Scheme I

2-2,5-²H   3-2,5-²H   2-3,6-²H

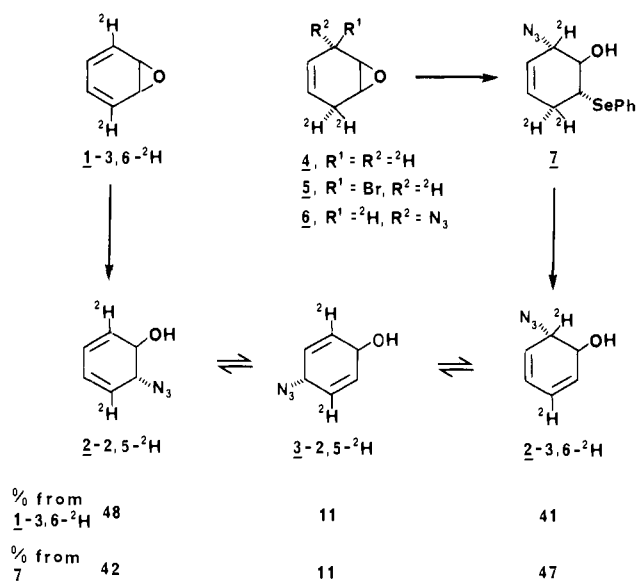|			
% from 1-3,6-²H	48	11	41
% from 7	42	11	47

cyclohexadienyl systems[3] have led us to question whether 1,4 or 1,6 addition of N_3^- to 1 does, in fact, occur. An alternative explanation for the results observed with 1-3,6-²H₂ would be to assume only trans-1,2 addition of N_3^- to afford 2-2,5-²H₂ which undergoes rapid thermal equilibration with 3-2,5-²H₂ and 2-3,6-²H₂ by consecutive [3,3]-sigmatropic rearrangements (or 1,3 shifts). The rearrangement of allyl azides is well documented,[4] including examples that occur at 25 °C.[4a,b]

Reaction of 1-3,6-²H₂ with NaN_3 in H_2O at room temperature followed by workup and chromatography (silica gel plate, 2:1 hexane/ethyl acetate, R_f 0.32) gave 2-2,5-²H₂, 3-2,5-²H₂,[5] and 2-3,6-²H₂ in the relative amounts indicated in Scheme I.[6] The ratio did not change on standing at room temperature. Attempts to monitor the course of the reaction in ²H₂O were not successful due to interference by ²HOH absorption. Consequently, we decided to develop a reaction sequence that would provide 2-3,6-²H₂ as the sole isomeric product.

Bromide 5 was prepared from 4[1] by the same procedure described for the undeuterated material.[7,8] Displacement of bromide 5 with N_3^- (1 h, room temperature) afforded 6 (83%) which reacted with PhSeLi in THF (1 h, room temperature) to provide 7 (53%). Oxidation of 7 with $(n\text{-Bu})_4N^+IO_4^-$ in MeOH gave the selenoxide which underwent selenoxide elimination at room temperature (6 h). Workup and chromatography (as above) gave 2-2,5-²H₂, 3-2,5-²H₂, and 2-3,6-²H₂ in the relative amounts indicated in Scheme I. The ratio did not change on standing at room temperature. These results establish the rapid thermal equilibrium among the three isomeric products at room temperature.[9] Within experimental error the product ratios from addition of N_3^- to 1-3,6-²H₂ and from selenoxide elimination from 7 are identical, and, as expected, 2-2,5-²H₂ and 2-3,6-²H₂ are present in equal amounts at equilibrium.

Furthermore, heating of azide 8,[10] at 120 °C in dimethylformamide for 10 h gave an equilibrium mixture of 8 (72%) and 9 (28%). The two isomers were easily separated by flash chro-

8   9

matography[11] on silica gel (4;1 hexane/ethyl acetate). Selenoxide elimination from 9 at room temperature (1.5 h) gave the same equilibrium mixture of 2 (88%) and 3 (12%) as that obtained from addition of N_3^- to 1 (87% 2 and 13% 3).[12]

Due to the rapid thermal equilibrium among 2-2,5-²H₂, 3-2,5-²H₂, and 2-3,6-²H₂, it is not possible to address the question of 1,2 vs. 1,4 vs. 1,6 addition of N_3^- to 1 on the basis of available data. Since PhS^- and MeO^- undergo nucleophilic addition to 1 solely by 1,2 addition,[1] it is reasonable to assume that addition of N_3^- to 1 occurs only by the 1,2 addition.

