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# SOLVENT EFFECTS IN NMR SPECTROSCOPY—III[1]

## CHEMICAL SHIFTS INDUCED BY BENZENE IN KETONES

D. H. WILLIAMS
University Chemical Laboratory, Lensfield Road, Cambridge

and

N. S. BHACCA
Varian Associates, Palo Alto, California

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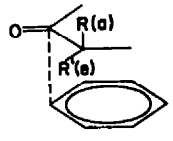
**Abstract**—Proton chemical shifts determined in deuterochloroform and benzene solutions for a large number of ketones are consistent with the formation of a collision complex between carbonyl groups and benzene solvent molecules. The solvent shifts ($\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$) associated with carbonyl groups frequently remain dominant even in the presence of other functionalities and are approximately additive. As a general rule, $\Delta$ values are negative for protons lying in front of the carbonyl group and positive for protons lying behind the carbonyl group. Solvent shifts are therefore useful in establishing the spatial relationships between ketones and protons whose resonances can be discerned in both solvents. The preferred orientation of the 17$\beta$-acetyl group in 5$\alpha$-pregnan-20-one has been deduced from solvent shifts.

IN A preliminary communication,[2] we reported the chemical shifts induced by benzene in some steroidal ketones and acetates. It was concluded that the ketones in benzene solution form a solute-solvent collision complex in which the $\pi$-electrons of the benzene ring interact with the partial positive charge on the carbonyl carbon atom in such a manner that the $\pi$-electrons are as far as possible from the partial negative charge on oxygen[3] (see, for example, I, schematic only).[3a] In practice, due to the diamagnetic anisotropy of the benzene ring, axial methyl groups (I, R = $CH_3$) or protons (I, R = H) are shielded, whereas equatorial methyl groups (I, R′ = $CH_3$) or protons (I, R′ = H) are either deshielded or barely influenced.[2] We have now extended our measurements




I

[1] Part II, D. H. Williams and N. S. Bhacca, *Tetrahedron* **21**, 1641 (1965).
[2] N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, 3127 (1964).
[3] J. V. Hatton and R. E. Richards, *Mol. Phys.* **5**, 139 (1962).
[3a] We emphasize, now, as previously,[2] that diagrams such as I must be regarded as schematic only. Obviously in many steroids studied in this paper, the presence of axial methyl groups near the C=O group prevents a planar association. Although our results are consistent with the formation of a collision complex,[2] in the light of solvent shifts reported since the submission of this manuscript (J. D. Connolly and R. McCrindle, *Chem. & Ind.* 379, 1965), the mechanism by which solvent shifts occur must still be open to debate. The reference plane (defined subsequently in this paper) for predicting the sign of solvent shifts has been independently proposed by the above authors.

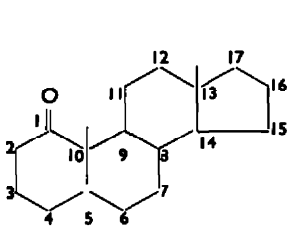
in the hope of formulating wider generalizations and indicating how solvent shifts may be of use in structural, stereochemical and conformational problems.

