated generalizations on the basis of results obtained for a wide variety of structurally different compounds in which the spatial relationship between a hydroxyl function and certain protons is fixed, it is convenient to consider examples in which the hydroxyl function is no longer rigidly fixed and is therefore free to assume a preferred rotational conformation with respect to the substituents on the adjacent carbon atom. The Δ values ($\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$) reported recently for 2-*exo*-9- and 2-*exo*-10-dihydroxybornane[15] (compounds **56** and **57**, respectively) are recorded in parentheses beside their respective protons.[16]

(14) (a) S. S. Danyluk, *Can. J. Chem.*, **41**, 387 (1963); (b) D. E. McGreer and M. M. Mocek, *J. Chem. Educ.*, 40, 358 (1963).

(15) K. Tori, Y. Hamashima, and A. Takamizawa, *Chem. Pharm. Bull.* (Tokyo), **12**, 924 (1964).

(16) The solvent shifts indicated in parentheses are the shifts which result from interaction of solvent pyridine molecules with the primary

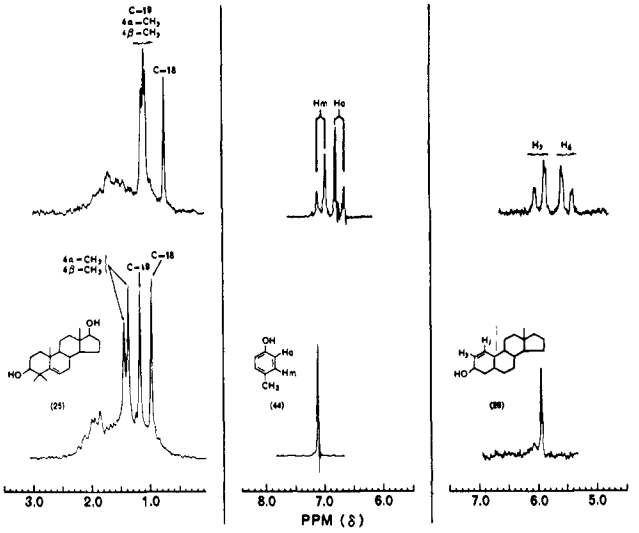
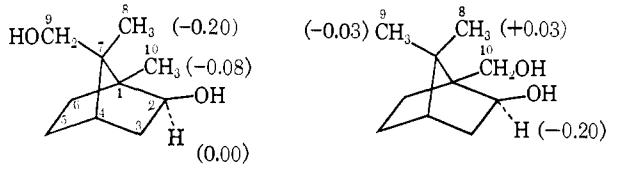


Figure 2. Portion of the nmr spectra of 4,4-dimethylandrosta-5-ene-3β,17β-diol (**25**), *p*-cresol (**44**), and androsta-1-en-3β-ol (**26**) in deuteriochloroform (upper) and pyridine-d_5 (lower).



56 **57**

If it can be assumed that the preferred rotamer of the $-CH_2OH$ moiety in this bicyclo ring system is approximately the same in pyridine and chloroform solutions, the observed solvent shifts (Δ values) can then be utilized to define the preferred rotational conformation of the $-CH_2OH$ group in these compounds.

In 2-*exo*-9-dihydroxybornane (**56**), three rotamers are possible and are illustrated in Figure 3. A solvent shift of -0.20 ppm for the 8-CH_3 protons in this compound is consistent with previous vicinal shift values observed for a dihedral angle θ of approximately 60° between methyl and hydroxyl groups (see Table IV). Thus, rotamers B and C are favored over A. Further evidence in support of the elimination of A as a possibility results from steric considerations, since, in this conformer, strong nonbonded interactions exist between the 9-hydroxy function and the two *exo* protons at C(5) and C(6). A choice between possibilities B and C can be made on the basis of the small solvent shift value for the 10-methyl protons ($\Delta = -0.08$ ppm) as well as, once again, from consideration of relative steric interactions. If C were the preferred rotamer, a Δ value for the 10-methyl group of much larger magnitude is anticipated (Δ expected = 0.2–0.4 ppm; see Table III) since it occupies a position 1,3-diaxial to the 9-hydroxy function. Furthermore, rotamer C is sterically the less favorable of the two, and thus rotamer B is expected to be the predominant species.

By similar reasoning, it is possible to speculate as to the most probable rotational preference of the 10-CH_2OH group in 2-*exo*-10-dihydroxybornane (**57**).

hydroxyl function *only*. Correction has been made for solvent shifts resulting from the 2-*exo*-hydroxyl function in both **56** and **57**.

