Acknowledgment.–The authors wish to express their gratitude to the George Washington Carver Foundation and the Research Corporation (Research-Cottrell, Inc.) who jointly supported this work.

Ring Nonplanarity and Aromaticity in Porphyrins. Nuclear Magnetic Resonance Spectra of Etioporphyrin II and Its N-Alkyl Compounds

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Received August 20, 1962

To account for the known existence of N-alkylporphyrins it has been proposed from considerations of steric factors and visible spectra[1,2] and, more recently, analog computations[3] that at least one pyrrole ring must be out of the over-all plane of the porphyrin ring. However, no detailed experimental investigations of the manner in which the porphyrin ring accommodates the alkyl group substituted on nitrogen at the center of the ring and of the effect such an accommodation has on the aromaticity of the macrocycle have been reported. Here we report the n.m.r. spectra of etioporphyrin II (Fig. 1, R = H),[4] N-methyletioporphyrin II (Fig. 1, R = CH_3), and N-ethyletioporphyrin II (Fig. 1, R = CH_2CH_3) in deuteriochloroform. These spectra are interpreted as indicating that the porphyrin ring in etioporphyrin II is planar, whereas in each of the N-alkyl compounds there are definite deviations from planarity. N-Alkylation results in only a small change in ring current field strength and, consequently, the aromaticity may also be considered to be altered only slightly.

With the presumably planar[5] etioporphyrin II the ring positions for each type of substituent appear equivalent (Fig. 2, I) and the assignments are clear (Table I).[4] The spectra of the N-alkyl etioporphyrins are characterized by non-equivalence in ring positions. The N-alkyl protons appear at extremely high field consistent with the findings for porphyrin nitrogen bound protons[4,6] and their being within a strong ring current field. The fact that both N—CH_3[7] and N—Et—CH_2 are at significantly higher fields than N—Et—CH_3 provides evidence for the ring current effect being stronger near the center of the macrocycle.

The nature of the non-equivalence of ring positions in the N-alkyl compounds proves to be consistent with a definite nonplanar conformation of the molecules. Upon examination of models, a most reasonable manner for the N-alkyl group to be accommodated involves: (1) pyrrole ring I (Fig. 1) being somewhat out of the over-all plane of the ring with its nitrogen above the plane and its β-carbons below; (2) rings II and IV being out of the plane, to a lesser extent, with their nitrogen atoms below and their β-carbons above; and (3) ring III remaining essentially in the plane. The n.m.r. spectra suggest this is indeed the case. Thus the R—CH_3 of ring I is considerably out of the over-all plane, those of rings II and IV somewhat out of the plane, and that of ring III in the plane. If it is assumed that the further the protons of a given R—CH_3 are out-of-plane the lesser will be the ring current field effect, then the R—CH_3 protons of types A, B, and C may be assigned to ring I, rings II and IV, and ring

