The position of the equilibrium is sensitive to the type of substituents at the periphery of the porphyrin ring. The more effectively electron-withdrawing (as reflected in basicity of the nitrogen atoms in metal-free porphyrins) is a substituent in the 2 and 4 positions,[3] the greater is the proportion of Species II relative to Species I (Table I).

TABLE I

| Compound | 2,4-Substituent | $D_{II}/D_I$ [a] | $pK_3$ [b] ($\pm 0.1$) |
|---|---|---|---|
| 1 | Ethyl | 0.28 | 5.8 |
| 2 | Hydrogen | 0.62 | 5.5 |
| 3 | 2-Ethoxycarbonylcyclopropyl | 0.74 | 4.8 |
| 4 | Acetyl | 2.63 | 3.4 |
| 5 | Formyl | 3.33 | 2.8 |

[a] $2.0 \times 10^{-5} M$ in pyridine at 30°. [b] These data pertain to the equilibrium between neutral metal-free porphyrin and monocation in 2.5% sodium dodecyl sulfate at 25° (J. N. Phillips and W. S. Caughey, unpublished; *cf.* J. N. Phillips, *Revs. Pure Appl. Chem.*, **10**, 35 (1960)).

The position of the equilibrium is independent of Ni(II) porphyrin concentration over the concentration ranges studied. For example, $D_{II}/D_I$ values obtained for Cpd. 2 in pyridine at 30° are 0.623, 0.617, 0.625 and 0.621 at molar concentrations of $3.3 \times 10^{-4}$, $3.3 \times 10^{-5}$, $3.3 \times 10^{-6}$ and $6.5 \times 10^{-7}$, respectively.

That basic solvent molecules are serving as ligands at the nickel atom giving rise to Species II is consistent with an increase in the proportion of Species II with increasing solvent basicity and decreasing temperature and porphyrin basicity. Solute–solute interactions observed in "magnetically anomalous" nickel complexes[4] evidently are not important here since the position of the equilibrium is independent of solute concentration. Also, an equilibrium between square-planar and tetrahedral complexes can be excluded in view of the high stability[5] and planarity[6] of Ni(II) porphyrins. A difference in spin-state with Species I diamagnetic, as it is in the solid,[7] and Species II paramagnetic (high-spin) might be expected on theoretical grounds[8] and in view of the magnitude and direction of spectral shifts[9] and findings with other nickel complexes.[4] Preliminary magnetic susceptibility studies in 0.01 *M* solutions do show pyridine solutions to be paramagnetic with respect to chloroform solutions to a degree consistent with such a spin-state difference.

These data, interpreted on the basis of solvent perturbation effects,[10] suggest Species I is a highly tetragonal complex experiencing weak perturbation along the $d_{z^2}$ axis perpendicular to the prophyrin plane and Species II is a less tetragonal complex experiencing strong axial perturbation. Separation between $d_{z^2}$ and $d_{x^2-y^2}$ energy levels increases with increasing porphyrin basicity and decreases with increasing solvent basicity. However, as yet conclusive evidence of the number of solvent ligands involved in these species has not been obtained.

The structural differences among the porphyrin moieties of hemoproteins and heme enzymes, particularly in the cytochromes,[11] suggest corresponding ligand field differences of the same order of magnitude as those encountered in this study.[12]

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[3] Each of the porphyrins are 2,4-disubstituted derivatives of deuteroporphyrin IX or 1,3,5,8-tetramethylporphin-6,7-dipropionic acid.

[4] R. H. Holm, *J. Am. Chem. Soc.*, **83**, 4683 (1961), and refs. included therein.

[5] W. S. Caughey and A. H. Corwin, *J. Am. Chem. Soc.*, **77**, 1509 (1955).

[6] M. B. Crute, *Acta Crystal.*, **12**, 24 (1959).

[7] F. Haurowitz and W. Klemm, *Ber.*, **68B**, 2312 (1935).

