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SOLVENT EFFECTS IN NMR SPECTROSCOPY—II

SOLVENT SHIFTS IN SOME STEROIDAL SAPOGENINS

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Abstract—The NMR spectra of a number of steroidal sapogenins have been determined employing both benzene and deuterochloroform as solvents. The Δ value ($\delta_{CDCl_3} - \delta_{C_6H_6}$) for a specific proton is dependent upon the location of the proton relative to polar sites in the molecule. Solvent shifts can therefore be of great utility in structural and stereochemical problems.

STEROIDAL sapogenins have been the subject of several NMR investigations,[1–3] as a result of which the stereochemistry of rings E and F can now be determined with relative ease. In the present study we have utilized the rigid framework of the steroidal sapogenins to illustrate how the solvent shifts of NMR resonances may be advantageously employed in structural and stereochemical problems.

The positions of readily discernible proton resonances in the spectra of diosgenin (I), diosgenin acetate (II), neodiosgenin (III), hecogenin acetate (IV), smilagenin (V), $\Delta^{1,4,6}$-spirostatrien-3-one (VI), sarsapogenin acetate (VII), sarsapogenin (VIII) and markogenin diacetate (IX), in both deuterochloroform and benzene solutions, are summarized in Table 1. Solvent shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$)[4,5] are indicated in the Table. In those cases where the position of the H-26 resonances is indicated as approximate only, this corresponds to a situation in which both C-26 protons resonate in the same region and give rise to a broad band; no accurate value of Δ is then calculable, so the approximate shift of the band is given.

The data for $CDCl_3$ solutions in Table 1 confirm the previous conclusion[2] that the chemical shifts of the C-26 protons are similar for sapogenins of the 25D series (I–VI, equatorial methyl group at C-25), but quite distinct for members of the 25L series (VII–IX, axial methyl group at C-25). As pointed out previously,[2] the chemical shift of the C-27 protons also reflects the stereochemistry at C-25 (contrast δ_{CDCl_3} for 27-H in I–VI and VII–IX).

Examination of the Δ values given in Table 1 leads one to the important conclusion that *the solvent shift for a given proton is approximately constant providing that the position of the proton relative to polar sites in the molecule is unchanged in*

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[1] W. E. Rosen, J. B. Zeigler, A. C. Shabica and J. N. Shoolery, *J. Amer. Chem. Soc.* **81**, 1687 (1959).

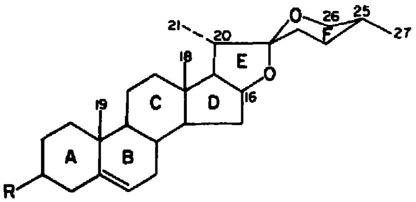
[2] J. P. Kutney, *Steroids* **2**, 225 (1963).

[3] J. P. Kutney, W. Cretney, G. R. Pettit and J. C. Knight, *Tetrahedron* **20**, 1999 (1964).

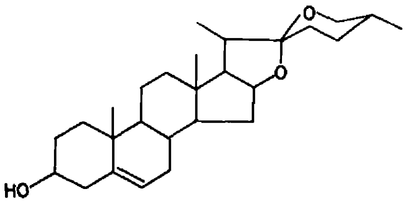
[4] N. S. Bhacca and D. H. Williams, *Tetrahedron Letters* 3127 (1964).

[5] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* pp. 163–176. Holden-Day, San Francisco (1964).

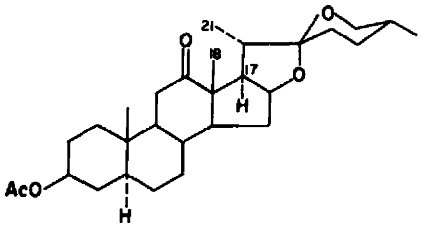
[6] The assignments given to the H-18 and H-19 protons of IV in Table 1 are opposite to those reported by Kutney,[2] but are confirmed by the data of Tori and Aono.[7]



