SYNTHESES AND STRUCTURAL PROPERTIES OF SEVERELY DISTORTED PORPHYRINS: *N*-METHYL DERIVATIVES

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Abstract - Syntheses and characterization of a series of *N*-methylated derivatives of sterically distorted porphyrins are reported; the work includes the first example of a tetra-*N*-methylated porphyrin obtained by methylation of an intact porphyrin.

N-Alkylated porphyrins are very interesting compounds from a chemical perspective, particularly with regard to the manner in which they differ from their parent porphyrins.[1] The development of interest in porphyrins substituted on the internal nitrogen atoms is largely due to the discovery that they are powerful inhibitors of ferrochelatase,[2] an enzyme essential for the biological production of heme. The considerable flexibility of porphyrins and porphinoid macrocycles as isolated molecules and in proteins, as well as the amount of distortions these molecules can undergo as a result of crystal packing, protein constraints, or steric effects, has been illustrated recently.[3] This conformational flexibility has become an area of intense research due to the possible role it may play in controlling the properties of tetrapyrrole derivatives in systems as wide-ranging as photosynthetic reaction centers, photosynthetic antenna systems, heme proteins, factor F_{430} from methanogenic bacteria, and vitamin B_{12} and B_{12}-dependent enzymes.[4]

Nonplanarity in porphyrin macrocycles can be induced in a variety of ways, including placement of sterically interacting substituents on the periphery,[3,5] insertion of substituents on the pyrrolic nitrogens,[6] and by connecting one side of the macrocycle to the opposite side with a short bridging strap.[7] Almost all of the nonplanar porphyrins used in model studies have been macrocycles possessing steric overload of the porphyrin periphery (dodeca-substitution of the *meso* and β positions). In order to determine what effect both dodeca-substitution and internal nitrogen substitution would have on these macrocycles, we have prepared a series of such compounds.

As vehicles for our *N*-methylation study, we chose three typical nonplanar dodecasubstituted porphyrins: 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetraphenylporphyrin (H_2OETPP), 2,3,7,8,12,13,17,18-octabromo-5,10,15,20-tetraphenylporphyrin (H_2Br_8TPP), and 2,3,5,7,8,10,12,13,15,17,18,20-dodecaphenylporphyrin (H_2DPP).[8] H_2OETPP and H_2DPP are both strong bases and therefore should *N*-alkylate

very easily. Since protonation of the pyrrolic nitrogens has been shown to prevent saddle inversion of these macrocycles, *N*-methylation will almost certainly also lock the saddle.

As the most basic of the three porphyrins, H_2OETPP was expected to be the most reactive towards *N*-methylation and this was shown to be the case. $N_{21}N_{22},N_{23},N_{24}$-tetramethyl-OETPP^{2+} I^{2-} (**1**) was synthesized [δ_{NMe} -3.15 (12H); λ_{max} 506 nm] in 56% yield by heating H_2OETPP in a THF solution of MeI and K_2CO_3. The X-ray crystal structure of **1** is shown in Figure 1.[9,10]