[8] L. E. Orgel, "An Introduction to Transition-Metal Chemistry Ligand Field Theory," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 64.

[9] R. Lemberg and J. W. Legge, "Hematin Compounds and Bile Pigments," Interscience Publishers, Inc., New York, N. Y., 1949, pp. 214–215 and 228.

[10] G. Maki, *J. Chem. Phys.*, **28**, 651 (1958); **29**, 162 (1958); **29**, 1129 (1958); C. J. Ballhausen and A. D. Liehr, *J. Am. Chem. Soc.*, **81** 538 (1959).

[11] S. Granick and D. Mauzerall in Greenberg, "Metalobic Pathways," Vol. 2, Academic Press, Inc., New York, N. Y., 1961, p. 554.

[12] The dimethyl esters of protoporphyrin IX and chlorocruoroporphyrin have $pK_3$ values of 4.8 and 3.7, respectively.

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## STEROIDS. CXCVII.[1a] SPECTRA AND STEREOCHEMISTRY. PART II.[1b] LONG-RANGE SPIN–SPIN COUPLING BETWEEN FLUORINE AND STEROID ANGULAR METHYL PROTONS

*Sir:*

Recently reports have appeared of resolvable long-range coupling between protons separated by four or more bonds. In some cases coupling takes place through the agency of sigma bond electrons alone,[2–4] whereas in others "communication" of spin state information also involves π bond electrons, though the π bond itself may,[5,6] or may not,[7] be a direct link in the connective bond chain between the coupling protons. Long-range spin–spin coupling of proton and fluorine also has been reported with comments on the importance of the stereochemical relationship of the coupling nuclei.[4] We are independently examining this problem and record here our results for a number of fluorinated steroids of known stereochemistry. In each of five cases spin–spin coupling of the protons at $C_{19}$ with fluorine leads to splitting of the characteristic 10-methyl three-proton singlet into a resolvable doublet (Table I).[8]

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[1] (a) Paper CXCVI, F. A. Kincl, H. J. Ringold and R. I. Dorfman, *Acta Endocrin.*, in press; (b) A. D. Cross, *J. Chem. Soc.*, 2817 (1961), constitutes Paper I of this series.

[2] F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

[3] J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769 (1961).

[4] D. R. Davis, R. P. Lutz and J. D. Roberts, *ibid.*, **83**, 247 (1961).

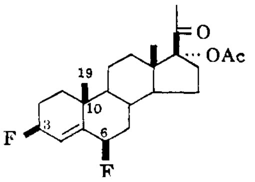
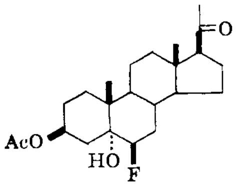
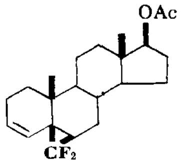
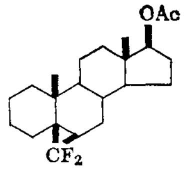
[5] C. N. Banwell, A. D. Cohen, N. Sheppard and J. J. Turner, *Proc. Chem. Soc.*, 266 (1959).

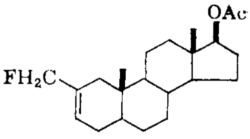
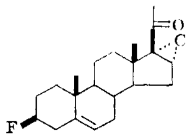
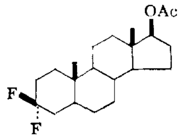
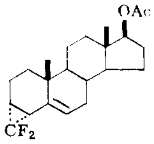
[6] A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, **83**, 231 (1961).

[7] J. R. Holmes and D. Kivelson, *ibid.*, **83**, 2959 (1961).

[8] N.m.r. spectra have been taken at 60 Mc. in carbon tetrachloride or purified chloroform solutions using tetramethylsilane as an internal reference. Varian HR-60 and A-60 instruments have been employed.

