Tetrahedron Letters No.42, pp. 3127-3132, 1964. Pergamon Press Ltd.
Printed in Great Britain.

SOLVENT EFFECTS IN N.M.R. SPECTROSCOPY. I. CHEMICAL SHIFTS INDUCED BY BENZENE IN SOME STEROIDAL KETONES AND ACETATES

Norman S. Bhacca
Varian Associates, Palo Alto, California
Dudley H. Williams
Department ot Chemistry, Stanford University, Stanford, California

(Received 21 August 1964)

The C-18 and C-19 methyl resonances of 5α-androstane occur at $\delta = 0.69$ p.p.m. and $\delta = 0.79$ p.p.m. in deuteriochloroform solution (I) and at $\delta = 0.71$ p.p.m. and $\delta = 0.79$ p.p.m. in benzene solution.* It therefore appears likely that in the absence of polar functional groups, no preferred geometrical relationship exists between solvent and solute molecules, since the position of the angular methyl resonances are barely influenced on passing from deuteriochloroform to benzene as solvent.

However, the positions of the C-18 and C-19 angular methyl resonances in the n.m.r. spectra of 5α-androstan-1-one, 5α-androstan-2-one, and 5α,14β-androstan-15-one (I) and 5α-androstan-11-one (II) are considerably different in deuteriochloroform and benzene solutions. The data are summarized in Table I; the calculated positions of the angular methyl resonances in deuteriochloroform solution ($\delta^{calc.}_{CDCl_3}$) were obtained by using the table of additive shifts compiled by Zürcher (1).

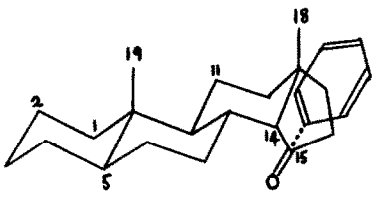
*All n.m.r. spectra discussed in this paper were determined on Varian A-60 or HR-100 spectrometers.

Table I

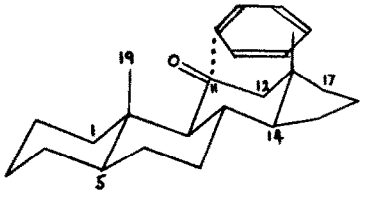
Solvent Effects on Angular Methyl Resonances in some Keto Steroids (δ values in p.p.m.)

COMPOUND		$\delta^{calc.}_{CDCl_3}$	$\delta^{obs.}_{CDCl_3}$	$\delta_{C_6H_6}$	$\Delta = \delta^{obs.}_{CDCl_3} - \delta_{C_6H_6}$
5α-Androstan-1-one	C-19	1.17	1.17	0.87	0.30
	C-18	0.71	0.69	0.69	0.00
5α-Androstan-2-one	C-19	0.77	0.75	0.59	0.16
	C-18	0.70	0.69	0.63	0.06
5α-Androstan-11-one (II)	C-19	1.01	1.03	1.17	-0.14
	C-18	0.66	0.67	0.56	0.11
5α,14β-Androstan-15-one (I)	C-19	0.73	0.73	0.72	0.01
	C-18	1.18	1.17	0.92	0.25

It can be seen from Table I that when the carbonyl group is relatively near C-19, but remote from C-18, as in 5α-androstan-1-one and 5α-androstan-2-one, the shielding effect on passing from deuteriochloroform to benzene solution ($\Delta = \delta^{obs.}_{CDCl_3} - \delta_{C_6H_6}$) is greater on C-19 (see I and II for the numbering of the steroid skeleton). Alternatively, Δ is small for C-19 but corresponds to a large shielding effect on C-18 in 5α,14β-androstan-15-one (I) in which compound the carbonyl group is in ring D. These results are consistent with the formation of a collision complex in which the π-electrons of the benzene ring interact with the partial positive charge on the carbonyl carbon atom in such a manner that the π-electrons are as far as possible from the partial negative charge on oxygen (see, for example, I). Similar 1:1 collision complexes have been postulated to explain the benzene-induced solvent shifts in the spectra of amides (2) and mesityl oxide (3).



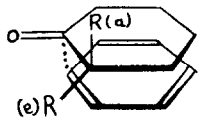
I



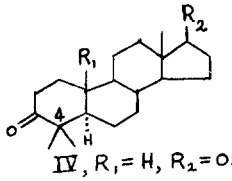
II

The negative value of Δ for the C-19 methyl group of 5α-androstan-11-one (II) is very interesting, because this is the sole example in Table I of deshielding being caused by benzene. This observation can very reasonably be interpreted in terms of the collision complex theory, since coordination of the benzene with a carbonyl group as illustrated in II would be anticipated to cause deshielding of the C-19 protons, which lie to the side of the coordinating benzene ring.

We have also determined the shifts induced by benzene on methyl groups adjacent (α) to a carbonyl function and find that these shifts are dependent upon the axial or equatorial nature of the methyl group. In 5α-androstan-1-one, 5α-androstan-12-one and 5α-androstan-17-one (see II for numbering of steroid skeleton), the C-19, C-18 and C-18 methyl groups, respectively, occupy axial positions adjacent to a carbonyl function. Each of these axial methyl resonances suffers an appreciable upfield shift ($\Delta = \delta^{obs.}_{CDCl_3} - \delta_{C_6H_6} = 0.2\text{-}0.3$ p.p.m.) on passing from deuteriochloroform to benzene solution. However, in 4α-methyl-5α-androstan-17-ol-3-one acetate and 2α-methylcholestan-3-one the equatorial methyl groups adjacent to the carbonyl function suffer a small downfield shift (Δ values of -.0.06 and -0.07 p.p.m. respectively). These results are also consistent with the formation of a collision complex such as III (R = CH_3, schematic only); the anisotropy of the benzene ring is such that axial methyl groups would be expected to be shielded, whereas equatorial methyl groups should be affected much less and perhaps even deshielded slightly, as observed in the two instances outlined above.