TABLE 1. Δ VALUES ($\delta_{CDCl_3} - \delta_{C_6H_6}$ PPM) FOR H-18 AND H-19 PROTON RESONANCES IN SOME KETO-STEROIDS

| Compound | Resonance | $\delta_{CDCl_3}$ | $\delta_{C_6H_6}$ | Δ |
|---|---|---|---|---|
| 5α-Androstan-1-one (II) | H-19 | 1·17 | 0·87 | 0·30 |
| | H-18 | 0·69 | 0·69 | 0·00 |
| 5α-Androstan-2-one (III) | H-19 | 0·75 | 0·59 | 0·16 |
| | H-18 | 0·69 | 0·63 | 0·06 |
| 5α-Androstan-3-one (IV) | H-19 | 1·02 | 0·65 | 0·37 |
| | H-18 | 0·72 | 0·62 | 0·10 |
| 5α-Androstan-6-one (V) | H-19 | 0·75 | 0·63 | 0·12 |
| | H-18 | 0·62 | 0·56 | 0·06 |
| 5α-Androstan-7-one (VI) | H-19 | 1·06 | 0·74 | 0·32 |
| | H-18 | 0·70 | 0·62 | 0·08 |
| 5α-Androstan-11-one (VII) | H-19 | 1·03 | 1·17 | −0·14 |
| | H-18 | 0·67 | 0·56 | 0·11 |
| 5α-Androstan-12-one (VIII) | H-19 | 0·87 | 0·63 | 0·24 |
| | H-18 | 1·01 | 0·75 | 0·26 |
| 5α-Androstan-15-one (IX) | H-19 | 0·80 | 0·70 | 0·10 |
| | H-18 | 0·80 | 0·58 | 0·22 |
| 5α-Androstan-16-one (X) | H-19 | 0·83 | 0·68 | 0·15 |
| | H-18 | 0·88 | 0·56 | 0·32 |
| 5α-Androstan-17-one (XI) | H-19 | 0·81 | 0·69 | 0·12 |
| | H-18 | 0·86 | 0·64 | 0·22 |
| 5α,14β-Androstan-15-one (XII) | H-19 | 0·73 | 0·72 | 0·01 |
| | H-18 | 1·17 | 0·92 | 0·25 |
| 5α-Pregnan-20-one (XIII) | H-19 | 0·79 | 0·71 | 0·08 |
| | H-18 | 0·61 | 0·58 | 0·03 |

In Table 1 there are summarized the chemical shifts, in benzene and deuterochloroform solutions, of the C-18 and C-19 methyl resonances for 5α,14α-androstanones containing the keto-group at all possible nuclear locations except C-4 (II–XI, see II for numbering of steroid skeleton). Also recorded in the Table are data for 5α,14β-androstan-15-one (XII) and 5α,14α-pregnan-20-one (XIII) and Δ values ($\delta_{CDCl_3} - \delta_{C_6H_6}$ ppm) for all compounds.

It is evident from the data in Table 1 that benzene causes shielding, relative to deuterochloroform, of methyl resonances lying behind a plane drawn through the carbonyl carbon atom and perpendicular to the direction of the C—O bond (see XIV). Thus the C-19 protons, which lie behind such a plane in 1-, 2-, 3-, 6-, 7- and 12-ketones



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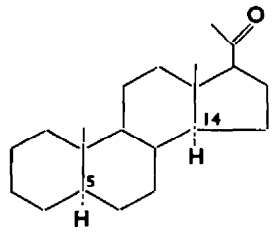
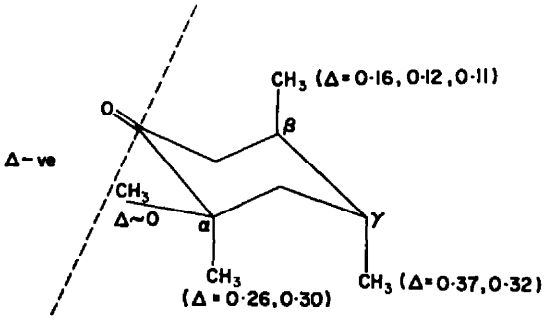


XIII

have positive Δ values (0·12–0·37) in these compounds (II–VI, VIII). In the absence of the carbonyl group i.e., in 5α-androstane, no shift is observed[2] and the shielding may therefore be attributed to a benzene–ketone collision complex as formulated in I.[4] If the keto-group is further away from the C-19 protons, as in steroids containing the functional group in ring C (IX–XII), the positive Δ values are, as anticipated, smaller (0·01–0·15). Similarly, the C-18 protons always lie behind the reference plane in compounds III–XII and therefore Δ is positive in these cases; large Δ values for C-18 protons are observed for ring C ketones (IX–XII, Δ = 0·22–0·32), but small values when the carbonyl group is in ring A (II–IV, Δ = 0·00–0·10). Moreover, the solvent shifts for an axial methyl group attached to a cyclohexanone ring chair are dependent upon the location of the methyl group at the β-position or α- and γ-positions (see XIV). Hence, Δ is larger in those steroids serving as a model for an α-axial methyl group (1- and 12-ketones) or a γ-axial methyl group (3- and 7-ketones) than in those containing a β-axial methyl group (2-, 6- and 11-ketones), as indicated in XIV.




