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# Steric Deformation. The Synthesis of N-Methyl Etioporphyrin I[1]

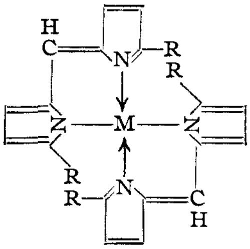
BY W. K. MCEWEN[1a]

The characteristic properties of color and physical stability of organic dyes are directly related to their so-called "aromatic" nature. Certain polypyrryl pigments, such as dipyrrylmethenes and porphyrins, are ideally suited for studies of the effect of steric interference on color and stability. These substances are essentially two-dimensional sheets of atoms bound together through conjugated "aromatic" bonds. The spatial configuration of lowest energy for such a bond system is with the three bonds in a plane, mutually separated by approximately 120°angles.[2] The component atoms of benzene closely approximate this optimum configuration. Usually, however, the bonds are distorted with a subsequent increase in energy of the system. Such an alteration is reflected in the color and physical stability of the substance.

Distortion or bending of bonds can arise from two causes. The first and simpler cause is bond bending to close a ring. An example would be cyclobutadiene which due to the energy increase from bond bending should be much less stable physically than benzene. Estimations of the resonance energy have been attempted by Wheland.[3] Biphenylene, which contains the four-membered aromatic ring, has been subjected to electron diffraction studies by Waser and Schomaker.[4] Estimates of the bond lengths and energies are given in their paper.

The second and more complicated cause of bond bending is steric interference, that is, the tendency of two or more atoms to occupy the same space. Here two energy variables apply, one of bond bending, the other of atomic compressibility. The actual configuration will be that combination of the two variables which gives the lowest energy for the molecule. At present, no method for measuring or calculating these energy functions is generally accepted. A qualitative experimental approach to the problem may be secured through the actual study of the spatial configuration and molecular energy of sterically distorted molecules.

The first phase of this problem has been projected by Porter.[5] Metallic complexes of the transition metals with co-ordination number of four, such as copper, with dipyrrylmethenes possess a resonating structure, the fundamental form of which is



Porter has inferred from chemical and physical properties that when R is methyl the molecule cannot possess the predicted flat configuration of minimum energy because of steric interference. When R is H, the decrease in the size of the groups might result in a planar structure. The determination of the spatial arrangement of atoms in these two structures will form a basis for the comparison of the energies involved.

Another phase of the problem is the determination of the total energy increase of the system resulting from the combination of bond bending and the atomic compression of steric interference. An experimental approach to this problem may be secured by studying the absorption spectra and chemical reactivities of suitably selected pairs with small and large groups.

The syntheses of di-N-methyl dipyrrylmethenes by Brunings and Corwin[6] provided examples of structures with high steric interference, the preferred positions of the carbons of the N—$CH_3$ groups almost coinciding. In the ordinary N—H compounds the methene, or aromatic, configuration was the stable form. The dipyrrylcarbinol was unstable. The first electronic transition was in the violet, thus confirming a considerable resonance energy or low total energy for the system. In the di—N—$CH_3$ compounds the cost resulting from bond bending and compression of atoms approaches the resonance energy. The spectrum moves toward the red, and the molecule readily assumes the carbinol structure.

For a number of years, we have studied N-alkyl porphyrins,[7] the objective being the examination of geometric isomers of the inner ring. These compounds are also of interest from the steric point of view. The resonance energy of the porphyrin ring is undoubtedly much greater than that of the dipyrrylmethenes. In addition, the inner ring is so compact that the placement of even one methyl group on a pyrrole nitrogen would require either deformation of the entire aromatic net, which is unlikely, or extreme bending of the bonds and compression of the atoms involved. The

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[1] Studies in the Pyrrole Series, XV; Paper XIV, Corwin and Buc, THIS JOURNAL, **66**, 1151 (1944).

[1a] Present address: 1410 Creighton Ave., Dayton 10, Ohio.

[2] Robertson, *J. Chem. Soc.*, 1204 (1936); Robertson and Woodward, *ibid.*, 221 (1937); 40 (1940).

[3] Wheland, *Proc. Roy. Soc.* (London), **A164**, 397–408 (1938).

[4] Waser and Schomaker, THIS JOURNAL, **65**, 1451–1455 (1943).

[5] Porter, *J. Chem. Soc.*, 368 (1938).

[6] Brunings and Corwin, THIS JOURNAL, **64**, 593 (1942); **66**, 337 (1944).

[7] McEwen, *ibid.*, **58**, 1127 (1936).

present paper reports a preliminary preparation and study of such a system.