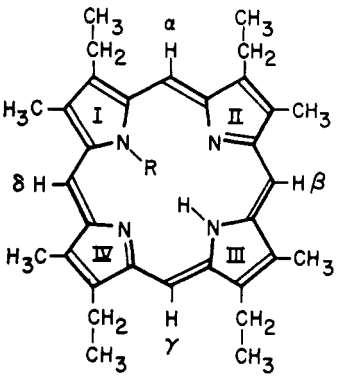

Figure 1

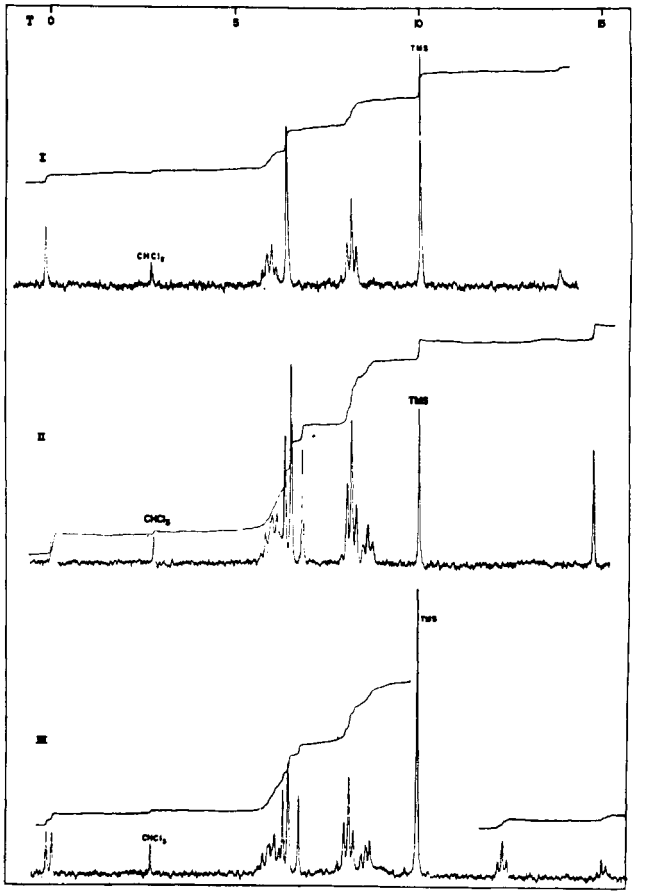

Fig. 2.—N.m.r. spectra in deuteriochloroform. I, etioporporphyrin II; II, N-methyletioporphyrin II; III, N-ethyletioporphyrin II.

(1) W. K. McEwen, *J. Am. Chem. Soc.*, **68**, 711 (1946).
(2) R. C. Ellingson and A. H. Corwin, *ibid.*, **68**, 1112 (1946).
(3) A. H. Corwin, J. Walter, and R. Singh, *J. Org. Chem.*, in press.
(4) W. S. Caughey and W. S. Koski, *Biochem.*, **1**, 923 (1962).
(5) M. B. Crute, *Acta Cryst.*, **12**, 24 (1959).
(6) E. D. Becker and R. B. Bradley, *J. Chem. Phys.*, **31**, 1431 (1959); J. Ellis, A. H. Jackson, G. W. Kenner, and J. Lee, *Tetrahedron Letters*, **2**, 23 (1960).
(7) For convenience the following abbreviations are used in this paper: R—CH_3 for ring methyl, R—Et—CH_3 for methyl of ring ethyl, N—CH_3 for nitrogen bound methyl, N—Et—CH_3 for methyl of nitrogen bound ethyl, R—Et—CH_2 for methylene of ring ethyl, N—Et—CH_2 for methylene of nitrogen bound ethyl.

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA

Protons[a]	Type	Etioporphyrin II	N-Methyletioporphyrin II	N-Ethyletioporphyrin II
N—Et—CH_3				12.37
N—Et—CH_2				15.16
N—CH_3			14.89	
N—H		13.79	13.12 (broad)	Not observed
R—Et—CH_3	A		8.58	8.61[b]
	B	8.13	8.15	8.14
R—CH_3	A		6.80	6.78
	B		6.50	6.48
	C	6.38	6.34	6.35
R—Et—CH_2	A		6.04	6.06
	B	5.89	5.86	5.88
Methine—H	A		0.03	0.04
	B	−.11	−.01	−.08

[a] See footnote 7. [b] This triplet is distorted somewhat by a weak broad band on the high field side. Although the origin of this band is uncertain, it is probably due, at least in part, to water which has often been observed in this region. This is an extremely low field position for N–H which, to be sure, was not observed elsewhere in the spectrum.

III, respectively. Integration data show a proton ratio of 3:6:3 for types A, B, and C, respectively. In the R—Et—CH_3 spectra integration shows three protons for type A and nine protons for type B. Here the type A triplet can be assigned to ring I and the R—Et—CH_3 groups of the other rings, being essentially equivalent, appear as type B. Assignments of the number of protons to each type of R—Et—CH_2 are not completely clear but the overlapping quartets are roughly equivalent in area. Slight non-equivalence is also found in the methine proton spectra. The α and δ protons can be expected to be essentially equivalent and different from the β and γ protons, which are also equivalent; a pair of peaks, each representing two protons, is indeed observed. These spectra might be compared with those of etioporphyrin II and thereby assign type A to the α and δ protons and type B to the β and γ protons. More likely, however, the nonplanar substituents in ring I result in less effective shielding of the α and δ protons than is the case with the β and γ protons and thereby make an opposite assignment the correct one. Thus for each of the N-alkyl compounds the n.m.r. data are consistent with and provide experimental evidence for a conformation with reasonable deviations from planarity. It should be added, however, that an evaluation of the effect of N-alkylation in the absence of conformational changes has not been attempted.