XIV

The C-18 protons of 5α-androstan-1-one (II) lie approximately in the reference plane and no solvent shift is observed for these protons. The sole example of a methyl group lying in front of the chosen reference plane is the C-19 methyl group of 5α-androstan-11-one (VII). This resonance provides the only instance of deshielding by benzene in Table 1, and therefore it is indicated that protons in front of the reference plane may be deshielded in benzene relative to deuterochloroform. The generality of this phenomenon is evident from the data compiled in Table 2.

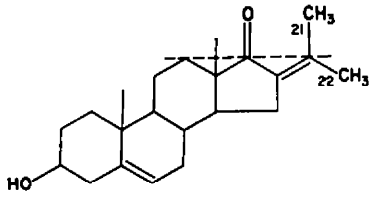
[4] The empirical correlations outlined in this paper are discussed in terms of $CDCl_3$ as reference solvent. In view of the possibility that $CDCl_3$ can itself co-ordinate to polar groups via hydrogen bonding, the definition $\Delta = \delta_{CCl_4} - \delta_{C_6H_6}$ is perhaps more desirable for precise studies of the benzene–ketone complex.[5] However, the use of $CDCl_3$-form as reference solvent is adequate when solvent shifts are being employed in structural problems.

[5] S. Bory, M. Fetizon, P. Laszlo and D. H. Williams, *Bull. Soc. Chim. Fr.* in press.

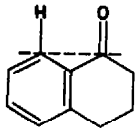
TABLE 2. SOME EXAMPLES OF DESHIELDING OF RESONANCES IN KETONES IN BENZENE SOLUTION

| Compound | Resonance | $\delta_{CDCl_3}$ | $\delta_{C_6H_6}$ | $\Delta$ |
|---|---|---|---|---|
| XV | H-21 | 2·22 | 2·32 | −0·10 |
| | H-22 | 1·83 | 1·53 | 0·30 |
| XVI | H-8 | 8·10 | 8·26 | −0·16 |
| VII | H-1 | 2·45 | 2·82 | −0·37 |
| XVII | H-19 | 1·00 | 1·10 | −0·10 |
| | H-1 | 2·35 | 2·67 | −0·32 |
| XVIII | H-19 | 1·07 | 1·31 | −0·24 |
| | H-1 | 3·10 | 3·37 | −0·27 |
| XIX | H-19 | 1·00 | 0·92 | 0·08 |
| | H-1 | 2·50 | 2·63 | −0·13 |

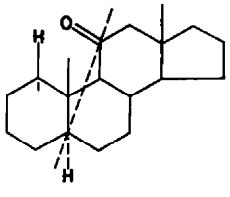
In the 16-isopropylidene ketone XV, the $\Delta$ value for the C-21 methyl group, which lies in front of the carbonyl group, is negative, while that for the C-22 methyl group, lying behind the reference plane, is positive. The C-8 proton in α-tetralone (XVI) suffers a paramagnetic shift in benzene. Similarly, the C-1 and C-19 protons in the 11-ketones VII and XVII–XVIII all have negative $\Delta$ values despite the presence of additional bromine and epoxide functions in XVII and XVIII respectively. However, the sign of $\Delta$ is changed in the instance of the H-19 resonance of 5α-androstan-3β-ol-11-one tosylate (XIX), which indicates that the proximity of a highly polar substituent can change the solvent shifts which are characteristic of an isolated keto-group; the influence of the tosylate group is not however sufficient to change the sign of $\Delta$ for the H-1 resonance of XIX and merely reduces the magnitude of the shift.