Supplementary Material Available: Spectra and physical data for 5-9 (2 pages). Ordering information is given on any current masthead page.

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(10) Azide 8 was prepared from unlabeled starting material by the same procedure for preparation of 7.

(11) Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923-2925.

(12) No line broadening or coalescence of signals was observed in the ¹H NMR spectrum of the mixture of 2-2,5-²H₂, 2-3,6-²H₂, and 3-2,5-²H₂ in C²HCl₂C²HCl₂ at temperatures up to 105 °C. Decomposition to HN₃ and phenol prevented investigation at higher temperatures.

Crystal Structure of *meso*-Tetratolylporphyrin: Implications for the Solid-State ¹⁵N CPMAS NMR

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There has been considerable interest in the N-H tautomerism of free-base porphyrins and chlorins, which has been interpreted in terms of Scheme I,[2-14] The recent observation of tautomerism

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(5) The stereochemistry of 3-2,5-²H₂ is assumed on the basis of its formation from 2-2,5-²H₂ and 2-3,6-²H₂ by thermal equilibration.
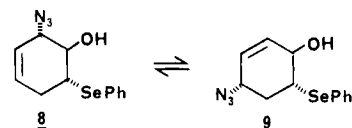
(6) Product ratios were determined by integration of the 250-MHz ¹H NMR spectrum in CDCl₃. Chemical shift data for 3 are given in ref 2; chemical shift data for 2 are given in ref 1.

(7) Kühlmeyer, R.; Keller, R.; Schwesinger, R.; Netscher, T.; Fritz, H.; Prinzbach, H. Chem. Ber. 1984, 117, 1765-1800.

(8) The sequence 4 → 7 and subsequent selenoxide elimination was first developed with undeuterated material.

(9) The possibility of a [1,5] shift of the azido group cannot be eliminated.

Communications to the Editor

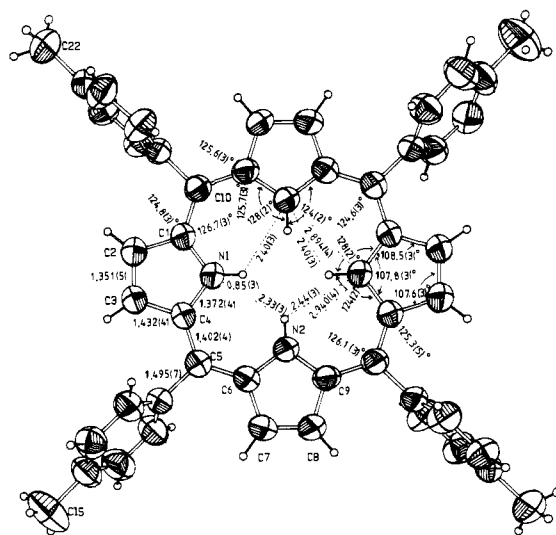J. Am. Chem. Soc., Vol. 107, No. 10, 1985   2979

Figure 1, ORTEP diagram of H_2TTP showing selected metrical details. Distances are in angstroms and angles in degrees. Thermal ellipsoids are drawn at the 60% probability level with hydrogen atoms drawn artificially small. Note the inequivalence in pairs of angles involving atoms C5 and C10, e.g., N1–C1–C10 and N1–C4–C5 vs. N2–C6–C5 and N2–C9–C10, associated with the unsymmetrical cis N⋯N separations. The numbers in parentheses are the estimated standard deviations derived from the scatter of chemically equivalent bonds about their means or the estimated standard deviation in an individual bond, whichever is the larger. Typical individual esd's are 0.004 Å for C–N and C–C(porphine) bond lengths and 0.3° for associated bond angles. Metrical accord among chemically equivalent parameters is very satisfactory.

