

# Use of NMR Spectroscopy To Determine Bond Orders between $\beta$ - and $\beta'$ -Pyrrolic Positions of Porphyrins: Structural Differences between Free-Base Porphyrins and Metalloporphyrins

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**Abstract:** The allylic interproton spin–spin coupling constant,  $^4J(\text{CH}_3\text{C}=\text{CH})$  ( $^4J_{\text{Me,H}}$ ), which has previously been established as a sensitive probe of bond order, was measured in a range of free-base porphyrins and metallo-2-methylporphyrins. The measured room temperature  $^4J_{\text{Me,H}}$  values in a range of substituted porphyrins ( $(1.02\text{--}1.45) \pm 0.03$  Hz) were correlated to the  $\pi$ -bond order of the four  $\beta$ - $\beta'$  pyrrolic linkages of the porphyrins. In 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) (average  $^4J_{\text{Me,H}}$  1.19  $\pm$  0.03 Hz), the bond order across the two  $\beta$ - $\beta'$  pyrrolic bonds involved in the aromatic delocalization pathway in each of the isolated tautomers, **2a** and **2b**, is considerably higher than the bond order in toluene and pyrrole and corresponds to a Pauling bond order of ca. 0.76 or a self-consistent field (SCF) bond order of ca. 0.66. The bond order across the two  $\beta$ - $\beta'$  pyrrolic bonds not involved in the delocalization pathway is similar to that found in “pure” double bonds, and these bonds may be regarded as essentially fully localized carbon–carbon double bonds. The room-temperature  $^4J_{\text{Me,H}}$  values in methylnitroporphyrins **5–10** ranged from 1.12 to 1.45 Hz and reflect the relative tautomer populations. Ground-state structural information about bond delocalization between the  $\beta$ - and  $\beta'$ -pyrrolic positions of metalloporphyrins was similarly obtained from measurement of the  $^4J_{\text{Me,H}}$  values for a series of 2-methylporphyrins (**15–18**) (M = Mg, Zn, Pd, Ni). The  $^4J_{\text{Me,H}}$  values lie in the range 1.14–1.21 Hz, i.e., a Pauling bond order of ca. 0.76 which clearly rules out the possibility of a 16-atom dianion structure with localized double bonds at the four  $\beta$ - $\beta'$  pyrrolic positions as has been previously proposed for a magnesium(II) porphyrin (Spangler, D.; Maggiora, G. M.; Shipman, L. L.; Christoffersen, R. E. *J. Am. Chem. Soc.* **1977**, *99*, 7470). Bond orders were determined on two free-base methylnitroporphyrins and their corresponding zinc(II) chelates. In the free-base methylnitroporphyrins **8** and **9**, the nitro group causes bond fixation such that one  $18\pi$  tautomer predominates over the other tautomeric form. In contrast, no such bond fixation was detected in the zinc chelates, **19** and **20**, respectively. These findings indicate that the bond order at all  $\beta$ - $\beta'$  pyrrolic positions in metalloporphyrins is intermediate between that of aromatic and localized bonds.

Detailed knowledge of the electronic structure of both free-base porphyrins and metalloporphyrins is crucial to the understanding of the chemistry of porphyrins, both in relation to their biological activity and in synthetic transformations.<sup>1</sup> The tautomeric structure of free-base porphyrins has been unequivocally established by NMR spectroscopy.<sup>2</sup> In solution, porphyrins exist as two equilibrating tautomers, each of which contains an [18]-annulene aromatic delocalization pathway and two localized  $\beta$ - $\beta'$  pyrrolic bonds (e.g., Figure 1).<sup>2,3</sup> We have previously shown that the position of the tautomeric equilibrium in both nonsymmetric 5,10,15,20-tetraphenylporphyrins and deuteroporphyrin derivatives is substituent dependent.<sup>3</sup> While theoretical calculations and other spectroscopic techniques have been applied to the study of this tautomerism,<sup>4</sup> NMR spectroscopy has proved to be the most sensitive probe of porphyrin structure, as it allows the location and bonding of the inner N–H protons to be established and hence

access to both the thermodynamics and kinetics of tautomerism.<sup>2,3</sup>

In contrast to the free-base porphyrins, where the inner N–H protons provide an excellent NMR probe for monitoring the tautomerism in the macrocycle, the electron distribution in metalloporphyrins is much more difficult to define. X-ray crystallography has shown that the metalloporphyrin structure retains effective  $D_{4h}$  geometry,<sup>5</sup> and hence it may be regarded, in valence-bond terms, as the resonance-stabilized sum of all possible valence-bond contributors to the resonance hybrid (Figure 2). The two contributors **3c** and **3d** are analogous to tautomers **1a** and **1b** (Figure 1) in the free-base porphyrins, in which the [18]-annulene aromatic delocalization pathway is maintained. In free-base porphyrins there are only two significant contributors to the tautomeric equilibrium, as other tautomeric forms, which are aromatic but contain the inner hydrogens on adjacent nitrogens, are of high energy due to severe van der Waals interactions and have never been directly observed.<sup>6</sup> However, in metalloporphyrins, these energetic constraints do not apply, and structures such as **3e** and **3f** may be significant contributors to the metalloporphyrin structure, provided the metal can accommodate the bonding to the porphyrin. Alternatively, the metalloporphyrin structure can be described in terms of an equilibrium between valence-bond tautomers (each of which has several resonance contributors), i.e., a synchronous shift of the  $\sigma$ - and  $\pi$ -electrons involving a relatively low energy barrier.<sup>7</sup> Both pictures are consistent with the aromatic nature and apparent  $D_{4h}$  symmetry of metalloporphyrins.<sup>5</sup>