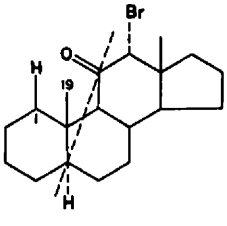

XV



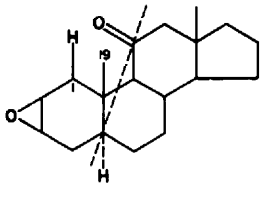

XVI



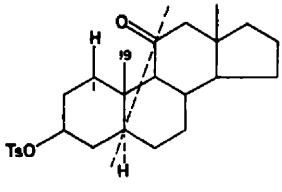

VII




XVII

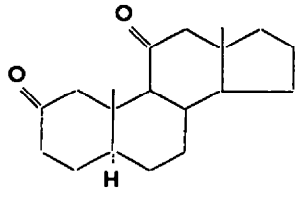



XVIII

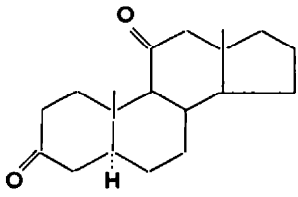



XIX

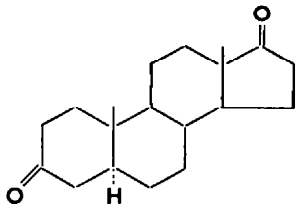
Solvent shifts in a number of diketones have also been examined and the results indicate that Δ values are approximately additive, as may be seen on examination of the data summarized in Table 3.



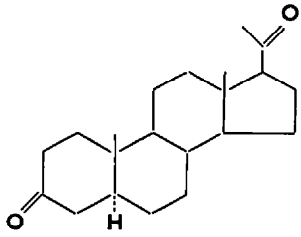
XX



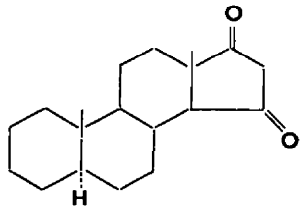
XXI



XXII



XXIII



XXIV

In Table 3, all calculated Δ values ($\Delta_{calc.}$) for H-18 and H-19 have been obtained from the data in Table 1. For example, Δ(H-19) for 5α-androstan-2-one (III) is 0·16 and for 5α-androstan-11-one (VII) is −0·14; $\Delta_{calc.}$ for 5α-androstan-2,11-dione (XX) is therefore 0·02 if one assumes a simple additivity of solvent shifts. The close agreement between values calculated in this way and observed shifts supports the additivity

TABLE 3. Δ VALUES ($\delta_{CDCl_3} - \delta_{C_6H_6}$ PPM) FOR PROTON RESONANCES IN SOME DIKETONES

| Compound | Resonance | $\delta_{CDCl_3}$ | $\delta_{C_6H_6}$ | $\Delta_{obs.}$ | $\Delta_{calc.}$ |
|---|---|---|---|---|---|
| XX | H-19 | 0·99 | 0·97 | 0·02 | 0·02 |
| | H-18 | 0·67 | 0·50 | 0·17 | 0·17 |
| | H-1 | 3·25 | 3·54 | −0·29 | −0·30 |
| XXI | H-19 | 1·25 | 1·02 | 0·23 | 0·23 |
| | H-18 | 0·71 | 0·51 | 0·20 | 0·21 |
| XXII | H-19 | 1·06 | 0·57 | 0·49 | 0·49 |
| | H-18 | 0·89 | 0·60 | 0·29 | 0·32 |
| XXIII | H-19 | 1·03 | 0·58 | 0·45 | 0·45 |
| | H-18 | 0·65 | 0·55 | 0·10 | 0·13 |
| XXIV | H-19 | 0·82 | 0·62 | 0·20 | 0·22 |
| | H-18 | 1·02 | 0·62 | 0·40 | 0·44 |

principle (Table 3). The calculated shift of the 1β-proton of 5α-androstan-2,11-dione (XX) is based upon Δ = 0·07 and Δ = −0·37 for this resonance in 5α-androstan-2-one (III) and 5α-androstan-11-one (VII), respectively.