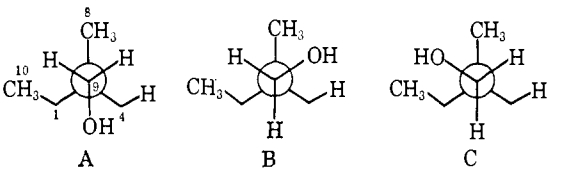


Figure 3. Possible rotamers of the 9-CH_2OH group in 2-*exo*-9-dihydroxybornane as viewed from the C(7)–C(9) bond.

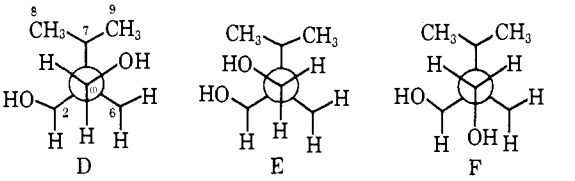


Figure 4. Possible rotamers of the 10-CH_2OH group in 2-*exo*-10-dihydroxybornane as viewed from the C(1)–C(10) bond.

Here again, three rotamers are possible as shown in Figure 4.

In compound **57** the Δ values observed for the 8- and 9-methyl groups are small ($\Delta = +0.03$ and -0.03 ppm, respectively), while for the tertiary 2-*endo* proton a relatively large value is observed ($\Delta = -0.20$ ppm). These pyridine-induced shifts strongly suggest that rotamer **F** is the most likely possibility of the three since in this rotamer, the 2-*endo* proton occupies a 1,3-diaxial relationship to the 10-hydroxy function. Consequently, a large Δ value is expected for the 2-*endo* proton, while a negligibly small Δ value is anticipated for both the 9- and 10-methyl protons. Furthermore, steric considerations are in support of rotamer **F**, since, in rotamers **D** and **E**, methyl–hydroxyl 1,3-diaxial interactions exist which are absent in **F**.

It is necessary to emphasize that a comparison of chemical shifts taken in pyridine with those taken in chloroform, for the purpose of determining conformational preferences about asymmetric centers, is only valid if the populations of the preferred rotamer remain approximately the same in both solvents.[17] This is believed to be the case in the above examples (**56** and **57**), but the need for caution in this approach cannot be overemphasized.

Stereochemical Nature of Solute–Solvent Association. In view of the very small shifts induced in pyridine relative to chloroform for the C-18 ($\Delta = +0.01$ ppm) and C-19 ($\Delta = +0.02$) methyl protons of nonfunctionalized 5α-androstane,[18] the large Δ values recorded in this study for a wide variety of structurally different alcohols (see Tables I and II) are rationalized in terms of specific molecular interactions involving complex formation between solvent and solute molecules. As a consequence of this coordination, aromatic pyridine molecules assume preferred orientations with respect to solute protons in the vicinity of the polar hydroxyl function. Because of the nature of the screening environment around aromatic systems,[6]

(17) A referee has suggested that this case can be strengthened by noting that chloroform is expected to hydrogen bond to the OH function as well. Both solvents, therefore, have the same effect in increasing the effective size of the hydroxyl group. Variations in rotamer populations for these and similar hydrogen-bonding solvents should be small, and consequently, this technique may have greater general utility than we have indicated above.

(18) D. H. Williams and D. A. Wilson, *J. Chem. Soc., B*, 144 (1966).

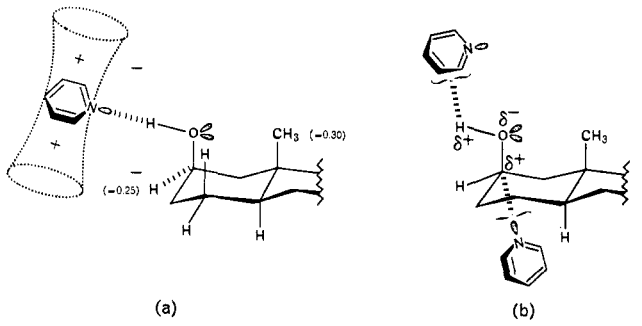


Figure 5. Stereochemical nature of solute–solvent association mechanisms: (a) hydrogen-bonding association and (b) collision complex association.

these protons can, as a result, be shielded or deshielded depending on the geometry of the solute–solvent complex.

Two distinct types of solute–solvent associations, namely, a hydrogen-bonding association and a collision complex association, are tentatively proposed for the saturated alcohols here presented. A qualitative picture of the stereochemical nature of both these solute–solvent associations[19] is illustrated in Figure 5 with reference to 5α-androstan-2β-ol as the solute molecule.

