is hydrolyzed at temperatures near 100 °C, and extrapolation allows an estimate of the rate constant for the spontaneous hydrolysis of **7** at 39 °C (50% aqueous dioxan) as 2.6×10^{-10} s^{-1}.[16] Thus **7** is cleaved over 10^{12} times more slowly[18] than the related axial acetal (**8**, R = Me, Ar = 2,4-dinitrophenyl), and essentially all of this large factor is a stereoelectronic effect on reactivity.

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Registry No. 7, 82390-99-6; **8** (R = CH_3; Ar = C_6H_5), 82391-00-2; **8** (R = CH_3; Ar = *m*-BrC_6H_4), 82391-01-3; **8** (R = CH_3; Ar = *m*-$NO_2C_6H_4$), 82391-02-4.

Supplementary Material Available: Kinetic data for the hydrolysis of **7** as a function of temperature and of three 2-(aryloxy)-2-methyltetrahydropyrans (**8**, Ar = Ph and 3-bromo- and 3-nitrophenyl) at 39 °C (1 page). Ordering information is given on any current masthead page.

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Crystal and Molecular Structure of a Free-Base *N*-Methylporphyrin: *N*-Methyl-5,10,15,20-tetrakis(*p*-bromophenyl)porphyrin

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Many of the properties of *N*-alkylporphyrins differ significantly from those of corresponding non-N-alkylated porphyrins, presumably due to distortion of the aromatic ring system from planarity. The opportunity to significantly alter the properties of a porphyrin was in fact the impetus leading to the first report concerning *N*-alkylporphyrins, authored by McEwen in 1936.[1] Subsequently, it has been found that *N*-alkylporphyrins form complexes with metal ions much more rapidly than corresponding non-*N*-alkylated porphyrins[2,3] and that they are more basic.[1,4-6]

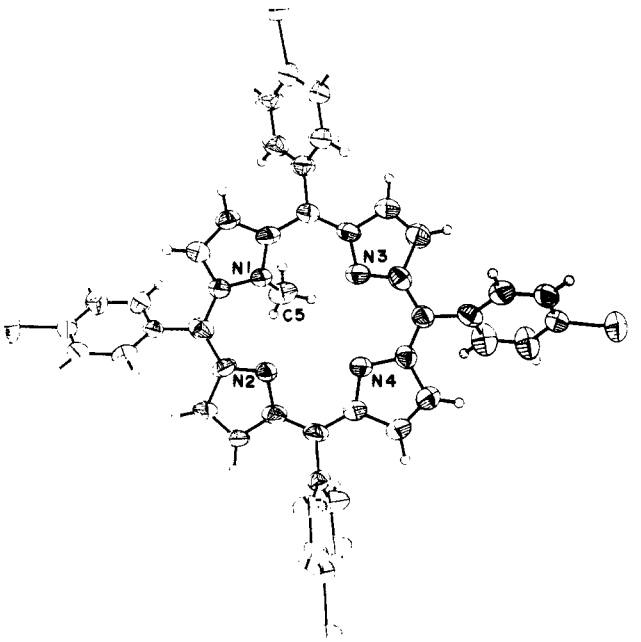

Figure 1. View of the *N*-CH_3HTPPBr$_4$ molecule. Hydrogen atoms have been rescaled for clarity, and the thermal ellipsoids have been drawn at the 50% probability level.

The *N*-alkylporphyrins exhibit visible absorption spectra that are quite similar in both energy and intensity to corresponding non-*N*-alkylated porphyrins,[4,6-8] indicating retention of a high degree of aromaticity. The proton NMR spectra of *N*-methylporphyrins show a large degree of shielding of the protons of the *N*-methyl group, in contrast to the deshielding typical of protons bound to the nitrogen atoms of porphyrins, indicating that the protons of the *N*-methyl group are significantly displaced from the plane of the aromatic system. Recent reports of the thorough characterization of *N*-alkylporphyrins as products of the decomposition of the prosthetic groups of cytochrome *P*-450 in vivo[9] add interest to a structural determination of nonmetalated species of this type.

The structures of a number of transition-metal complexes of *N*-alkylporphyrins,[10-14] together with one structure of a protonated nonmetallo *N*-substituted porphyrin,[15] have been reported, but no structures of neutral free-base *N*-alkylporphyrins have previously been described. Herein we describe the structure of such a species, *N*-methyl-5,10,15,20-tetra(*p*-bromophenyl)porphyrin, *N*-CH_3HTPPBr$_4$, which was synthesized by standard methods[6,16] and recrystallized several times from dichloromethane/acetonitrile mixtures. Using a Nicolet R3 diffractometer, we measured the intensities of 3860 unique observed reflections ($I > 2.5\sigma(I)$) by θ-2θ scans, employing Cu Kα radiation (graphite monochromator). All non-hydrogen atoms were refined with anisotropic thermal parameters, and hydrogen atoms bound to carbon were included in calculated positions. The single hydrogen atom on nitrogen in this neutral free base was strongly indicated to be on N4 by the position of the highest peak in the vicinity of the porphyrin

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Figure 2. Side-on view of the N-$CH_3HTPPBr_4$ molecule indicating the relative orientations of the pyrrole rings. The position of the hydrogen atom on nitrogen is strongly indicated to be across from the methylated pyrrole.

core in the final electron density map. At this point, $R = 0.082$ and $R_w = 0.098$.[17] The crystallographic numbering scheme used for this N-methylporphyrin is displayed in Figure 1, and the side-on view of the structure shown in Figure 2 emphasizes the distortions of the porphyrin core from planarity (see below).