After formulating generalizations on the basis of results obtained for compounds in which the spatial relationship between the carbonyl group and certain protons is fixed, it is convenient to consider the Δ values obtained for 5α-pregnan-20-one (XIII). In this compound, Δ(H-18) is very small (+0·03), despite the proximity of the functionality and the C-18 methyl group. If one assumes that the preferred conformation of the C-17 sidechain is approximately the same in benzene and deuterochloroform solutions, the small solvent shift implies that the C-18 methyl group must lie near a

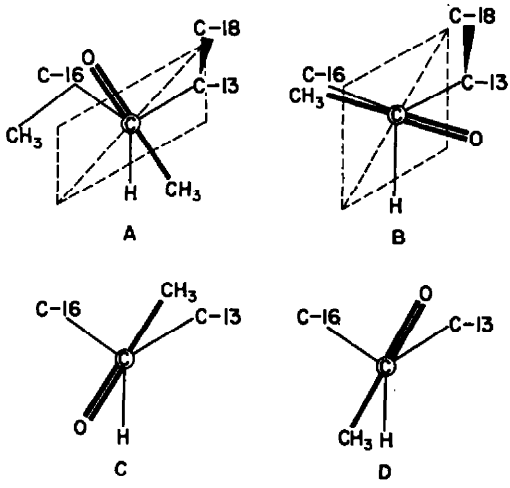



FIG. 1 Conformations of C-17 sidechain in 5α-pregnan-20-one (XIII) as viewed from C-20 to C-17. (Reference planes in A and B shown by dashed lines.)

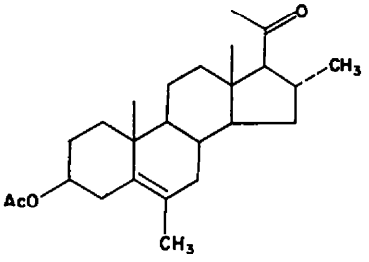
plane drawn through the carbonyl carbon atom and perpendicular to the C—O bond i.e. conformations A and B are indicated, and conformations B and C excluded as popular conformations (Fig. 1). A decision between the possibilities A and B can be made on the basis of the very small Δ values for *both* the H-18 and 16α-$CH_3$ resonances of 6,16α-dimethyl-$\Delta^5$-pregnen-3β-ol-20-one acetate [XXV, Δ(H-18) = +0·03, Δ(16α-$CH_3$) = −0·01]. These results indicate that the protons of both methyl groups must lie near the reference plane as previously defined and are therefore only consistent with a preferred conformation A (in which a 16α-methyl group has been drawn—see Fig. 1); conformation B would require a positive value of 0·2 to 0·4 for the 16α-$CH_3$ protons. Thus the solvent shifts show that the population of conformation A must be considerably greater than that of any other conformation. This result is consistent with dipole moment data[6] and has very recently been confirmed by a consideration of conformational analysis, optical rotatory dispersion and variable temperature circular dichroism studies.[7] It should be noted that the above comparison of solvent shifts for XIII and XXV to deduce the preferred conformation of the 17β-acetyl sidechain in XIII is only valid if the 16α-methyl substituent does not change the orientation about the 17–20 bond. The *trans*-nature of the C-16 and C-17 substituents makes any such modification unlikely and is indeed precluded by the similarity of the circular

[6] N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.* **83**, 4256 (1961).
[7] K. M. Wellman and C. Djerassi, *J. Am. Chem. Soc.* **87**, 60 (1965).

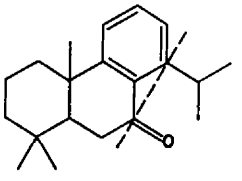
dichroism curves of 16α-substituted 20-keto-pregnanes and 16-unsubstituted pregnanes,[8] and the virtual identity of the optical rotatory dispersion curves of progesterone and 16α-methylprogesterone.[9] However, the presence of β-substituents at C-16 does alter the conformational preference of the acetyl sidechain.[7]

In 7-ketototarol acetate (XXVI), although any conformational preference for the isopropyl group has not been determined, it is evident that whatever the conformation, all the protons of this group must lie in front of the carbonyl function. The tertiary proton of the isopropyl group does in fact have a large negative Δ value (−0·45) and both secondary methyl groups are also deshielded in benzene relative to deuterochloroform ($\delta_{C_6H_6}$ = 1·40 and 1·60; $\delta_{CDCl_3}$ = 1·20 and 1·35). Thus solvent shifts may be utilized to confirm a peri-relationship between a substituent and a carbonyl group.