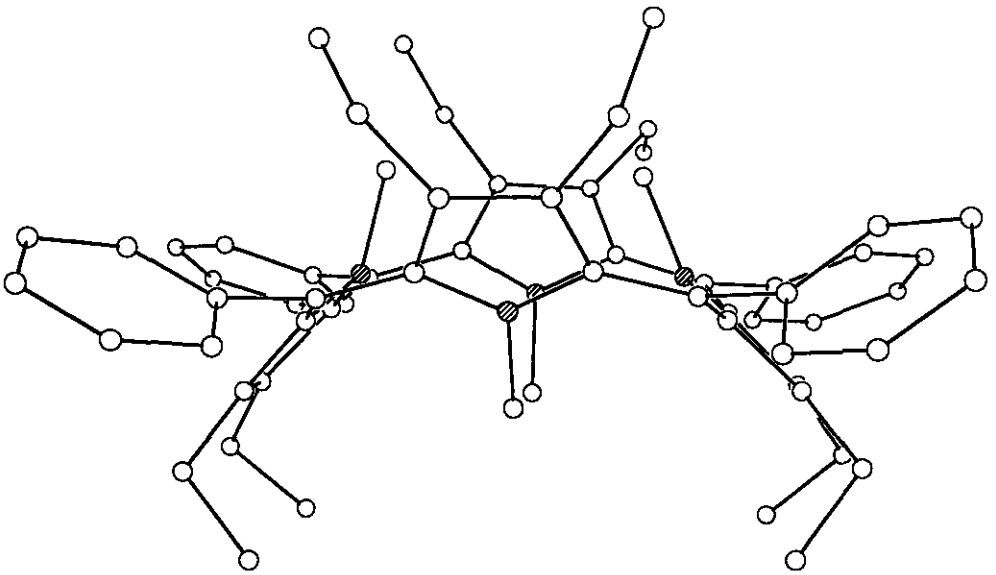
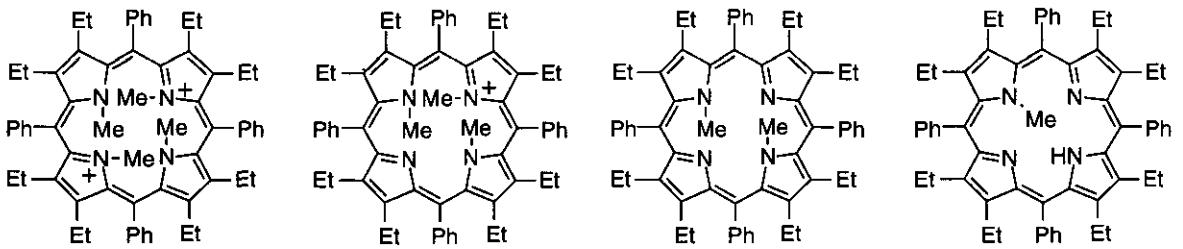


Figure 1: Molecular Structure of $N_{21},N_{22},N_{23},N_{24}$-Tetramethyl-OETPP^{2+} 2(I) (**1**)



The synthesis of N_{21},N_{22},N_{23}-trimethyl-OETPP$^+$ (**2**) required the use of a different methylating agent, diphenylmethylsulfonium tetrafluoroborate,[12] with K_2CO_3 in CH_2Cl_2/MeOH at reflux. Compound (**2**) was isolated as the BF_4^- salt in 69% yield [δ_{NMe}, -4.57 (3H), -2.57 (6H); λ_{max} 492 nm]. Upon treatment of H_2OETPP with MeI in CH_2Cl_2 at reflux, *cis*-N_{21},N_{23}-dimethyl-OETPP (**3**) was obtained in 27% yield [δ_{NMe}, -2.58 (6H); λ_{max} 488 nm]. In addition, the molecular structure of **3** was confirmed by X-ray crystallography (Figure 2).[10,13] The final product in the OETPP series, N-methyl-HOETPP (**4**) [δ_{NMe},

-3.95 (3H); λ_{max} 474 nm] was synthesized in 51% yield using $Ph_2SMe^+ BF_4^-$ (2 eq.) in CH_2Cl_2 at reflux, followed by addition of NEt_3.