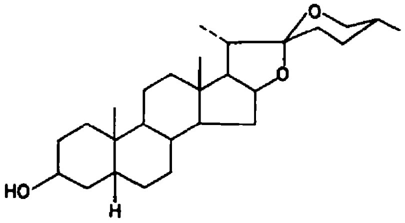
I, R=OH
II, R=OAc



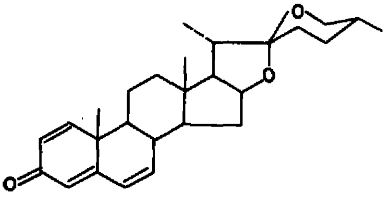
III



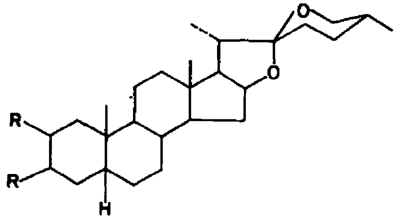
IV



V



VI



VII, R=H, R'=OAc
VIII, R=H, R'=OH
IX, R=R'=OAc

the various compounds. For example, the C-16 proton, which has the 16α-configuration in all cases, and whose polar environment is unchanged in rings B, C, D, E and F in compounds V and VII–IX, exhibits only a small range of Δ values (−0·22 to −0·26). Similarly, the shifts of the C-26 two-proton multiplet are always similar in I–VI (approximate range of Δ = −0·12 to −0·15) and VII–IX (Δ = −0·06 to −0·08 and Δ = −0·18 to −0·21 for the C-26 axial and equatorial protons, but not necessarily respectively).

However, the solvent shifts for the protons of the C-27 methyl group are obviously dependent on its equatorial (I–VI, Δ = 0·08 to 0·13) or axial (VII–IX, Δ = −0·02) nature; these variations in Δ reflect the change in spatial relationship

TABLE 1. SOLVENT SHIFTS ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$ ppm) OF PROTON RESONANCES IN THE NMR SPECTRA OF STEROIDAL SAPOGENINS

Compound		Resonance					
		16α-H	26-H	27-H	21-H	19-H	18-H
I	δ_{CDCl_3}	4·38	∼3·45	0·79	0·97	1·03	0·79
	$\delta_{C_6H_6}$	4·57	∼3·57	0·67	1·20	0·92	0·83
	Δ	−0·19	∼−0·12	0·12	−0·23	0·11	−0·04
II	δ_{CDCl_3}	—	∼3·42	0·78	0·97	1·04	0·78
	$\delta_{C_6H_6}$	—	∼3·56	0·67	1·20	0·90	0·81
	Δ	—	∼−0·14	0·11	−0·23	0·14	−0·03
III	δ_{CDCl_3}	4·41	∼3·45	0·78	1·14	1·02	0·97
	$\delta_{C_6H_6}$	4·58	∼3·60	0·70	1·14	0·94	0·99
	Δ	−0·17	∼−0·15	0·08	0·00	0·08	−0·02
IV	δ_{CDCl_3}	—	∼3·45	0·80	1·07	0·93	1·05
	$\delta_{C_6H_6}$	4·44	∼3·58	0·67	1·50	0·91	0·54
	Δ	—	∼−0·13	0·13	−0·43	0·02	0·51
V	δ_{CDCl_3}	4·40	∼3·43	0·79	0·97	0·98	0·76
	$\delta_{C_6H_6}$	4·63	∼3·57	0·67	1·22	0·94	0·82
	Δ	−0·23	∼−0·14	0·12	−0·25	0·04	−0·06
VI	δ_{CDCl_3}	4·30	∼3·40	0·79	0·97	1·22	0·91
	$\delta_{C_6H_6}$	4·51	∼3·55	0·67	1·15	0·75	0·85
	Δ	−0·21	∼−0·15	0·12	−0·18	0·47	0·06
VII	δ_{CDCl_3}	4·40	3·30/3·95	1·08	1·00	1·00	0·77
	$\delta_{C_6H_6}$	4·63	3·38/4·14	1·10	1·22	0·91	0·82
	Δ	−0·23	−0·08/−0·19	−0·02	−0·22	0·09	−0·05
VIII	δ_{CDCl_3}	4·40	3·30/3·95	1·08	1·00	0·98	0·77
	$\delta_{C_6H_6}$	4·62	3·36/4·13	1·10	1·20	0·93	0·81
	Δ	−0·22	−0·06/−0·18	−0·02	−0·20	0·05	−0·04
IX	δ_{CDCl_3}	4·40	3·30/3·91	1·06	1·05	1·05	0·77
	$\delta_{C_6H_6}$	4·66	3·38/4·12	1·08	0·89	0·89	0·78
	Δ	−0·26	−0·08/−0·21	−0·02	0·16	0·16	−0·01

between the C-27 protons and the ether functions of rings E and F. Of course, similar inferences as to the C-27 stereochemistry may also be drawn merely from the δ values for 27-H in either deuterochloroform or benzene solutions (Table 1). Nevertheless, a consideration of the variations in Δ for 18-H and 21-H resonances illustrates that additional information may often be forthcoming from a consideration of solvent shifts. Thus, the downfield shifts of 18-H and 21-H resonances in the spectrum of neodiosgenin (III) in deuterochloroform, relative to their positions in diosgenin (I) and diosgenin acetate (II), can only indicate a change in the electronic environment of both C-18 and C-21 protons, the deshielding perhaps being due to mutual steric interaction.[1] However, the solvent shifts in Table 1 suggest that the position of the C-18 methyl group relative to the basic skeleton is the same in I, II and III (Δ = −0·04, −0·03, −0·02 respectively), whereas the C-21 protons of neodiosgenin (III, Δ = 0·00) must have a different orientation with respect to rings E and F to that existing in diosgenin (I, Δ = −0·23) and diosgenin acetate (II, Δ = −0·23). Therefore, even in the absence of any chemical considerations as to which centre may be epimerized in the conversion of diosgenin (I) to neodiosgenin (III), the solvent shifts indicate epimerization at C-20 and further, that the C-21 methyl group has moved into the region of the C-18 methyl group (similar Δ values) rather than *vice versa*.