Quantum mechanical calculations on magnesium porphyrins have suggested that the structure is best represented as a dianion

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(4) See, for example: (a) Silvers, S. J.; Tulinsky, A. *J. Am. Chem. Soc.* **1967**, *89*, 3331. (b) Lauher, J. W.; Ibers, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 5148. (c) Zeller, M. V.; Hayes, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3855. (d) Reynolds, C. H. *J. Org. Chem.* **1988**, *53*, 6061.

(5) Hoard, J. L. In *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed.; Elsevier: Amsterdam, 1975; Chapter 8, p 317.

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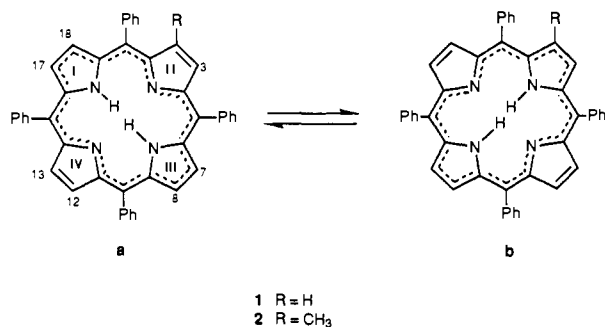


Figure 1. Tautomerism in free-base porphyrins.

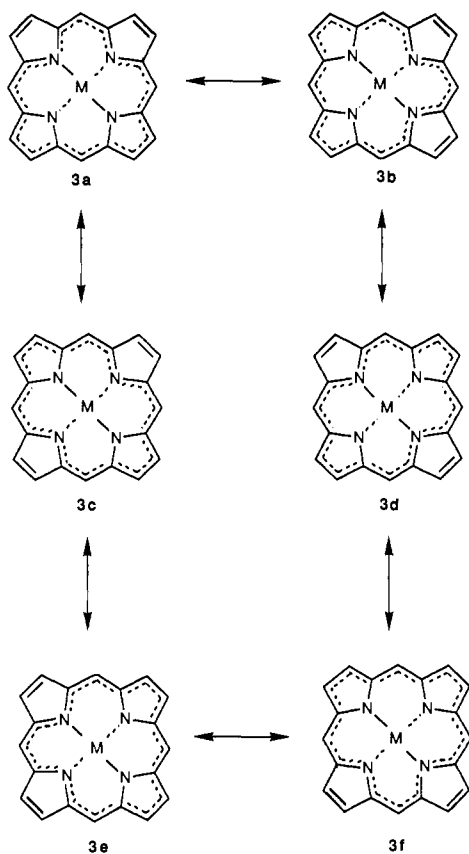


Figure 2. Valence-bond tautomerism in metalloporphyrins. The  $\beta$ -substituents are omitted for clarity.

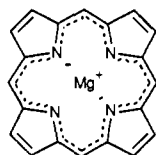


Figure 3. Structure of magnesium(II) porphyrins proposed in ref 8.

that contains a [16]-atom "inner" aromatic delocalization pathway with four localized  $\beta$ - $\beta'$  pyrrolic bonds on the periphery (Figure 3).<sup>8</sup> This model has also been assumed to interpret magnetic circular dichroism (MCD) data on metalloporphyrins.<sup>9</sup> However, bond lengths measured by X-ray crystallography<sup>5</sup> and the chemistry of the zinc(II) chelate of 2-hydroxy-5,10,15,20-tetraphenylporphyrin<sup>3c</sup> cannot be explained by this model but are consistent with an electron delocalization pathway that involves the  $\beta$ - $\beta'$  pyrrolic bonds.

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Several fundamental questions regarding metalloporphyrin structure need to be addressed. First, does the overall structure of the metalloporphyrin depend on the electronegativity of the central metal ion; metal coordination may be effectively used to control the redox properties and reactivity of the macrocycle.<sup>9-11</sup> Secondly, do the peripheral substituents significantly alter the electron distribution in metalloporphyrins in a manner similar to that observed in nonsymmetric free-base porphyrins, where  $\beta$ -substitution alters the thermodynamic stability of the two tautomers.<sup>3</sup> Substituent effects on metalloporphyrins have been recognized as having an influence on the  $\sigma$ -donor and  $\pi$ -acceptor properties of the metal  $d$ -orbitals which controls the effectiveness of metal-ligand binding.<sup>10</sup> The origin of these effects, specifically whether they arise through changes in bond order within the metalloporphyrin, remain a topic of discussion.