Scheme I
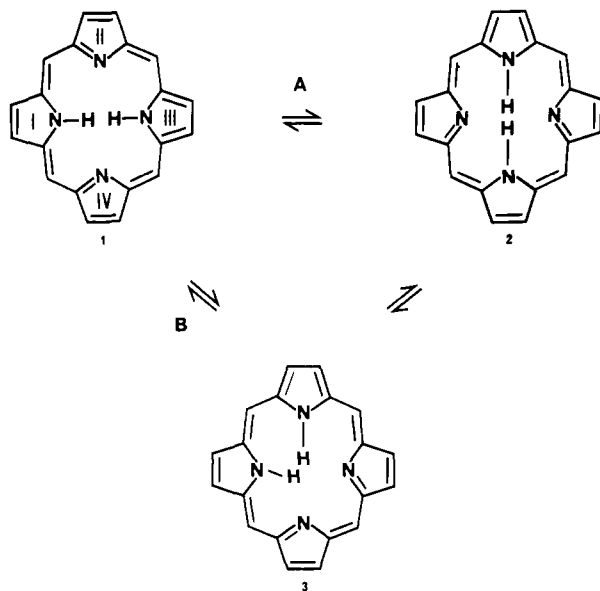
in the solid state for *meso*-tetraphenylporphyrin (H_2TPP) and *meso*-tetratolylporphyrin (H_2TTP)[15,16] adds a new dimension to

a still controversial problem. ^{15}N CPMAS NMR showed that at room temperature in the triclinic phase of H_2TPP the amino protons were moving freely between two unequally populated tautomers,[15] consistent with the room temperature structure which showed proton localization on opposite nitrogen atoms.[17] For H_2TTP the NMR results showed that at room temperature the protons moved rapidly between essentially equally populated tautomers,[15] apparently in a symmetric double-minimum potential. No crystal structure has been reported for H_2TTP.

We find that in the crystal structure of H_2TTP[20a] (see Figure 1) the hydrogen atoms are disordered (as found also for the structures of tetragonal H_2TPP[18] and one form of H_2P[19a]), a result consistent with the ^{15}N CPMAS NMR results. However, we find that these crystals are monoclinic and that the symmetry imposed is only $\bar{1}$. Within the limits of error in the X-ray diffraction experiment, the two amino proton sites are equally populated by well-localized hydrogen atoms. Moreover, this disorder can be confirmed unequivocally by indirect means, since several bond angles in the porphyrin skeleton have been shown to be sensitive to imino vs. amino nitrogen atoms in ordered structures.[21] For example, the C_a–N–C_a angles of 107.9 (3)° and 107.7 (3)° in H_2TTP lie midway between average values for imino and amino nitrogen atoms of 105.8 (4)° and 109.8 (6)°, respectively; these latter averages and their associated esd's are calculated from eight free-base porphyrin structures.[21] A similar pattern is seen for the N–C_a–C_b angles (108.5 (4)° for H_2TTP vs. 110.5 (6)° (imino) and 107.2 (4)° (amino)).

The nitrogen positions are also sensitive to the proton disorder and reflect the $\bar{1}$ symmetry. The trans-annular N⋯N separations with the values of 4.079 (6) and 4.154 (6) Å for H_2TTP are significantly different and fall between the average values of 4.06 (1) (imino) and 4.19 (1) Å (amino) observed in ordered structures. The N⋯N separations between adjacent nitrogen atoms are also unequal (2.894 (4) and 2.940 (4) Å), in marked contrast to triclinic H_2TPP where the values are 2.921 (5) and 2.914 (5) Å.

The proton disorder and structural parameters thus provide impressive confirmation of the predictions from ^{15}N CPMAS NMR data.[15] However, there are several interesting points arising from the crystal structure of H_2TTP. Limbach et al. had suggested that "since H_2TTP and H_2TPP exhibit the same proton dynamics in solution, the difference in the behavior of the two compounds in the solid state may be due to induction of a more symmetrical crystal structure by the methyl groups".[15] In both the triclinic H_2TPP and monoclinic H_2TTP the molecules reside in potentials

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(16) Abbreviations: H_2TPP, *meso*-tetraphenylporphyrin; H_2TTP, *meso*-tetratolylporphyrin; H_2P, porphyrin; H_2OEP, 2,3,7,8,12,13,17,18-octaethylporphyrin; H_2TPrP, *meso*-tetrapropylporphyrin; CPMAS, cross-polarization magic angle spinning.