It has been well documented for some time that hydrogen-bond formation causes a shift of the resonance signal of the proton involved to lower field.[20] Consequently, since the hydroxyl protons in the compounds utilized in this study all have considerably lower field values in pyridine relative to chloroform ($\delta_{CDCl_3}^{OH} - \delta_{C_5D_5N}^{OH} \simeq 3$ ppm), hydrogen-bond association is definitively indicated. The stereochemical nature of this association is discussed with reference to Figure 5a.

In the case of hydrogen bonding of a hydroxyl proton to pyridine, it is assumed that the N···H–O bond is colinear, *i.e.*, the O–H bond lies along the axis of symmetry of the nitrogen lone-pair electrons, or very nearly so. For steric reasons, hydrogen-bond association must take place from the side of ring A directly away from the C-19 methyl group. This supposition is supported by evidence arising from nmr hydrogen-bonding studies in DMSO which indicate that the rotational preference of axial hydroxyl protons in conformationally rigid cyclohexane ring systems is cisoid to the α-tertiary methine proton.[21,22] Thus, in light of the presently known screening mechanism by which deshielding can occur, the geometrical relationship, illustrated in Figure 5a, explains at least qualitatively the Δ values observed for the OH, C-19, and $H_{2\alpha}$ protons in compound **5**.

An alternate, but equally probable, deshielding mechanism involves the formation of time-averaged collision types of complexes formerly postulated for the carbonyl–benzene system[7] and illustrated in Figure 5b. Since it has been established that this type of coordination takes place at electropositive sites within the solute molecule, two seemingly possible sites for coordination in the pyridine–alcohol system are at the C(2) carbon atom and along the OH bond (probably closer to the hydroxyl proton in order for the π electrons of the aromatic system to be situated as far as possible from the negatively polarized oxygen atom).

If reasonable N···H–O hydrogen-bond and collision complex lengths were assumed, it would then be possible, with the aid of appropriately measured parameters on molecular models, to estimate in a quantitative manner individual screening contributions made to the total screening coefficient of various protons within the solute molecule, arising from the magnetic anisotropy of the aromatic pyridine system (employing the Johnson and Bovey approach[23]) and the electric field effect of the nitrogen lone-pair electrons[24–26] (employing the Buckingham electric field expression[11]). However, owing to the strong possibility that other complicating screening factors may be involved, such as (a) modified electric and magnetic field effects of the O–H and C–O hydroxyl bonds arising from increased electron density at the oxygen atom as a result of hydrogen-bond formation and (b) the presence of associated species with greater than 1:1 stoichiometry, any theoretical treatment of this physical situation at this point can only be speculative. As a result, attempts to form a precise physical picture of the above-described solute–solvent associations will have to be left to a more rigorous theoretical study.

Experimental Section

Methods. Nmr spectra were measured on a Varian HA-60 spectrometer at the normal probe operating temperature (*ca.* 30°). Sample concentrations were *ca.* 5% w/v and chemical shifts were measured relative to TMS as internal reference. Resonance peaks were measured directly from calibrated chart paper; the calibration was checked frequently against the chemical shift difference (436 Hz) between TMS and $CHCl_3$. Shift values reported are thus considered to be accurate to ± 2 Hz. For compounds not having first-order spectra, chemical shift assignments were verified by spin–spin decoupling.

Acknowledgments. Compounds **5–16,** shown in Table I, were made by P. V. D. during research studies at the School of Pharmacy, University of London. All compounds have the requisite spectral properties and give correct elemental analysis. Experimental details regarding the synthesis of these compounds will be published elsewhere. We kindly acknowledge the permission of Professor W. B. Whalley to utilize these compounds in this study.

(19) In Figure 5b brackets are inserted between solute and solvent molecules in order to indicate that it is uncertain whether collision complex associations formed in these systems are of the n type (association due to attraction of the nitrogen lone pair to electropositive site in solute), or π type (association due to attraction of aromatic π electrons to electropositive site in solute), or both.

(20) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, Chapter 4.

(21) R. J. Ouellette, *J. Amer. Chem. Soc.*, **86**, 4378 (1964).

(22) C. P. Rader, *ibid.*, **88**, 1713 (1966).

(23) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(24) Pyridine has been shown to have a dipole moment of 2.15 D,[25] of which 0.5 D can be attributed to the sum of the π electron and C_4–H bond moments.[26] Therefore, an electric dipole moment of 1.7 D may be attributed to the nitrogen lone-pair electrons. The magnitude of this moment is sufficient to cause reasonable electric field screening effects.

(25) B. B. De More, W. S. Wilcox, and J. H. Goldstein, *J. Chem. Phys.*, **22**, 876 (1954).

(26) R. D. Brown and M. L. Heffernan, *Aust. J. Chem.*, **10**, 493 (1957).