A measure of electron delocalization across a carbon-carbon bond is given by the  $\pi$ -bond order. Theoretical and experimental results on a wide range of frameworks have established that the cisoid allylic coupling constant,  ${}^4J(\text{CH}_3\text{C}=\text{CH})$  (abbreviated as  ${}^4J_{\text{Me,H}}$ ), measured between two protons separated across three single bonds and one double bond, is an excellent tool for the measurement of  $\pi$ -bond orders in conjugated systems.<sup>12</sup> This parameter is particularly useful since the size of  ${}^4J_{\text{Me,H}}$  coupling is essentially independent of ring size and substituent effects and has been applied in probing the electronic structure of quinonoid, hydroaromatic, heterocyclic, and other systems.<sup>12</sup>

This paper reports the NMR parameters for a range of free-base porphyrins and metalloporphyrins containing the allylic fragment. The  ${}^4J_{\text{Me,H}}$  values measured in this study were correlated to the  $\pi$ -bond order in free-base porphyrins. The values obtained, which are accessible through one NMR measurement, show that there are significant differences between the bond orders that occur in free-base porphyrins and those in metalloporphyrins. As all the naturally occurring porphyrins contain multiple  $\beta$ -substituents and a metal ion, these results have direct implications for understanding of the activity of the biological porphyrins and the interpretation of spectral data that have been measured in functionalized porphyrin systems.

## Materials

Proton NMR spectra were recorded on a Bruker WM400 (400-MHz) spectrometer at 298 K in  $\text{CD}_2\text{Cl}_2$  locked on solvent deuterium and referenced to TMS as the internal standard. Temperature was calibrated by the shift difference in methanol.<sup>13</sup> Samples were ca. 0.02 M and were degassed. Spectral parameters were adjusted to give digital resolution of at least 0.03 Hz/point. Ultraviolet spectra were recorded on a Hitachi 150-20 spectrometer in chloroform. Mass spectra were recorded on an A.E.I. MS 902 spectrometer at 70 eV. Column chromatography was performed on Merck silica gel Type 7734. Light petroleum refers to the fraction of bp 55-60 °C. Compounds 2 and 5-13 were prepared as previously described.<sup>3a,d,e,15</sup>

**2-Methyl-5,10,15,20-tetraphenylbacteriochlorin (4).** 2-Methyl-5,10,15,20-tetraphenylporphyrin (2) (65 mg, 0.10 mmol) and potassium carbonate (0.2 g, 1.4 mmol) were vigorously stirred in dry pyridine (20 mL) under nitrogen and protected from light. (*p*-Toluenesulfonyl)-

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hydrazine was added at 15–20-min intervals (30 mg, 0.02 mmol per addition) over 6 h which resulted in strong ultraviolet absorbance at  $\lambda = 742$  nm.<sup>14</sup> The solution was diluted with water and the product extracted into chloroform. The combined extracts were washed with dilute hydrochloric acid (2 M), saturated sodium hydrogen carbonate and water, and dried over sodium sulfate, and the solvent removed. The crude product was chromatographed in the dark on silica (chloroform/light petroleum 1:4) to remove the partially reduced porphyrins. The least polar pink band, which gave a dichroic green/pink solution, was collected and the solvent removed. The solid obtained was washed with pentane and methanol to give 2-methyl-5,10,15,20-tetraphenylbacteriochlorin (**4**) as a dark green solid (20 mg, 31%); mp >300 °C; NMR –1.35 (bs, NH on ring I), –1.06 (bs, NH on ring III), 2.24 (d, *J* 1.02 Hz, –CH<sub>3</sub>), 3.88, 3.92 (2s, –CH<sub>2</sub>CH<sub>2</sub>–), 7.58–7.67 (m, H<sub>m,p</sub>), 7.73–7.82 ppm (m, H<sub>o</sub> and H<sub>3,12,13</sub>); UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 358 (5.03), 382 (5.08), 490 (3.73), 520 (4.64), 678 (3.80), 742 (4.98) nm; MS *m/z* 632 (M, 6.4%), 630 (M – 2H, 8.8), 628 (M – 4H, 5.8), 615 (M – 2H – CH<sub>3</sub>, 0.6), 69 (100); HRMS found M<sup>+</sup> 632.2999 (C<sub>45</sub>H<sub>36</sub>N<sub>4</sub> requires 632.2939), 630.2761 (C<sub>45</sub>H<sub>34</sub>N<sub>4</sub> requires 630.2783), 628.2654 (C<sub>45</sub>H<sub>32</sub>N<sub>4</sub> requires 628.2626), 615.2524 (C<sub>45</sub>H<sub>30</sub>N<sub>4</sub> requires 615.2548).