The ring current field strength appears to be only slightly less in the N-alkyl compounds than in etioporphyrin II. This can be concluded from the similarity in the spectra for protons remaining inplane (the methine protons and R—CH_3 and R—Et protons assigned to ring III) in the N-alkyl compounds compared with etioporphyrin II spectra.[4] If a single large ring current field is considered to be present and the strength of this field to be a measure of the degree of π-electron delocalization and consequently a measure of aromaticity, as has been done with six π-electron systems,[8] annulenes,[9] and porphyrins,[4] it is apparent that the deviations from planarity encountered here do not markedly affect the aromaticity of these compounds. (Metal ions complexed with the central nitrogen atoms and electron-withdrawing peripheral substituents do affect ring current field strengths.[4]) Furthermore these data suggest that appreciable deviations from over-all ring planarity can occur at the expense of little energy. Therefore the possibility of such nonplanarity must be given careful consideration in porphyrins and metalloporphyrins. The possibility of nonplanarity in palladium (II) complexes was suggested previously.[4]

(8) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

(9) R. A. Raphael, *Proc. Chem. Soc.*, 97 (1962).

Experimental

The n.m.r. spectra were obtained with a Varian A-60 spectrometer in ~ 0.09 *M* deuteriochloroform solutions with tetramethylsilane as an internal standard. Concentrations were varied without significant effect on the spectra. The data are reported as τ values.

Materials.—Etioporphyrin II was prepared as described previously.[4] N-methyletioporphyrin II and N-ethyletioporphyrin II were kindly supplied by Professor A. H. Corwin.

Acknowledgment.—This work was supported by grants from the U.S. Public Health Service (H-6079 and RG-7274).

Synthesis of 2β-Hydroxy Steroids. II[1,2]

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Received August 27, 1962

We have previously described a method for the synthesis of 2β-hydroxylated steroids which resulted in the synthesis of 2β-hydroxytestosterone.[1] The chemistry of the 2β-hydroxyl group is interesting since, from a thermodynamic standpoint, the 2β-configuration (axial) would be expected to be less stable when compared with the 2α-configuration (equatorial) and thus would tend to isomerize to the more stable 2α-form. In agreement with this, synthetic studies have shown that prolonged treatment of 2β-hydroxylated-Δ^4-3-keto steroids with potassium acetate in acetic acid does isomerize the 2β-function to the stable 2α-form.[4] However, since our communication[1] still other 2β-hydroxylated steroids have been obtained from microbiological incubations.[5] In view of this increased interest in

(1) P. N. Rao and L. R. Axelrod, *J. Am. Chem. Soc.*, **82**, 2830 (1960), should be considered as Part I of the series.

(2) This work was supported by a grant (A-3270) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

(3) This paper represents part of a thesis submitted by H. R. Gollberg to the Graduate School of St. Mary's University, San Antonio, Tex., in partial fulfillment of the requirements for the degree of Master of Science.

(4) (a) F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953); (b) R. L. Clark, K. Dobriner, A. Mooradian, and C. M. Martini, *ibid.*, **77**, 661 (1955).

(5) (a) M. Shirasaka, M. Tsuruta, and M. Nakamura, *Bull. Agr. Chem. Soc. Japan*, **22**, 273 (1958); (b) M. Shirasaka, R. Takasaki, R. Hayashi, and M. Tsuruta, *ibid.*, **23**, 245 (1959); (c) K. Tanabe, R. Takasaki, R. Hayashi, and M. Shirasaka, *Chem. Pharm. Bull.* (Tokyo), **1**, 804 (1959); (d) M. Shirasaka and M. Tsuruta, *Arch. Biochem. Biophys.*, **87**, 338 (1960); (e) L. L. Smith, H. Mendelsohn, T. Foell, and J. J. Goodman, *J. Org. Chem.*, **26**, 2859 (1961).