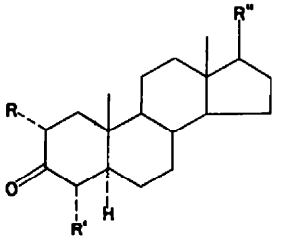
Finally, we present data in Table 4 for a number of 3-ketones in which structural modifications relative to 5α-androstan-3-one (IV) have been made, both by the introduction of polar and non-polar substituents. It will be noted that the Δ values for H-19 are always of the expected sign and on introduction of an equatorial α-methyl group or 17β-acetate only show small deviations from the Δ value (0·37) for 5α-androstan-3-one (IV) (see data for XXVII, XXVIII and XXIX in Table 4). If the conformation of ring A is changed by the introduction of a 4,4-dimethyl moiety, a

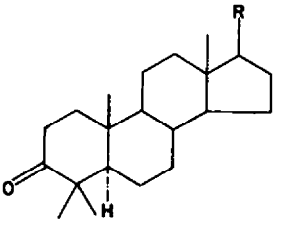



XXV




XXVI




IV, R = R' = R" = H
XXVII, R = $CH_3$, R' = H, R" = $C_8H_{17}$
XXVIII, R = R' = H, R" = OAc
XXIX, R = H, R' = $CH_3$, R" = OAc
XXXII, R = Br, R' = H, R" = $C_8H_{17}$
XXXIII R = Cl, R' = Br, R" = $C_8H_{17}$

XXX, R = H
XXXI, R = $C_8H_{17}$

[8] P. Crabbé, F. McCapra, F. Comer and A. I. Scott, *Tetrahedron* **20**, 2455 (1964).
[9] W. A. Struck and R. L. Hautmann, *J. Org. Chem.* **26**, 3883 (1961).

modified solvent effect must be anticipated and indeed Δ is somewhat smaller for 4,4-dimethyl-5α-androstan-3-one (XXX) and 4,4-dimethylcholestan-3-one (XXXI). The introduction of one and two equatorial halogen atoms immediately adjacent to the keto-group has the effect of causing successive increases in Δ (see data for XXXII and XXXIII).

TABLE 4. Δ VALUES ($\delta_{CDCl_3} - \delta_{C_6H_6}$ PPM) FOR H-19 RESONANCES IN SOME SUBSTITUTED 3-KETONES

| Compound | IV | XXVII | XXVIII | XXIX | XXX | XXXI | XXXII | XXXIII |
|---|---|---|---|---|---|---|---|---|
| Δ(H-19) | 0·37 | 0·31 | 0·39 | 0·39 | 0·28 | 0·27 | 0·48 | 0·58 |

In summary, the results described in this paper and previous publications[1,2,10] indicate that solvent shifts can be used to differentiate between axial and equatorial protons or methyl groups adjacent to carbonyl,[2,10] and to locate protons behind or in front of the keto-group. The knowledge derived in this manner is obviously of great utility in the determination of structure,[1] stereochemistry and conformation.

## EXPERIMENTAL

All spectra were determined using Perkin–Elmer 60 Mc or Varian A-60 NMR Spectrometers. Tetramethylsilane was employed as internal reference for both deuterochloroform and benzene solution spectra.

*Acknowledgement*—The authors wish to thank Professor C. Djerassi for generous gifts of many steroid samples and record their gratitude to Miss Pat Grist for skilful technical assistance in obtaining some of the spectra. We are indebted to Dr. C. Enzell for a sample of 7-ketototarol acetate.

[10] N. S. Bhacca and D. H. Williams, *Applications on NMR Spectroscopy in Organic Chemistry*. Holden-Day, San Francisco (1964).