**(2-Methyl-5,10,15,20-tetraphenylporphyrinato)palladium(II) (15).** 2-Methyl-5,10,15,20-tetraphenylporphyrin (**2**) (22 mg, 0.035 mmol), palladium(II) chloride (0.35 g, 1.87 mol), and sodium acetate (0.35 g) were dissolved in glacial acetic acid (35 mL) and protected from light. The mixture was heated at reflux under nitrogen for 2 h, cooled, and added to water (50 mL) and chloroform (100 mL). The organic layer was retained, washed with water (100 mL), and dried over sodium sulfate, and the solvent removed. The products were separated by preparative (dichloromethane/light petroleum 2:1) to yield starting porphyrin **2** (*R<sub>f</sub>* 0.68, 10 mg, 45%), and palladium complex **15** (*R<sub>f</sub>* 0.85, 11 mg, 42%), as an orange solid: mp >300 °C; NMR 2.53 (d, *J* 1.22 Hz, –CH<sub>3</sub>), 7.66–7.76 (m, H<sub>m,p</sub>), 8.01 (m, H<sub>o</sub> at C20), 8.11–8.16 (m, H<sub>o</sub> at C5,10,15), 8.55 (apparent d, *J* 1.23 Hz, H<sub>3</sub>), 8.58 and 8.72 (ABq, *J* 4.97 Hz, H<sub>17,18</sub>), 8.73 and 8.77 ppm (ABq, *J* 4.96 Hz, H<sub>7,8</sub>), 8.77 (s, H<sub>12,13</sub>); UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 417 (4.19), 524 (4.11), 557 (3.34) nm; MS *m/z* 732 (M, 25%), 28 (100); HRMS found M<sup>+</sup> 732.1521 (C<sub>45</sub>H<sub>30</sub>N<sub>4</sub>Pd requires 732.1505).

**(2-Methyl-5,10,15,20-tetraphenylporphyrinato)nickel(II) (16).** 2-Methyl-5,10,15,20-tetraphenylporphyrin (**2**) (25 mg, 0.04 mmol) was treated with nickel(II) acetate according to the method of Fuhrhop and Smith.<sup>14</sup> The crude porphyrin obtained was chromatographed on silica (dichloromethane/light petroleum 1:1). The major red band was collected and the solvent removed, and the residue, on recrystallization from dichloromethane/pentane, afforded metalated porphyrin **16** as purple crystals (27 mg, 73%); mp >300 °C; NMR 2.39 (d, *J* 1.18 Hz, –CH<sub>3</sub>), 7.59–7.69 (m, H<sub>m,p</sub>), 7.85 (m, H<sub>o</sub> at C20), 7.94–8.01 (m, H<sub>o</sub> at C5,10,15), 8.44 (q, *J* 1.15 Hz, H<sub>3</sub>), 8.66, 8.67, 8.68, 8.69, 8.71, 8.712 ppm (6d, *J* 4.96, 4.92, 5.25, 4.95, 4.92, 4.91 Hz, H $\beta$ ); UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 414 (5.30), 531 (4.13), 740 (1.40) nm; MS *m/z* 684 (M, <sup>58</sup>Ni, 88%), 685 (100), 686 (M, <sup>60</sup>Ni, 76), 687 (M, <sup>62</sup>Ni, 35). Anal. Calcd for C<sub>45</sub>H<sub>30</sub>N<sub>4</sub>Ni: C, 78.9; H, 4.4; N, 8.2. Found: C, 78.5; H, 4.6; N, 7.9.

**(2-Methyl-5,10,15,20-tetraphenylporphyrinato)zinc(II) (17).** 2-Methyl-5,10,15,20-tetraphenylporphyrin (**2**) was treated with zinc(II) acetate according to the method of Fuhrhop and Smith<sup>14</sup> to yield the crude porphyrin quantitatively as a dark pink solid. Recrystallization of the solid from dichloromethane/pentane afforded metalated porphyrin **17** as mauve crystals: mp >300 °C; NMR 2.58 (d, *J* 1.21 Hz, –CH<sub>3</sub>), 7.68–7.78 (m, H<sub>m,p</sub>), 8.06 (m, H<sub>o</sub> at C20), 8.16–8.23 (m, H<sub>o</sub> at C5,10,15), 8.67 (d, *J* 1.21 Hz, H<sub>3</sub>), 8.74 and 8.88 (ABq, *J* 4.68 Hz, H<sub>17,18</sub>), 8.89 and 8.94 (ABq, *J* 4.68 Hz, H<sub>7,8</sub>), 8.91 and 8.92 ppm (ABq, *J* 4.68 Hz, H<sub>12,13</sub>); UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 442 (5.74), 481 (4.18), 556 (4.27), 494 (3.80), 635 (3.55) nm; MS *m/z* 692 (M, <sup>66</sup>Zn, 69%), 690 (M, <sup>64</sup>Zn, 100); HRMS found M<sup>+</sup> 690.1724 (C<sub>45</sub>H<sub>30</sub>N<sub>4</sub>Zn requires 690.1761).

**(2-Methyl-5,10,15,20-tetraphenylporphyrinato)magnesium(II) (18).** 2-Methyl-5,10,15,20-tetraphenylporphyrin (**2**) (60 mg, 0.01 mmol) and magnesium perchlorate (1.0 g, 8.0 mmol) were refluxed in dry pyridine (30 mL) under nitrogen and protected from light for 60 h. Pyridine was removed in vacuo and the residue washed with water to remove excess perchlorate salt. The product was extracted into chloroform and dried over sodium sulfate and the solvent removed to give shiny purple crystals. Purification was effected on Sephadex LH-20 (chloroform) and the major violet band collected. Removal of the solvent afforded starting material **2** and title porphyrin **18** as purple crystals (28 mg, 45%); mp >300 °C; NMR (d, *J* 1.14 Hz, –CH<sub>3</sub>), 7.69–7.80 (m, H<sub>m,p</sub>), 8.06 (m, H<sub>o</sub> at C20), 8.19–8.23 (m, H<sub>o</sub> at C5,10,15), 8.61 (q, H<sub>3</sub>), 8.63 and 8.75 (ABq, *J* 4.73 Hz, H<sub>17,18</sub>), 8.75 and 8.80 (ABq, *J* 4.75 Hz, H<sub>7,8</sub>), 8.86 (ABq, H<sub>12,13</sub>); UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 426 (5.55), 524 (3.31), 563 (4.06), 602 (3.68) nm; MS *m/z* 650 (M, <sup>24</sup>Mg, 100%), 651 (M, <sup>25</sup>Mg,