Direct methylation of etioporphyrin I with methyl iodide yields a mixture of unchanged starting material, a component, A, having a formula compatible with a methiodide but having properties which suggest that this is not the correct formulation, and a component, B, which is believed to be the desired N-methyl porphyrin. The most convincing piece of evidence in favor of this assumption is the N-methyl micro-analysis performed according to the method of Pregl. The analyses found 0.95 and 0.92 of a methyl group present. There are no methoxyl groups to complicate the results. The carbon and hydrogen analyses check with the theoretical values but the determinations were not accurate enough to distinguish between the presence or absence of one methyl group. Additional evidence supporting the N-methyl structure is the type of metallic complex which was formed. The fact that the complexes analyze as porphyrin metal chloride instead of porphyrin-metal as is the case with etioporphyrin adds weight to the belief that one of the imide nitrogens is blocked with a methyl group.

That the component A is probably not the methiodide is indicated by the fact that treatment with base does not liberate the free porphyrin. It was necessary to reflux the material with silver nitrate in methanol for four hours and a half to form one equivalent of silver iodide. Another unexplained phenomenon in connection with this component is the existence of a marked difference between the spectrum in methanol and that in ether containing a drop of pyridine, recorded in the experimental section. Finally, the material does not form metallic complexes, a property which was turned to advantage in its isolation.

The fact that it is possible to prepare N-methyl etioporphyrin shows that accommodations which must involve considerable energy can be made within the molecule. This provides an excellent system, then, for studies on the nature of steric accommodation. Detailed analysis of the spectra of the substance and its derivatives, studies of the potentials of porphyrin and N-methyl porphyrin to their leuco forms and particularly X-ray diffraction studies on these substances should yield information of fundamental value. The present paper reports a preliminary preparation and study of such a system.

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## Experimental

**Preparation of Etioporphyrin I.**[8]—Better yields were obtained with the succinic acid melt for the condensation of methenes to the porphyrin than with the formic acid melt. Eight grams of methene may be used with 16 g. of succinic acid. The product was purified by distillation in an apparatus similar to that described by Carothers and Hill.[9]

One gram of etioporphyrin could be distilled from the hot-plate at 450° (m. p. of etioporphyrin *ca.* 400°) onto the condenser at 250° in one hour's time under a pressure of $6 \times 10^{-3}$ mm. of mercury with a yield of about 70%. Actually the process was not molecular distillation as the distance between the distilling and condensing surfaces exceeded the mean free path of the molecules.

*Anal.* Calcd. for $C_{32}H_{38}N_4$: C, 80.28; H, 8.01. Found: C, 79.16, 79.67; H, 7.70, 7.80.

The compound has a clean sharp spectrum but still contains a trace of bromoporphyrin, for the compound gave a faint Beilstein test.

Investigations undertaken subsequent to the methylation experiments recorded below have shown that the positive Beilstein test is caused by the use of slightly impure kryptopyrrole in the synthesis of etioporphyrin. The presence of 2,4-dimethylpyrrole gives a β-bromoporphyrin as an impurity. The 2,4-dimethylpyrrole is formed from 2,4-dimethyl-3,5-dicarbethoxypyrrole which is present in small quantities as an impurity in 2,4-dimethyl-3-acetyl-5-carbethoxypyrrole unless special precautions are taken in its preparation. The whole chain of impurities may be eliminated by isolating the isonitrosoethyl acetoacetate[10] and recrystallizing it before the condensation with acetylacetone.

**Preparation of the Potassium and Sodium Salts of Etioporphyrin I.**—The potassium salt was formed by treating etioporphyrin in dry benzene solution with either potassium phenyldimethylmethane (potassium salt of cumene) or with potassium tertiary amylate. The potassium salt, made by both these methods, gave the same spectrum and gave the original etioporphyrin on hydrolysis. The sodium salt was prepared by the addition of either sodium triphenyl methyl or sodium tertiary amylate to a benzene solution of the porphyrin. The sodium salt likewise gave the characteristic salt spectrum and yielded unchanged etioporphyrin on hydrolysis.

A 100-cc. bulb, with side arm to the condenser, was cleaned, dried, six glass pearls added to it, constricted, and attached to the receiver which in turn was attached to a vacuum pump. The bulb was baked out under vacuum. It was then filled with pure dry nitrogen and a solution of 50 mg. of etioporphyrin added. The benzene solution of the potassium tertiary amyl alcoholate was filtered in against a current of nitrogen. The apparatus was stoppered and the liquids distilled off under high vacuum.

**Methylation of the Sodium Salt. (a) Dimethyl Sulfate.**—Dimethyl sulfate (1 cc.) was distilled directly into the bulb containing the sodium salt. Any sulfuric acid or methyl hydrogen sulfate which might be present in the dimethyl sulfate should not distil over. However, four separate trials showed that, despite all precautions, the color of the mixture changed from that of the purple disodium salt to the pink porphyrin. The bulbs were heated to 100° for twelve to fifteen hours, on the chance that methylation might occur. All that could be found after acid fractionation was unchanged etioporphyrin. The time of heating was even increased to two weeks without effect.