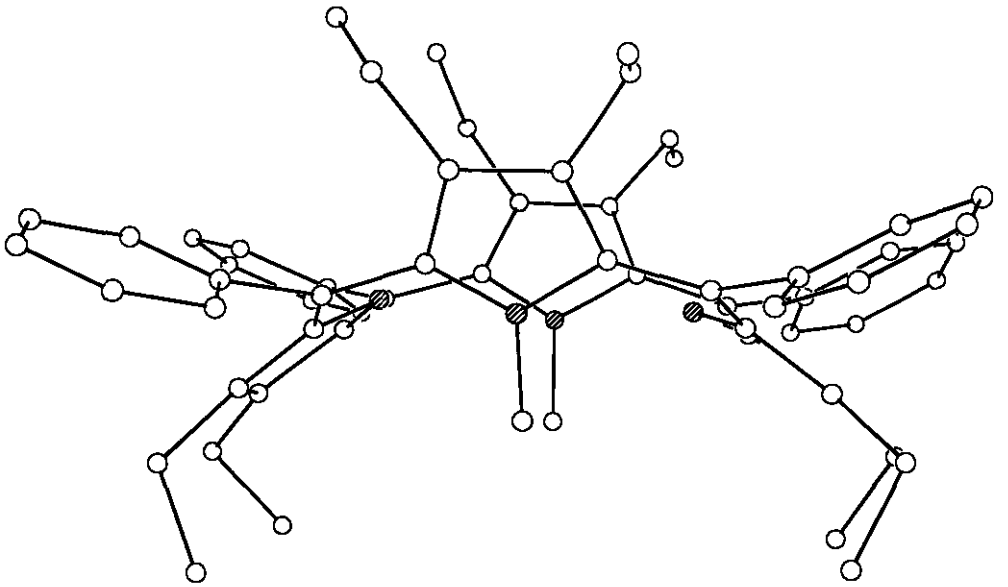
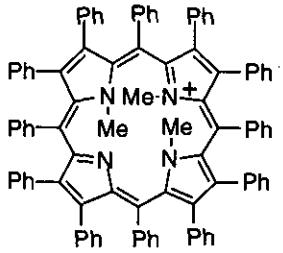


Figure 2: Molecular Structure of *cis*-N_{21},N_{23}-Dimethyl-OETPP^{2+} (I^-)(Cl^-) (**3**)

The next most reactive macrocycle toward exhaustive *N*-methylation proved, as anticipated, to be H_2DPP; under several typical sets of reaction conditions it was not possible to synthesize the tetramethylated dication of DPP. When using MeI, K_2CO_3, CH_2Cl_2, and MeOH at reflux a mixture of N_{21},N_{22},N_{23}-trimethyl-DPP$^+I^-$ [**5**, 16% yield, δ_{NMe}, -3.59 (3H), -1.69 (6H); λ_{max} 504 nm] and the *cis*-N_{21},N_{23}-dimethyl-DPP[14] [**6**, 55% yield, δ_{NMe}, -1.32 (6H); λ_{max} 498 nm] was obtained. Exhaustive methylation under the same reaction conditions for several hours produced only (N-Me)$_3$DPP$^+$ I^- (**5**). When H_2DPP was heated in a solution of $Ph_2SMe^+ BF_4^-$ (4.5 eq.), K_2CO_3, 1,2-dichloroethane, and THF, the *trans*-N_{21},N_{22}-dimethyl-DPP[14] (**7**) was obtained (10% yield) along with the *N*-monomethyl-HDPP (**8**) as the major product (34% yield). Compounds (**7**) and (**8**) displayed spectra typical of *N*-substituted porphyrins [δ_{NMe}, -2.86 (6H) (**7**), δ_{NMe}, -1.84 (3H) (**8**); λ_{max} 494 (**7**), 488 nm (**8**)].

The least reactive dodeca-substituted porphyrin used for our *N*-methylation study proved to be H_2Br_8TPP. Not only was it impossible to obtain the tetramethylated dication of Br_8TPP, but we were also unable to isolate the trimethylated monocation. However, after numerous attempts, we successfully synthesized the *trans*-N_{21},N_{22}-dimethyl-Br_8TPP [**9**, 8% yield, δ_{NMe}, -3.39 (6H); λ_{max} 504 nm] and the *N*-monomethyl-HBr_8TPP [**10**, 75%, δ_{NMe}, -2.84 (3H); λ_{max} 482 nm], by heating in MeI and CH_2Cl_2, followed by addition of DBU. X-ray crystallography was used to confirm the molecular structure of porphyrin (**9**) (Figure 3).[10,15]



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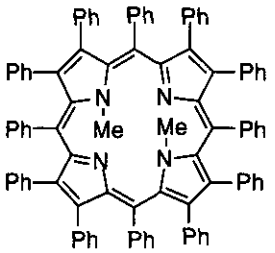