64), 652 (M, <sup>26</sup>Mg, 36); HRMS found M<sup>+</sup> 650.2308 (C<sub>45</sub>H<sub>30</sub>N<sub>4</sub>Mg requires 650.2320).

**(2-Methyl-18-nitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (19).** 2-Methyl-18-nitro-5,10,15,20-tetraphenylporphyrin (**8**<sup>15</sup>) was treated with zinc(II) acetate according to the method of Fuhrhop and Smith<sup>14</sup> to give metalloporphyrin **19** in quantitative yield. The product was washed with pentane and methanol to give the title porphyrin as a dark green solid: mp >300 °C; NMR 2.39 (d, *J* 1.19 Hz, –CH<sub>3</sub>), 7.60–7.80 (m, H<sub>m,p</sub>), 8.06 (m, H<sub>o</sub> at C20), 8.15 (m, H<sub>o</sub> at C5,10,15), 8.56 (q, H<sub>3</sub>), 8.84 and 8.88, 8.85 and 8.89 (2ABq, *J* 4.70, 4.68 Hz, H<sub>7,8</sub> and H<sub>12,13</sub>), 9.06 ppm (s, H<sub>17</sub>); UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 428 (5.12), 600 (3.67), 561 (3.82) nm; IR (KBr disc)  $\nu_{\max}$  750 (s), 800 (m), 1330, 1440, 1500, 1600, 2900 cm<sup>-1</sup>; MS *m/z* 735 (M, <sup>64</sup>Zn, 26%), 737 (M, <sup>66</sup>Zn, 20), 705 (100); HRMS found M<sup>+</sup> 735.1612 (C<sub>45</sub>H<sub>29</sub>N<sub>5</sub>O<sub>2</sub>Zn requires 735.1612).

**(2-Methyl-12-nitro-5,10,15,20-tetraphenylporphyrinato)zinc(II) (20).** The title porphyrin (**20**) was prepared quantitatively as for compound **19** as a green solid; mp >300 °C. Insufficient material prevented full spectral characterization: NMR 2.53 (d, *J* 1.28 Hz, –CH<sub>3</sub>), 7.67–7.80 (m, H<sub>m,p</sub>), 8.04 (m, H<sub>o</sub> at C20), 8.15 (m, H<sub>o</sub> at C5,10,15), 8.62 (q, H<sub>3</sub>), 8.69 and 8.85, 8.83 and 8.97 (2ABq, *J* 4.70 Hz, H<sub>7,8</sub> and H<sub>12,13</sub>), 9.17 ppm (s, H<sub>3</sub>); UV (CHCl<sub>3</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 428 (5.12), 600 (3.67), 561 (3.82) nm.

## Results and Discussion

**2-Methyl-5,10,15,20-tetraphenylporphyrin.** In order to relate directly the measured <sup>4</sup>*J*<sub>Me,H</sub> value to bond order parameters, it was desirable to obtain the allylic coupling constants in isolated tautomers **2a** and **2b**, which contain the “localized” and “delocalized” allylic fragments, respectively. In principle, these values are directly available from low-temperature spectra of **2**, where the tautomerism **2a** ⇌ **2b** is slow on the NMR time scale and each tautomer gives rise to a methyl signal.<sup>3a</sup> Variable-temperature analysis of the NMR spectrum of **2** showed two broad singlets in a ratio of ca. 80:20 at  $\delta$  2.48 and 2.25 ppm, respectively, in the temperature range 200–210 K. However, due to high solvent viscosity and line broadening at low temperature, it was not possible to resolve the signals. A study of the corresponding deuterated porphyrin [*N,N'*-D<sub>2</sub>]-**2**, in which the inner hydrogens are replaced with deuteriums, proved more informative. Substitution of the inner hydrogens for deuteriums removes the coupling between the  $\beta$ -pyrrolic protons and the NH protons and, due to the large isotope effect in porphyrins,<sup>2,3b</sup> allowed the tautomerism to be studied at a higher temperature. The tautomeric exchange of the dideuterated derivative of **2** was slow on the NMR time scale in the range 240–260 K, and two distinct signals were observed in the methyl region of the spectrum. The major methyl peak was assigned to tautomer **2b**.<sup>3a</sup> Resolution enhancement of the data resolved the signal to a doublet <sup>4</sup>*J*<sub>Me,H</sub> 1.11 Hz. This value gives a direct measure of the electron delocalization in the [18]annulene system. The minor methyl peak arising from tautomer **2a** was present at too low a concentration to allow resolution.