The solvent shifts for hecogenin acetate (IV)[6] indicate that the keto-group in this molecule must be located to produce a downfield shift of 21-H in benzene solution [Δ(21-H) is an abnormally large, negative value for (IV)] and a large upfield shift of 18-H in the same solvent. The association between a benzene solvent molecule and a carbonyl group of a solute molecule is such as to barely influence equatorial protons or methyl groups α to the ketone, but strongly shield axial α-H or α-CH_3 moieties; groups behind the carbonyl are shielded, while those in front of the carbonyl are deshielded (Fig. I).[4,5,8,8a] Therefore it is immediately evident that C-12 is the most likely location of the carbonyl group (see IV). A very interesting feature of the downfield region (Fig. 2, $\delta = 2{\cdot}5$–$5{\cdot}0$ ppm) in the spectrum of hecogenin acetate (IV) in benzene is the appearance of a one proton resonance centered at 2·77 ppm; this resonance is hidden within the bounds of the methylene envelope when the spectrum is determined in deuterochloroform solution. The resonance appears as a quartet with splittings of 6 c/s and 8 c/s and must therefore be due to the 17α-proton; inspection of a Dreiding model of hecogenin acetate (IV) in fact reveals that the 17α-proton lies in front of the carbonyl group, exactly where deshielding in benzene

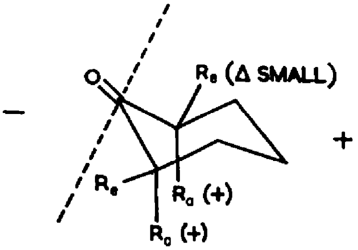


FIG. 1. Signs of Δ values induced by benzene-ketone collision complex (R = H or CH_3).

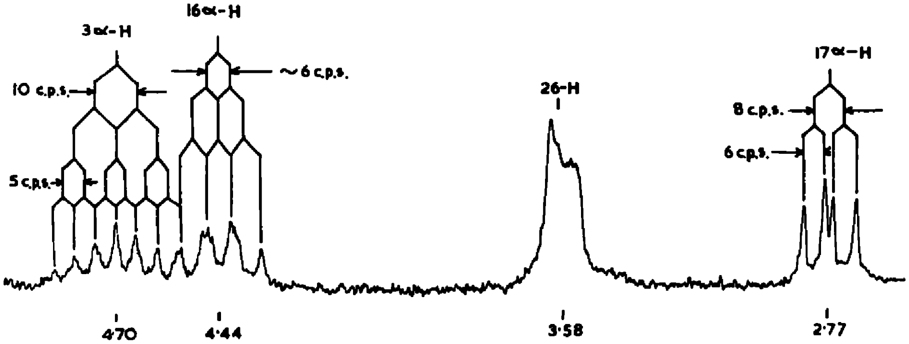


FIG. 2. 100 Mc spectrum of hecogenin acetate in benzene (δ = 2·5 − 5·0 ppm).

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[7] K. Tori and K. Aono, *Annual Report of the Shionogi Research Laboratory* No. 14. Osaka, Japan (1964).

[8] N. S. Bhacca and D. H. Williams, unpublished work.

[8a] Note added in proof: Since the submission of this manuscript, data have been reported (J. D. Connolly and R. McCrindle, *Chem. & Ind.* 379, 1965) which indicate that appreciable solvent shifts occur even when association between benzene and carbonyl groups is sterically unfavourable. The mechanism by which solvent shifts occur must therefore still be regarded as an open question. These authors have independently proposed the same reference plane for predicting the sign of Δ and we wish to thank them for sending us a copy of their manuscript prior to publication.

[9] Ref. 5, pp. 80–81 and 179–180.

solution should occur. The 3α-proton resonance at 4·70 ppm is evident as the characteristic seven-line pattern associated with an equatorial acetate function[9]; one line of the pattern overlaps the 1 : 3 : 3 : 1 quartet centered at 4·44 ppm, which is attributed to the 16α-proton undergoing three approximately equal interactions to vicinal neighbours attached to C-15 and C-17.

EXPERIMENTAL

All spectra were determined using Perkin-Elmer 60Mc, Varian A-60 and/or 100 Mc NMR Spectrometers. Tetramethylsilane was employed as internal reference for both $CDCl_3$ and benzene solution spectra.

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