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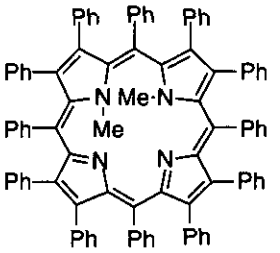

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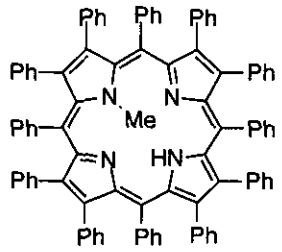

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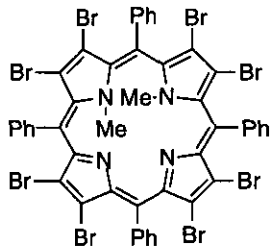

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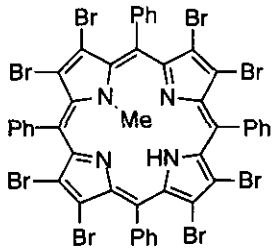

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A clear trend in the reactivities of the three parent porphyrins is apparent; the macrocycle with the most electron-donating substituents is the most reactive toward *N*-methylation. Another point of interest resides in the regiochemistry of the individual *N,N'*-dimethyl compounds. It has been shown that *N,N'*-dimethylporphyrins result from the thermal decomposition of the corresponding *N,N',N"*-trimethylporphyrin;[16] however, this does not appear to be the case for H_2OETPP and H_2DPP. Both of the trimethylated derivatives (**2** and **5**) show no decomposition when stirred in refluxing toluene for 24 hours; therefore, it seems likely that no thermal decomposition to the *N,N'*-dimethylporphyrins occurs under the standard reaction conditions.

The selectivity observed when forming the *N,N'*-dimethyl derivatives is a factor which should be addressed. It was previously postulated[16b] that increased deviation from planarity caused by *meso*-phenyl substituents accounted for the absence of N_{21},N_{23}-dimethyl derivatives; however, we have shown that this is not the case in our series of compounds. For H_2Br_8TPP, no methylation occurs until DBU is added; thus, it can be assumed that deprotonation of the pyrrolic nitrogen must take place in order for methylation to proceed. The monomethyl porphyrin then reacts with MeI from the less sterically hindered side, forming the *trans*-N_{21},N_{22}-dimethyl compound (**9**). In the case of H_2OETPP and H_2DPP, dimethylation using MeI produces the *cis*-N_{21},N_{23}-dimethyl derivatives (**3** and **6**) despite the steric interactions generated between the two *N*-methyls, presumably because the B ring nitrogens are unavailable for nucleophilic attack. We theorize that this is a consequence of the saddle-shaped configuration adopted by the monomethyl derivatives. Two complementary explanations can be taken into account: i) the corresponding monomethyl porphyrins exist as monocations, due to their increased basicity, and the imine nitrogen available for attack is therefore found on pyrrole ring C, or ii) the less sterically encumbered tautomers of **4** and **8** have the *N*-CH_3 and the NH on adjacent pyrrole rings, with the B and D rings sharing the pyrrole H *via* fast tautomerization favored by the saddle configuration, possibly blocking the formation of the N_{21},N_{22}-

dimethyl porphyrin. When $Ph_2SMe^+ BF_4^-$ is utilized to methylate H_2DPP, monomethylation occurs, but the sulfonium salt is too bulky to react with the pophyrin on the same face as the *N*-CH_3; thus the path to the N_{21},N_{23}-dimethyl isomer is blocked. We suspect that at high temperature, the more sterically hindered tautomer of porphyrin **8** exists, having an imine nitrogen on ring B (monocation) or on both rings B and D (freebase), thus facilitating formation of the *trans*-N_{21},N_{22}-dimethylporphyrin.