On the basis of data collected on a wide range of cyclic compounds, the allylic coupling constant across a fully localized carbon–carbon double bond (i.e., bond order 1) is 1.52 Hz in the absence of unusual substituent effects, while the allylic coupling constant across a fully delocalized carbon–carbon bond (i.e., bond order 0.5) is 0.702 Hz.<sup>12</sup> Of particular relevance to the present study are the bond orders that have been observed in other aromatic and heteroaromatic systems. The value obtained for **2** is considerably higher than the value in toluene (0.702 Hz)<sup>16</sup> and lies between the value for the 9–10 bond of phenanthrene (1.16 Hz,  $\eta_{\text{Pauling}}$  0.800,  $\eta_{\text{SCF}}$  0.685) and that for the  $\alpha$ - $\beta$  bond in naphthalene (0.99 Hz,  $\eta_{\text{Pauling}}$  0.667,  $\eta_{\text{SCF}}$  0.609).<sup>12</sup> The value for the 3–4 bond in 3-methylpyrrole (0.55 Hz),<sup>17</sup> which may be considered to be a model of the individual pyrrolic units that make up porphyrins, is only half of the value observed for **2**. Further, the value of <sup>4</sup>*J*<sub>Me,H</sub> across the 2–3 bond in pyrrole is 1.02 ± 0.03 Hz.<sup>15</sup> Thus there is no trace left of the “pyrrolic” electron configuration in the [18]annulenic electron configuration in the free-base porphyrin.

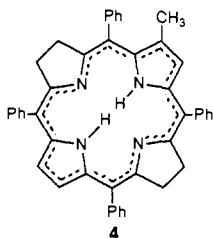
(16) Schaefer, T.; Sebastian, R.; Penner, G. H. *Can. J. Chem.* **1985**, *63*, 2957.

(17) Hatton, P.; Sternhell, S. Unpublished data.

The room-temperature  $^1\text{H}$  NMR spectrum of 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) contained a doublet at  $\delta$  2.59 ppm with  $^4J_{\text{Me,H}}$   $1.19 \pm 0.03$  Hz. This value represents a time averaged coupling constant due to the tautomerism **2a**  $\rightleftharpoons$  **2b** and reflects the fact that, in **2**, the allylic fragment is "aromatic" 80% of the time (tautomer **2b**) and "olefinic" 20% of the time (tautomer **2a**). By intrapolation, we deduce that the annulenic  $\beta$ - $\beta'$  pyrrolic bond in 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) has a bond order of ca.  $\eta_{\text{Pauling}}$  0.76 or ca.  $\eta_{\text{SCF}}$  0.66. Given the existence of some substituent effects and experimental uncertainty in the measurement of  $^4J_{\text{Me,H}}$ , we do not consider any more detailed quantification to be justified.

Supporting data for the high bond order in the [18]annulene system of the isolated tautomers of **2** was obtained from the NMR spectrum of 2-methyl-5,10,15,20-tetraphenylbacteriochlorin (**4**) in which the aromatic pathway is restricted to the [18]annulene system shown. The reduced analogue was prepared as an appropriate model compound from which data could be directly extracted without complications due to tautomerism. No evidence for additional tautomeric forms of **4** was detected in the NMR spectrum at 200 K. Several other possible tautomers may be formulated, but all involve either charge separated structures or require the inner hydrogens to reside on adjacent ring nitrogens, which is sterically unfavorable and necessitates the use of a lone pair of electrons from nitrogen to maintain a 17-atom  $18\pi$ -electron delocalization pathway. In work on keto-enol and prototypic tautomerism of 2-hydroxy-5,10,15,20-tetraphenylporphyrin,<sup>3c</sup> such 17-atom  $18\pi$ -electron tautomers were possible but were not detected. These tautomers would be expected to have less stabilization energy than the 18-atom  $18\pi$ -electron tautomers by analogy with the different properties of benzene and pyrrole.

The NMR spectrum of **4** contained a doublet at  $\delta$  2.15 ppm with  $^4J_{\text{Me,H}}$   $1.02 \pm 0.03$  Hz, which is entirely consistent with the value found above and corresponds to a bond order of ca.  $\eta_{\text{Pauling}}$  0.7 or  $\eta_{\text{SCF}}$  0.6. This relatively high bond order for a fully



delocalized carbon-carbon bond in bacteriochlorins is consistent with the recent X-ray data on both free-base and zinc(II) bacteriochlorins,<sup>18</sup> in which the  $\beta$ - $\beta'$  pyrrolic bond length is shorter than the bond lengths in benzene.