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(20) (a) H_2TTP was a gift from Professor W. P. Hambright and was purified by recrystallization from 1,2-dichloroethane/methanol, yielding diffraction quality crystals. The material used in this study showed no evidence, using ^{1}H NMR analysis, of chlorin contamination. The material used in the ^{15}N CPMAS NMR study contained a significant quantity of an impurity assumed to be tetratolylchlorin. Dr. H. H. Limbach has informed us that chlorin-free material behaves in the same manner. A total of 3734 reflections in the range (sin θ)/λ < 0.7049 Å^{-1} were collected on a Nicolet P3m diffractometer using Zr-filtered Mo Kα radiation. Crystal data: space group $P2_1/n$, a = 9.878 (3) Å, b = 9.286 (2) Å, c = 20.991 (5) Å, β = 99.91 (2)°, V = 1896.7 Å³, z = 2. The structure was solved by MULTAN80 and refined using the ENRAF-NONIUS SDP and those 1535 data with $I > 3\sigma(I)$ to final values for R and R_w (on F) of 0.043 and 0.050. All hydrogen atoms were located from difference Fourier syntheses. The weighting scheme used was $w = 1/\sigma^2$ where $\sigma^2 = \sigma^2$(counting) + $(0.05F_o^2)^2$. All non-hydrogen atoms were refined anisotropically and all hydrogen atoms isotropically. Tables of atomic parameters and structure factors have been deposited as supplementary material. (b) Crystal packing coefficients were calculated from the ratio of the van der Waals molecular volume (multiplied by the number of molecules per unit cell) to the unit cell volume. van der Waals volume increments for molecular fragments are from: Kitaigorodsky, A. I. "Molecular Crystals and Molecules"; Academic Press: New York, 1973.

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of only Ī symmetry. H$_2$TTP does not sit at, nor is it structurally near, a site of 4̄ symmetry, as found for tetragonal H$_2$TPP where amino hydrogen disorder is crystallographically imposed and there is consequently a symmetric double-minimum potential. Significant perturbations from various 4-fold symmetries include slightly different orientations of the two independent phenyl groups (see Figure 1) and a pattern of atomic displacements from the least-squares plane of the 24-atom porphyrin skeleton (maximum deviation 0.044 Å, mean absolute deviation 0.021 Å) that lacks any 4-fold symmetry. The most important deviations from 4-fold symmetry are the trans annular and adjacent N⋯N separations given above. The structure of H$_2$TTP is, therefore, *less symmetrical* than that of triclinic H$_2$TPP. Thus the symmetric double-minimum potential apparently present for monoclinic H$_2$TTP, if it is symmetric, is only accidentally so.

We have examined the structures of the symmetrically substituted porphyrins, tetragonal (4̄) H$_2$TPP,[18] triclinic (Ī) H$_2$TPP[17] and H$_2$OEP,[22] monoclinic (Ī) H$_2$TTP and H$_2$TPrP,[23] and monoclinic (no symmetry imposed) H$_2$P,[19c] for clues to proton order and disorder and as to the nature of the reaction coordinate in the proton migration. The adjacent protons in H$_4$TPP^{2+} [24] lead to a highly domed structure. There is not room in the crystal lattice for this type of distortion and no abnormal thermal motion parameters are shown perpendicular to the plane of the porphyrin in any of the above structures. This precludes a stepwise migration via path B of Scheme I (predicted by high-temperature CNDO calculations[13b]). The molecular packing coefficients[20b] of the above materials do not show any trends: both modifications of H$_2$TPP have a packing coefficient of 0.75. For H$_2$TTP the value is 0.71, for H$_2$OEP 0.70, and for H$_2$TPrP 0.77, while for H$_2$P[19c] the value is 0.80. Neither nearly planar nor substantially buckled porphyrin skeletons are associated with the presence of proton order or disorder.