III



IV, $R_1 = H$, $R_2 = OH$

V, $R_1 = CH_3$, $R_2 = H$

This type of correlation may prove to be very useful in the assignment of methyl resonances, especially in the triterpene field where a large number of unsplit methyl signals are encountered. Since the 4,4-dimethyl-3-keto moiety is very common among triterpenes, a number of 4,4-dimethyl-3-keto steroids have been examined as model compounds.

In the spectra of both 19-nor-4,4-dimethyl-5α-androstan-17β-ol-3-one (IV) and 4,4-dimethyl-3α-androstan-3-one (V), determined in deuteriochloroform solution, the two C-4 methyl resonances are coincident at 1.06 p.p.m. The benzene solution spectrum of IV exhibits the C-4 methyl resonances at 1.16 and 0.83 p.p.m., whereas they appear at 1.14 and 0.95 p.p.m. in the corresponding spectrum of V. It can be seen that these results are consistent with deshielding of the equatorial 4α-methyl groups in IV and V by benzene (Δ = -0.10 and -0.08 p.p.m., respectively) and shielding of the axial 4β-methyl groups (Δ = +0.23 and +0.11 p.p.m. respectively). The spectra of several other steroidal α-dimethylketones are consistent with a downfield shift (negative Δ) of the equatorial methyl group adjacent to carbonyl and an upfield shift (positive Δ) of the corresponding axial resonance (4). However, it is emphasized that it is not yet known how these apparently characteristic shifts may be affected by additional functional groups.

In ten steroids containing the 17β-acetyl moiety, the Δ values (as defined in Table 1) observed for the C-20 methyl resonance always lay in the range + (0.25 - 0.45 p.p.m.). These results illustrate that the geometry of the benzene-carbonyl collision complex is such as to shield the protons of a methyl ketone. As might be anticipated, a similar range of Δ values is observed for the methyl resonance of an acetate function. The results for some 3β- and 17β-acetates are summarized in Table 2. In the right hand column of the table the Δ values observed for the 3α- and 17α-protons of the 3β- and 17β-acetates, respectively, are given; with one exception, these protons suffer a small downfield shift.

Table 2

Solvent Shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$) of Methyl and Methine Proton Resonances ($CH_3COO-\dot{C}H-$) for some 3β- and 17β-Acetates

COMPOUND	$\Delta(CH_3)$ p.p.m.	$\Delta(H)$ p.p.m.
5α-Androstan-17β-ol-3-one acetate	0.28	- 0.10
4α-Methyl-5α-androstan-17β-ol-3-one acetate	0.31	- 0.10
19-Nor-10-formyl-Δ^5-androsten-3β-ol-17-one acetate	0.24	- 0.12
5,6-Dihydroergosterol 3β-acetate	0.23	- 0.08
6,16α-Dimethyl-Δ^5-pregnene-3β,7α-diol-20-one 3β-acetate	0.24	- 0.18
Δ^5-Androsten-3β-ol-7,17-dione acetate	0.29	+ 0.05

Some solvent shifts of protons adjacent to carbonyl ($-C\underline{H}_2-\dot{C}=O$) are given in Table 3. It is evident that in the compounds so far studied, axial protons adjacent to carbonyl are shielded by benzene (Δ = +0.03 to +0.66 p.p.m.), whereas the corresponding equatorial protons are either barely moved or shifted downfield (Δ = +0.06 to -0.37 p.p.m.). Thus protons adjacent to carbonyl suffer shifts which are reminiscent to those occurring for methyl groups adjacent to carbonyl. The results may be interpreted in terms of the usual collision complex (III, R = H).

Table 3

Solvent Shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$) for Axial and Equatorial Protons Adjacent to Carbonyl

Compound	Proton	Configuration	Δ (p.p.m.)
5α-Androstan-11-one	12α	a	+0.37
	12β	e	-0.03
5α-Androstan-3β-ol-11-one tosylate	12β	e	+0.06
2α,3α-Epoxy-5α-Androstan-11-one	12α	a	+0.39
	12β	e	-0.02
5α-Androstan-2,11-dione	12α	a	+0.35
	12β	e	+0.03
5α-Androstan-2-one	1β	e	+0.05
Δ^{16}-5α-Androsten-3β-ol-11,20-dione acetate 20-oxime	12α	a	+0.03
	12β	e	-0.37
2α-Bromocholestan-3-one	2β	a	+0.43
2α-Chloro-4α-bromo-cholestan-3-one	2β	a	+0.70
	4β	a	+0.66
Methyl 4β-Bromo-12α-acetyloxy-3-one cholanate	4α	a	+0.35
12α-Bromo-5α-androstan-11-one	12β	e	-0.01
Δ^{16}-5α-Androsten-3β-ol-11,20-dione acetate	12α	a	+0.16
	12β	e	-0.26

The results described in this paper suggest that a study of chemical shifts induced by benzene in carbonyl-containing compounds may be of great assistance in structural and stereochemical problems.

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