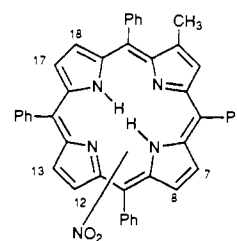
**Methylnitroporphyrins.** The results obtained on **2** were used to assess the effect of substituents on the  $\pi$ -bond order in non-symmetric porphyrins. For porphyrins where **1a** is the dominant tautomer<sup>3a</sup> (R = CN, NO<sub>2</sub>, OCOPh, Cl, Br, CHO, OMe, SPh, NHCOMe, OH), there is, on average, reduced bond order in the  $\beta$ -pyrrolic bonds in rings I and III and increased bond order in the  $\beta$ -pyrrolic bonds in rings II and IV, compared to 5,10,15,20-tetraphenylporphyrin (**1**, R = H). Conversely, **1b** is the dominant tautomeric form in porphyrins where R = CH<sub>2</sub>OH, CH=CH<sub>2</sub>, NH<sub>2</sub>, (CH<sub>2</sub>)<sub>3</sub>Me, Me, and CHMe<sub>2</sub>, and hence, on average, the bond order of the  $\beta$ -pyrrolic bonds is increased in rings I and III and decreased in rings II and IV relative to the unsubstituted porphyrin. We have previously monitored these substituent effects by variable-temperature NMR spectroscopy.<sup>3a-c</sup> An independent measure of the perturbed equilibrium in these porphyrins is given by the average bond order of the four  $\beta$ - $\beta'$  pyrrolic bonds, measurable from derivatives of the 2-substituted 5,10,15,20-tetraphenylporphyrins containing the allylic fragment (CH<sub>3</sub>C=CH). However, the synthesis of porphyrins containing

**Table I.** Calculated and Observed Values of  $^4J_{\text{Me,H}}$  (Hz) in Methyltetraphenylporphyrins at 298 K

compd	substitution pattern	population tautomer b <sup>a</sup>	$^4J_{\text{Me,H}}$ (calcd) <sup>b</sup>	$^4J_{\text{Me,H}}$ (obsd) $\pm$ 0.06
<b>2</b>	2-methyl-	0.72 $\pm$ 0.07	1.14 $\pm$ 0.10	1.19
<b>8</b>	2-methyl-18-nitro-	0.86 $\pm$ 0.09	1.07 $\pm$ 0.11	1.14
<b>7</b>	2-methyl-17-nitro-	0.77 $\pm$ 0.08	1.11 $\pm$ 0.11	1.15
<b>6</b>	2-methyl-8-nitro-	0.81 $\pm$ 0.08	1.08 $\pm$ 0.12	1.15
<b>5</b>	2-methyl-7-nitro-	0.87 $\pm$ 0.09	1.06 $\pm$ 0.12	1.16
<b>9</b>	2-methyl-12-nitro-	0.15 $\pm$ 0.02	1.43 $\pm$ 0.14	1.35
<b>10</b>	2-methyl-13-nitro-	0.18 $\pm$ 0.02	1.44 $\pm$ 0.14	1.44

<sup>a</sup> Error extrapolated from integrals of low-temperature spectra ( $\pm 10\%$ ) assuming  $\Delta S = 0$ ; see ref 3f. <sup>b</sup> See text.

a substituent as well as the allylic fragment is difficult, and the present study was therefore restricted to methyl-nitro isomers **5**-**10**.<sup>3c</sup>



**5** 2-Me-7-NO<sub>2</sub>

**6** 2-Me-8-NO<sub>2</sub>

**7** 2-Me-17-NO<sub>2</sub>

**8** 2-Me-18-NO<sub>2</sub>

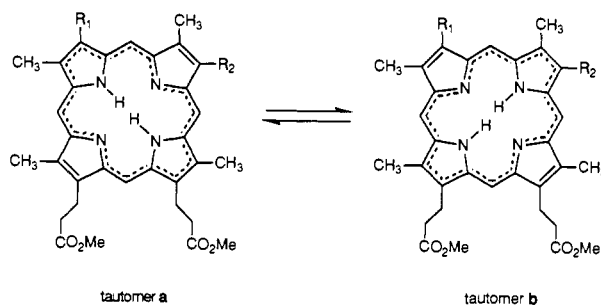
**9** 2-Me-12-NO<sub>2</sub>

**10** 2-Me-13-NO<sub>2</sub>

The values of  $^4J_{\text{Me,H}}$  obtained in isomers **5**-**10** ranged from 1.14 to 1.45 Hz (Table I). The major tautomers of **5**-**8** are structurally similar since the equilibrium lies in the direction of the "nitro-ene" tautomer, which contains the methyl group substituted on the aromatic delocalization pathway.<sup>3c</sup> In support of this, the  $^4J_{\text{Me,H}}$  values in these porphyrins were less than the average value in 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) (Table I). In the remaining two isomers **9** and **10**, the  $^4J_{\text{Me,H}}$  values increased compared to 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) to 1.35 and 1.44 Hz, respectively. These values reflect the increase in bond order across the allylic fragment in these porphyrins since, in both cases, the major tautomer, which is  $>95\%$  populated at room temperature,<sup>3c</sup> contains both the methyl and nitro groups substituted at  $\beta$ -pyrrolic positions outside the aromatic delocalization pathway.

Low-temperature NMR spectra of 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) and the six isomeric methylnitroporphyrins (**5**-**10**) allowed measurement of the tautomeric populations,<sup>3c</sup> and resolution of the major methyl doublets in the spectra of **5** and **6** provided values of  $1.17 \pm 0.08$  and  $1.09 \pm 0.08$  Hz, which compare favorably, within experimental error, with the value obtained in the model reduced methylporphyrin **4** (1.02 Hz). The minor methyl peak was present at too low concentration to provide accurate coupling information, and resolution of the major doublet was not possible for all porphyrins studied due to the high solvent

(18) (a) Barkigia, K. M.; Fajer, J.; Chang, C. K.; Young, R. J. *Am. Chem. Soc.* **1984**, *106*, 645. (b) Barkigia, K. M.; Miura, M.; Thompson, M. A.; Fajer, J. *Inorg. Chem.* **1991**, *30*, 2233.