Three types of N-alkylporphyrin structures may now be compared—that of the free base N-$CH_3HTPPBr_4$, that of the protonated species 21-(ethoxycarbonylmethyl)octaethylporphyrin hydrogen iodide,[15] and that of a typical transition-metal complex. The structures of the transition-metal complexes are quite similar, and that of ClFeN-CH_3TPP[14] will be used for purposes of comparison since its coordination geometry presumably very closely resembles that of the intermediate in cytochrome P-450 decomposition.[18] In each of these cases, the bulk of the N-alkyl group forces the substituted ring to be the most highly canted from the reference N1-N2-N3 plane (27.7, 19.1, and 36.6°, respectively), and the two adjacent pyrrole rings are tilted in the direction opposite to that of the N-alkylated ring (by 10.2 and 11.9°, 4.8 and 2.2°, and 9.8 and 11.3°, respectively). The N-alkylated ring and the pyrrole ring opposite to it are tilted in the same direction in the free base (27.7 and 8.1°) while the corresponding nonalkylated ring in the protonated N-ethoxycarbonylmethyl species and the iron complex is canted in the same direction as the adjacent rings (11.7 and 6.4°, respectively).

It is evident from van der Waals radii and the size of the cavity of a planar porphyrin[19] that a hydrogen atom and a methyl group with a N(sp^2)-C bond cannot simultaneously reside in the cavity. The structure of N-$CH_3HTPPBr_4$ shows that the steric requirements of the N-methyl group are accommodated in several ways. First, the angle betwewen the N1-C5 bond and the plane of the N1 pyrrole ring is considerably less than 180° (120.2°). In addition, the N-alkylated pyrrole ring is tilted (by 27.7°), and the adjacent pyrrole rings are rotated away from the alkyl group (10.2° and 11.9°). For the N-$CH_3HTPPBr_4$ and N-(ethoxycarbonylmethyl)octaethylporphyrin hydrogen iodide, the unprotonated pyrrole rings (N2 and N3 for the neutral species and N4 for the hydrogen iodide salt) are tilted away from the alkyl group to a similar extent (10.2 and 11.9° for the present structure and 11.7° for the hydrogen iodide case). The protonated pyrrole rings, however, are oriented very differently in these two nonmetalated species, however (-8.1° for the present case, compared with 4.6 and 2.2° for the protonated hydrogen case).

These tilting distortions of the pyrrole rings result in exposure of the nonbonding electrons on N2 and N3 of the free-base N-methylporphyrin, and thus a metal ion should be able to bind readily. In this regard, the similarity of the orientation of the N2 and N3 pyrrole rings in N-$CH_3HTPPBr_4$ and ClFe(N-CH_3TPP) is striking. The distortion from planarity and, presumably, the resulting loss of resonance stabilization are greater for the free-base N-alkylporphyrin studied, N-$CH_3HTPPBr_4$, than for the protonated N-substituted porphyrin (N-(ethoxycarbonylmethyl)-octaethylporphyrin hydrogen iodide) previously studied.[15] Since the opposite effect is expected when a nonalkylated porphyrin becomes distorted on protonation,[20] the greater basicity of N-alkylporphyrins appears to be consistent with structural properties. As noted above, only part of the steric requirement of the alkyl group is met by rotation of the alkylated pyrrole ring, and the free base retains a large degree of aromaticity. The observed position of the N-methyl group is consistent with the large upfield shifts observed in proton NMR spectra (4.1 ppm for N-$CH_3HTPPBr_4$) for the protons of the N-methyl moiety.

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Registry No. N-$CH_3HTPPBr{\cdot}CH_2Cl_2$, 82414-87-7.

Supplementary Material Available: Table I listing atomic coordinates for non-hydrogen atoms of N-$CH_3HTPPBr_4{\cdot}CH_2Cl_2$ and Table II listing anisotropic thermal parameters (4 pages). Ordering information is given in any current masthead page.

(17) A larger data set will be collected with Mo Kα radiation, and the complete structural analysis using these data will be reported subsequently. Crystal data for $C_{45}H_{28}H_4Br_4{\cdot}CH_2Cl_2$ are currently as follows: monoclinic, space group $P2_1/c$ ($Z = 4$), $a = 15.440$ (2) Å, $b = 16.261$ (2) Å, $c = 17.534$ (2) Å, $\beta = 108.16$ (1)°, $V = 4183.0$ Å^3, formula weight = 1029.31, ρ calcd. = 1.64 g cm^{-3}. The relatively high R and R_w reported are primarily due to thermal motion of the CH_2Cl_2 found to occur as lattice solvent. No absorption corrections were made.

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Total Synthesis of Milbemycin β_3

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In 1975, research laboratories of Sankyo Co., Ltd., Japan, reported isolation of a new family of antibiotics from a cultured *Stretptomyces* strain (B-41-146), demonstrating highly potent pesticidal activity against a variety of species of mites, beetles, and tent caterpillers without phytotoxicity.[1] Milbemycins α_1-α_{10} and β_1-β_3 have been identified, and these closely related structures have been primarily assigned following NMR studies and X-ray crystallographic analysis.[2] Subsequently a family of eight disaccharides, known as the avermectins, were discovered at Merck, Sharp and Dohme, and these compounds were found to be structurally related to the milbemycins.[3] The avermectins are highly efficacious agents for elimination of essentially all gastrointestinal and systemic nematodes and demonstrate extraordinary toxicity to mites, ticks, and larvae of biting flies.[4]

Our chemical investigations have led to the successful preparation of milbemycin β_3 (**1**), the simplest member of the milbemycin-avermectin family, along a highly convergent route. By

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