TABLE I

| | | | | |
|---|---|---|---|---|
| Steroid |  |  |  |  |
| | I | II | III | IV |
| $C_{19}$-proton absorptions (c./s. from TMS) | 70.6, 72.5 | 68.1, 72.4 | 61.9, 63.7 | 61.0, 63.2 |
| $J_{H-F}$, (c./s.) | 1.9 | 4.3 | 1.8 | 2.2 |
| Minimum no. of bonds connecting coupling nuclei | 5 | 5 | 5 | 5 |
| Ref. | *a* | *b* | *c* | *c* |

| | | | | |
|---|---|---|---|---|
| Steroid |  |  |  |  |
| | V | VI | VII | VIII |
| $C_{19}$-proton absorptions (c./s. from TMS) | 46.9, 43.1 | 63.9 | 51.0 | 57.2 |
| $J_{H-F}$, (c./s.) | 3.8 | ... | ... | ... |
| Minimum no. of bonds connecting coupling nuclei | 6 | 6 | 6 | 6 |
| Ref. | *a* | *d* | *e* | *c* |

[a] J. A. Edwards, unpublished results. [b] A. Bowers, unpublished results. [c] L. H. Knox, forthcoming publication. [d] R. Villotti, unpublished results. [e] J. S. Mills, unpublished results.

In the 3β,6β-difluoro compound (I) spin–spin coupling is believed to be occurring between the 19-protons and the 6β-fluorine, since coupling is also observed in the 6β-fluoro steroid (II) but not in the 3β-fluoropregnane (VI) or 3α,3β-difluoroandrostane (VII).[9] In both (I) and (II) the possibility of communication of spin-state information *across space* cannot be ruled out in view of the very favorable proximity of the coupling nuclei. Splitting of the $C_{19}$-proton absorption owing to a hindered rotation of the 10-methyl is implausible since this should manifest itself in a splitting pattern equivalent to three different $C_{19}$-protons. The same rationale applies to the observed doublets for the $C_{19}$-protons of the two 5β,6β-cyclopropyl steroids (III) and (IV). A 3α,4α-cyclopropyl steroid (VIII) showed no splitting due to proton–fluorine coupling.[11] Fluorosteroid (V), which shows a 10-methyl doublet from H–F spin–spin coupling, bears a 2-fluoromethyl group and coupling through space is improbable in view of the much larger distance between the coupling nuclei (interatomic distances have been measured with Dreiding, and with Barton, models). Coupling must take place through no less than 6σ bonds. In sigma systems geminal to a double bond, as in acetone or this Δ²-steroid (V), the triplet state of the carbonyl or olefinic link can make a significantly large contribution to the long-range spin–spin coupling.[7] Moreover it should be noted that in this fluorinated methyl steroid the fluorine atom can assume a position on the same side of the steroid molecule as the 10-methyl which may prove ultimately to be a desirable feature for this type of long-range coupling. Compounds (I–IV) possess such a stereochemistry of the proton and fluorine involved in the coupling. It also has been shown in independent work that the long-range five-bond H–F coupling between the methyl group and one of the fluorines of 1,1-difluoro-2,2-dichloro-3-phenyl-3-methylcyclobutane is likely to be a *cis*-interaction.[12] Further investigations are in progress to clarify this problem.

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[9] This point cannot be considered rigidly established since n.m.r. spectral examination of many steroids has revealed subtle effects on chemical shifts owing to small changes of stereochemistry and of dipoles.[10]

[10] A. D. Cross, unpublished observations.

[11] A detailed spectral study of these and other cyclopropyl steroids will be presented later, with special reference to their stereochemistry: A. D. Cross, L. H. Knox and P. W. Landis, unpublished results.

[12] M. Takahashi, D. R. Davis and J. D. Roberts., *J. Am. Chem. Soc.*, submitted for publication. The authors are indebted to Professor Roberts for this information prior to publication.

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