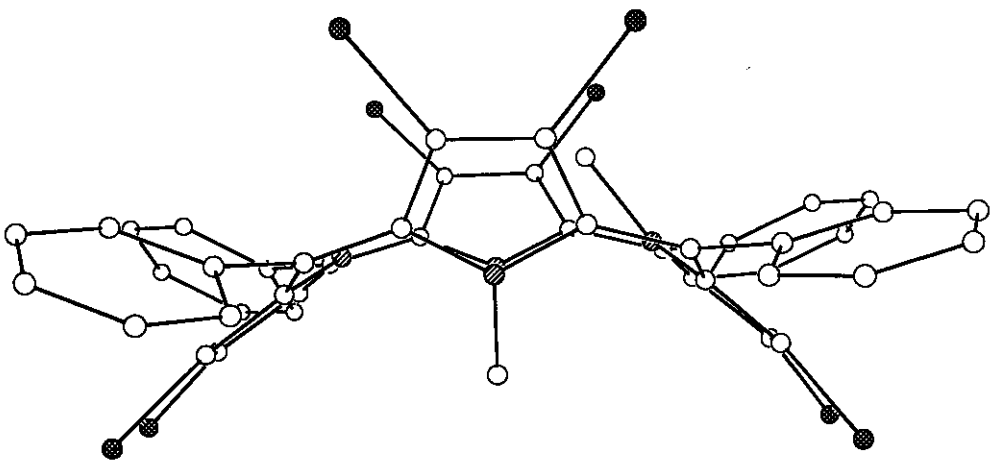

Figure 3: Molecular Structure of *trans*-N_{21},N_{22}-Dimethyl-Br_8TPP (**9**)

Crystallographic investigations of the *N*-methylated porphyrins have confirmed that these porphyrins posses highly pronounced saddle conformations (Figures 1-3). We have observed the following mean deviations of the core atoms from their respective porphyrin mean planes:[17] 0.608 Å (dication **1**), 0.587 Å (monocation **2**), 0.613 Å (dication **3**), 0.584 Å (**9**), and 0.571 Å (**10**). In contrast to the free base forms of these compounds,[18] steric encumbrance encountered in the porphyrin cores as a result of the *N*-methylations account for substantial increases in macrocyclic non-planarity. Among this type of porphyrin, the most extreme distortions in the porphyrin macrocycles (evidenced in the pyrrole tilt angles) occur when *N*-methyl substituents are present on both of an opposing pair of pyrroles (**1**,**2**,**3**); the second greatest macrocyclic distortions are observed when a pyrrole bearing an *N*-methyl substituent opposes a pyrrole bearing a hydrogen (**10**). In the structure of **9**, a porphyrin with no opposing pyrrolic *N*-substituents (methyl or H), steric interactions are minimized and we observe the smallest distortion of the porphyrin macrocycle for any of the *N*-methylated porphyrins.

ACKNOWLEDGMENTS

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9. A green parallelepiped crystal of dication (**1**) [$C_{64}H_{72}N_4^{2+}$ $2(I^-)$, $3(CHCl_3)$] with dimensions 0.76 x 0.54 x 0.12 mm was selected for cell determination and data collection on a Siemens R3m/V diffractometer [λ(Mo $K\alpha$) = 0.71073 Å] equipped with a modified Nonius low temp apparatus operating at 130(2) K. Data were collected in ω scan mode to $2\theta_{max}$ = 60.2°. The unit cell was triclinic $P\bar{1}$ with dimensions a = 13.713(3) Å, b = 14.855(3) Å, c = 19.783(4) Å, α = 70.83(3)°, β = 70.14(3)°, γ = 67.31(3)°, V = 3405(1) Å^3, and Z = 2. Of 19993 independent reflections measured (+h, ±k, ±l), 14241 had $I > 2\sigma$ (T_{min} = 0.55, T_{max} = 0.83, μ = 1.319 mm^{-1}). Hydrogen atom positions were generated by their idealized geometry and refined using a riding model. One of the iodine anions was disordered over two half occupied sites. All non-hydrogen atoms were refined with anisotropic thermal parameters. The final structure had 745 parameters with $R1$ = 0.069 and $wR2$ = 0.211.

10. All of the structures herein presented were solved by direct methods and refined (based on F^2 using all independent data) by full matrix least-squares methods (Siemens SHELXTL V. 5.03). Empirical absorption corrections were applied to the datasets with XABS2.[11] Reported R factors are $R1$ (based on observed data) and $wR2$ (based on all data). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center (CCDC). Any

request to the CCDC (http://www.ccdc.cam.ac.uk) for this material should quote the full literature citation.