We do find two clues as to the nature of the reaction coordinate. First, in contrast to the symmetrical placement of the amino hydrogen atoms in triclinic H$_2$TPP and the equivalence in separations between these nitrogen atoms, no such symmetry is apparent for H$_2$TTP. The two pairs of H–N–C$_a$ bond angles are both 124 (2)° and 128 (2)°. When combined with the asymmetrical N⋯N separations, N1⋯H2 separations of 2.33 (3) and 2.44 (3) Å and N2⋯H1 separations of 2.40 (3) and 2.40 (3) Å result. A similar bending was observed for H$_2$P.[19c] Thus one conformation of lowest energy in the solid state lies partway along a plausible proton-transfer reaction coordinate that involves the asymmetric N–H bending mode.

The second clue, of greater statistical significance, is the cis-annular N⋯N separations. The triclinic form of H$_2$TPP entombs the equilibrium geometry of one of the two degenerate tautomers of the solution state where the nitrogen atoms form a rhombus, analogous to an ordered Jahn–Teller system. Tetragonal H$_2$TPP represents the disordered Jahn–Teller-type system in the crystalline state. In monoclinic H$_2$TTP the molecule, with its lower symmetry than both of the above, appears to be held in a nonequilibrium conformation of the solution state that, as previously noted, may lie on the reaction coordinate to the transition state between one tautomer and the other in solution. In those porphyrin structures examined to date ordered protons are found where crystal packing is accompanied by a symmetrical rhombic (but not square) arrangement of nitrogen atoms.

The trans-annular separation of the nitrogen atoms provides a clue as to the origin of the degree of proton disorder in triclinic H$_2$TPP ($K = 0.149$, 302 K[15]) and monoclinic H$_2$TTP ($K = 1$). The amino nitrogen separations are 4.20 and 4.154 Å; the imino nitrogen separations 4.06 and 4.079 Å, respectively. This expansion of some 0.02 Å on the short axis, coupled with slightly asymmetric proton placement, provides sufficient space on the short axis for two trans protons to fit without significant unfavorable van der Waals interaction.

It appears that the crystal packing forces in free-base porphyrins can entomb any of a variety of closely related molecular conformations. Subtle differences in these structures will control the characteristics of the N–H tautomerism in the solid state and a clear understanding of these structures is required for an interpretation of any kinetic solid-state effect observed. We are pursuing low-temperature X-ray diffraction and neutron diffraction studies on these free-base porphyrins in order to obtain structures of the required detail and accuracy.

Supplementary Material Available: Tables of final atomic positions, isotropic temperature factors, anisotropic thermal parameters for non-hydrogen atoms and structure factor amplitudes for H$_2$TTP (12 pages). Ordering information is given on any current masthead page.


Iron/Copper Promoted Fragmentation Reactions of α-Alkoxy Hydroperoxides. The Conversion of Octalins into 14-Membered Ring Macrolides

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There has been considerable interest in recent years in the field of macrolide synthesis. The attractive features of the macrolides include their unusual structure as well as their ability to inhibit bacterial protein synthesis.[1] Macrocyclization techniques represent the most common method of forming the lactone ring, and these have been employed in the synthesis of many members of this class.[2,3] Nevertheless, the success of these cyclization procedures would appear to be strongly correlated to the substitution pattern of the acyclic precursor.[4] Convincing evidence for this was provided by the investigations of Woodward et al.[5b] which culminated in the synthesis of erythromycin A.[5]

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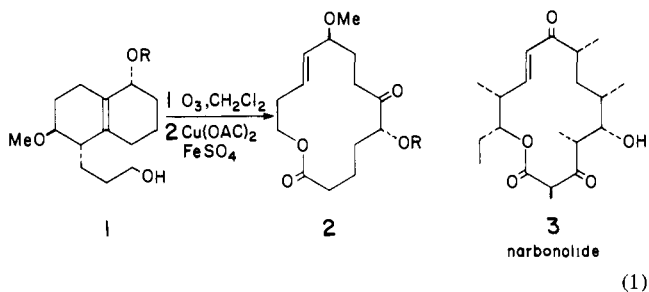
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(22) Lauher, J. W.; Ibers, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 5148–5152.

(23) Codding, P. W.; Tulinsky, A. *J. Am. Chem. Soc.* **1972**, *94*, 4151–4157.

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