(b) **Methyl Iodide.**—Methyl iodide (3 cc.) was added to the 100-cc. bulb containing the sodium salt, the bulb sealed off and heated to 100° for twelve to fifteen hours. This formed a small amount of "altered" porphyrin, along with a trace of a side reaction which was shown to be an

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[8] Fischer and Orth, "Die Chemie des Pyrrols," Vol. II, Akad. Verlag, Leipzig, 1937, p. 193.

[9] Carothers and Hill, This Journal, **54**, 1557 (1932).

[10] Corwin and Ellingson, *ibid.*, **66**, 1150 (1944).

oxidation product caused by the presence of some air. The major portion of the compound was unchanged etioporphyrin. This "altered" etioporphyrin was produced by the presence of methyl iodide as neither benzene and iodine, nor methyl alcohol would produce it from etioporphyrin. However, treatment of etioporphyrin with methyl iodide would form this "altered" etioporphyrin without benefit of the sodium salt. This resulted in a modified methylation procedure.

(c) **Modified Methylation Procedure.**—Distilled etioporphyrin (2 g.) was heated twelve days with 50 cc. of freshly distilled methyl iodide (Eastman Kodak Co., not kept over mercury) under dry, oxygen-free nitrogen at 100° in a sealed bulb in the dark. Then, after opening the bulb, the methyl iodide was distilled off, the residue was taken up and fractionated with ether–aqueous hydrogen chloride.[11] The "altered" etioporphyrin was crystallized to constant properties; m. p. *ca.* 180°.

*Anal.* Calcd. for mono-N-methyl etioporphyrin, 5.9%; iodine, 0.0%. Found: N-methyl, 3.08%; $I_2$, 2.13% (by Carius tube method). Thus this was found to be a mixture of at least two components.

**Separation of the Components of "Altered" Etioporphyrin.**—The residue is taken up in warm methanol. To this zinc acetate is added in excess, the solution heated for a short while, transferred to ether, washed with water, then with 6% hydrochloric acid. This removes a component, A, which does not form a zinc complex. The zinc complexes in the ether layer are then decomposed with 18% hydrochloric acid. An aqueous layer is neutralized with ammonia and the zinc-free material thrown back into ether. The material is then acid fractionated with aqueous hydrogen chloride. A component, B, with an acid number of 0.02 is first removed. Component B was shown to be N—$CH_3$ etioporphyrin. The remaining material, removed at 2 is unaltered etioporphyrin.

**Component A:** m. p. *ca.* 260°; acid number, <0.01.

*Anal.* Calcd. for $C_{32}H_{38}N_4 \cdot CH_3I$: C, 63.90; H, 6.47; I, 20.52; $CH_3I$, 23.0. Found: C, 63.79, 64.13; H, 6.94, 7.05; I, 21.34, 19.95; $CH_3I$, 9.3 (17.6).

**Spectra.**—Neutral: (1) 1 mg./30 cc. ether + 3 cc. pyridine, 50 mm. tube; I, 657.5···650.0; II, 608.5–594.5; III, 561···540.5–524.0···; E. A. 470.0. Order E. A.: III, II, I, color; red-brown. (2) 1 mg./30 cc. $CH_3OH$, 50 mm. tube: I, 624.5···618.0; II, 585.5–565.5; III, 549.0···522.0; E. A. 455.0. Order E. A.: II, I; color; violet. Acid: 6% HCl, 50 mm. tube: I, 614.0···604.5; II, 568.5–557.0; E. A. 439.0. Order E. A.: II, I; color violet.

Solubility: Very soluble in methyl alcohol, acetone, chloroform, acetic acid and pyridine. Slightly soluble in ether and benzene. Insoluble in petroleum ether and ligroin.

**Properties.**—The compound is weakly basic, forming a hydrochloride when hydrogen chloride gas is passed into a dry ether solution of it. It exhibits the typical acid spectrum of porphyrins and its solution is dichroic, being green when viewed in small amount and red in larger layers.

The compound exhibits no acidic properties. No zinc or copper complex could be formed on treatment with zinc acetate, copper acetate, or copper hydroxide. No sign of salt formation occurred when the substance was treated with sodium ethylate, sodium tertiary amylate or sodium triphenyl methyl. Upon melting, methyl iodide is given off and the compound changes to etioporphyrin.