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13. A green diamond shaped crystal of dication (**3**) [$C_{62}H_{68}N_4^{2+}$ I^- Cl^-, 3($CHCl_3$)] with dimensions 0.30 x 0.20 x 0.20 mm was selected for cell determination and data collection on a Syntex $P2_1$ diffractometer [λ(Cu $K\alpha$) = 1.54178 Å] equipped with a modified LT-1 apparatus operating at 130(2) K. Data were collected in $\theta/2\theta$ scan mode to $2\theta_{max}$ = 114.16°. The unit cell was orthorhombic $P2_12_12_1$ with dimensions a = 13.496(3) Å, b = 18.657(4) Å, c = 26.905(4) Å, V = 6775(2) Å^3, and Z = 4. Of 5494 reflections measured (+h,+k,+l), 5412 were independent (R_{int} = 0.028) and 4712 had $I > 2\sigma$ (T_{min} = 0.16, T_{max} = 0.29, μ = 7.657 mm^{-1}). Core hydrogens were located on a difference map and allowed to refine freely; all other hydrogen atom positions were generated by their idealized geometry and refined using a riding model. The anions (I^- and Cl^-) and one of the core nitrogens were disordered with each of these atoms occupying two positions; one of the three solvate chloroforms exhibited disorder. All non-hydrogen atoms were refined with anisotropic thermal parameters with the exception of the disordered $CHCl_3$ which was refined with isotropic thermal parameters. The structure was refined as a racemic twin with 692 parameters; $R1$ = 0.079 and $wR2$ = 0.282.

14. X-ray structures for compounds (**6**) and (**7**) have not been determined. The isomeric identity of these compounds was determined by comparison of the proton NMR signals of the O*Me* groups in the analogous dimethylated products from 5,10,15,20-tetra(4-methoxyphenyl)-2,3,7,8,12,13,17,18-octaphenyl-porphyrin; the N_{21},N_{23}-dimethyl compound showed only one type of O*Me*, while the N_{21},N_{22}-dimethyl product showed three O*Me* signals in a 1:2:1 ratio.

15. A green diamond shaped crystal of (**9**) [2($C_{46}H_{26}N_4Br_8$), 2.9($CHCl_3$)] with dimensions 0.60 x 0.22 x 0.10 mm was selected for cell determination and data collection on a Siemens R3m/V diffractometer [λ(Mo $K\alpha$) = 0.71073 Å] equipped with a modified Nonius low temp apparatus operating at 130(2) K. Data were collected in ω scan mode to $2\theta_{max}$ = 45.0°. The unit cell was triclinic $P\bar{1}$ with dimensions a = 14.174(8) Å, b = 16.998(8) Å, c = 23.34(1) Å, α = 85.39(4)°, β = 80.07(4)°, γ = 70.90(4)°, V = 5231(5) Å^3, and Z = 4. Of 13674 independent reflections measured (+h, ±k, ±l), 8586 had $I > 2\sigma$ (T_{min} = 0.32, T_{max} = 0.59, μ = 6.399 mm^{-1}). Hydrogen atom positions were generated by their idealized geometry and refined using a riding model. The structure contained two porphyrin molecules per asymmetric unit; one molecule showed no disorder while the other exhibited disorder in that one of its *N*-methyls had split occupancy among two positions connecting to opposing nitrogens. Additionally there were four $CHCl_3$ sites exhibiting varying degrees of occupancy and disorder. All non-hydrogen atoms were refined with anisotropic thermal parameters with the exception of the disordered *N*-methyls (which were refined with isotropic thermal parameters) and the

partially occupied and disordered chloroform molecules (which were refined with fixed isotropic thermal parameters). The final structure had 1046 parameters with $R1 = 0.094$ and $wR2 = 0.293$.

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17. Herein 'porphyrin mean plane' refers to the least-squares plane calculated for the 24 core carbon and nitrogen atoms for a given porphyrin.

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