Several attempts were made to effect the loss of hydrogen iodide. Treatment for various lengths of time with 3% methanol–potassium hydroxide resulted in either no reaction or disintegration depending on the length of the reaction. On heating with pyridine for a half hour there was no change. When heated with zinc powder to 240° the compound lost methyl iodide giving etioporphyrin. There was no reaction with moist silver oxide in the cold. Prolonged treatment in boiling methanol gave a precipitate of silver iodide. The product or products could not be identified.

Further investigations will be necessary before a satisfactory structure can be assigned.

**Component B** (N-methyl etioporphyrin): m. p. *ca.* 245°, acid number 0.02; acidity $pK = 14–15$.[7]

*Anal.* Calcd. for $C_{33}H_{40}N_4$: C, 80.50; N, 8.12; N—$CH_3$, 5.90. Found: C, 79.49, 79.92; N, 8.00, 8.15; N—$CH_3$, 5.64, 5.47.

**Spectra.**—Neutral: 1 mg./30 cc. ether + 1 drop pyridine, 50 mm. tube; I, 646.0–642.0; II, 619.5···614.5; III, 598.0···588.0–583.5; IV, 536.0–530.0; V, 515.5–489.0; E. A. 444.0. Order E. A.: I, IV, V, III, II; color brown with red fluorescence. Acid: 1% HCl, 50 mm. tube; I, 605.5···590.5; II, 564.5–541.0; E. A. 430.0. Order E. A.: II, I; color red-violet.

Solubility: Very soluble in methyl alcohol, hydrochloric acid, acetone, acetic acid, pyridine. Slightly soluble in ether and benzene. Insoluble in petroleum ether and ligroin.

**Formation of the Metallo Complexes of N—$CH_3$ Etioporphyrin.**—Twenty-seven milligrams of the porphyrin and 0.3 g. of zinc chloride (or 0.4 g. of $CuCl_2 \cdot 2H_2O$) were dissolved in methanol and boiled for three minutes. The solution was then cooled and poured into ether, which was then washed with water to remove the unreacted zinc or copper salts and the methanol. The ether solution was then washed with 4% hydrochloric acid to take out any free porphyrin. The ether was dried over anhydrous sodium sulfate, concentrated, and petroleum ether (b. p. 20–40°) was added to diminish the solubility of the complex in the ether. The solution was filtered and the crystals were finally washed with petroleum ether. The yield was about 10 mg. Both complexes give strong qualitative tests for chloride.

*Anal.* Calcd. for $C_{33}H_{39}N_4ZnCl$: C, 66.89; H, 6.64; Zn, 11.0. Calcd. for $C_{33}H_{38}N_4Zn$: C, 71.28; H, 6.89; Zn, 11.8. Found: C, 66.43, 66.20; H, 6.98, 6.40; Zn, 11.2, 10.3.

Unstable to 14% HCl with decomposition to etioporphyrin.

**Spectrum.**—1 mg./30 cc. ether + 1 drop pyridine: I, 627.0···622.0; II, 593.0–569.0; III, 545.0–529.0; E. A. 449.0. Order E. A.: II, III, I; color purple.

Solubility: Very soluble in methyl alcohol. Slightly soluble in ether. Insoluble in petroleum ether. Crystals, purple needles.

*Anal.* Calcd. for $C_{33}H_{39}N_4CuCl$: C, 67.09; H, 6.66; Cu, 10.8. Calcd. for $C_{33}H_{38}N_4Cu$: C, 71.51; H, 6.91; Cu, 11.5. Found: C, 66.15, 66.76; H, 6.62, 5.88; Cu, 13.4, 13.1.

Stable to concentrated hydrochloric acid.

**Spectrum.**—1 mg./30 cc. ether + 1 drop pyridine, 50 mm. tube: I, 563.0–555.0; II, 528.0···514.5; E. A. 462.0. Order E. A.: I, II; color reddish brown with red fluorescence.

Solubility: Very soluble in methyl alcohol. Slightly soluble in ether. Insoluble in petroleum ether.

**Methylation of Other Porphyrins.**—Mesoporphyrin IX methyl ester and rhodoporphyrin methyl ester were heated in a Carius tube with an excess of methyl iodide. Methylation appeared to take place as with etioporphyrin. This was concluded because of the shift in acid number and spectrum of a portion of the product. The main product was unchanged ester. Because of the small quantities used, analytical samples of the methylated products were not isolated.

## Summary

The synthesis of N-methyl etioporphyrin is described. Since the free space in the center of the porphyrin ring is too small for a methyl group, accommodation must take place by bending of bonds and compression of atoms. The significance of this accommodation is discussed. Metallic complexes of this substance with the central space occupied by the metal atoms are also described.

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[11] Willstätter and Mieg, *Ann.*, **350**, 1 (1906).