**Table II.** Calculated and Observed Values of  ${}^4J_{\text{Me,H}}$  (Hz) in Substituted Deuterioporphyrin IX Dimethyl Esters in  $\text{CD}_2\text{Cl}_2$  at 298 K

compd	substitution pattern		population tautomer b <sup>a</sup>	${}^4J_{\text{Me,H}}$ (calcd) <sup>b</sup>	${}^4J_{\text{Me,H}}$ (obsd)
11	R <sub>1</sub> OAc	R <sub>2</sub> H	0.13 ± 0.02	1.07 ± 0.12	1.16 ± 0.04
12	H	OAc	0.87 ± 0.09	1.07 ± 0.12	1.17 ± 0.04
13	CH(OH)CH <sub>3</sub>	H	0.59 ± 0.06	1.30 ± 0.11	1.24 ± 0.03

<sup>a</sup>Error extrapolated from integrals of low-temperature spectra (±10%) assuming  $\Delta S = 0$ ; see ref 3e. <sup>b</sup>See text.

**Table III.**  ${}^4J_{\text{Me,H}}$  (Hz) in Metal Complexes of 2-Methyl-5,10,15,20-tetraphenylporphyrin

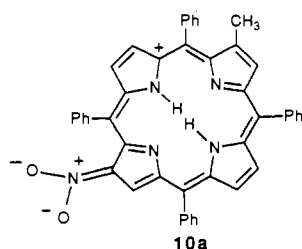
compd	M	electronegativity <sup>a</sup>	${}^4J_{\text{Me,H}} \pm 0.06$
15	Pd	2.33	1.22
2	2H	2.10	1.19 <sup>b</sup>
16	Ni	1.91	1.18
17	Zn	1.65	1.21
18	Mg	1.31	1.14

<sup>a</sup>Taken from ref 11. <sup>b</sup>Average value.

viscosity at low temperatures. Simultaneous analysis of the tautomeric populations and  ${}^4J_{\text{Me,H}}$  values of porphyrins **2** and **5–10** were consistent with the two values of  ${}^4J_{\text{Me,H}}$  1.00 ± 0.06 and 1.50 ± 0.06 Hz across a fully localized  $\beta$ - $\beta'$  pyrrolic bond. To test the validity of these values, the observed values of  ${}^4J_{\text{Me,H}}$  in porphyrins **2** and **5–10** were compared to the values calculated assuming the idealized values of 1.5 and 1.0 Hz (Table I). A larger error is associated with the calculated values as the tautomeric populations measured at low temperature need to be extrapolated to room temperature. Nevertheless, good agreement between the observed and calculated values was obtained.

The results for the nitro-methyl derivatives **5–10** (Table I) confirm the value of  ${}^4J_{\text{Me,H}}$  obtained for 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) and, in addition, give a value of ca. 1.5 Hz for the  ${}^4J_{\text{Me,H}}$  across the "isolated" double bond. This value is so close to that for  ${}^4J_{\text{Me,H}}$  in isolated double bonds in cycloalkenes<sup>12</sup> that this bond can be considered to be essentially of fully double bond character. Even if larger values for  ${}^4J_{\text{Me,H}}$  are taken, the main conclusions remain.

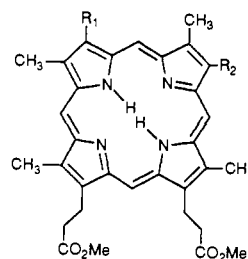
It should be noted that the data in Table I assumes the  ${}^4J_{\text{Me,H}}$  values are independent of the nitro (and methyl) substituents. Benzylic coupling constants in ring substituted toluenes and other aromatic systems show relatively small substituent effects,<sup>12</sup> but exceptions occur in those cases in which substituents cause appreciable bond fixation, such as 2-nitro-4-methylphenol. The contribution of canonical forms such as **10a** to the  ${}^4J_{\text{Me,H}}$  values



in porphyrins **5–10** was assumed to be small. The nitro group is considerably out of plane with the porphyrin  $\pi$ -system, and hence the conjugative stabilization of this structure to the resonance

hybrid was expected to be small. The consistency of the results obtained in this work and studies of substituent effects in other systems indicate that this assumption is justified.

**Deuterioporphyrin Derivatives.** The generality of the results presented above was examined by measurement of  ${}^4J_{\text{Me,H}}$  in the deuterioporphyrin IX dimethyl ester derivatives **11–13**. The



- 11 R<sub>1</sub> = OAc      R<sub>2</sub> = H  
 12 R<sub>1</sub> = H        R<sub>2</sub> = OAc  
 13 R<sub>1</sub> = CH(OH)CH<sub>3</sub>    R<sub>2</sub> = H

tautomeric populations and NMR parameters<sup>3d</sup> are summarized in Table II and are compared to the calculated values assuming that the  ${}^4J_{\text{Me,H}}$  values of 1.5 and 1.0 Hz are for the fully localized and delocalized systems, respectively.

For the two isomeric acetylporphyrins, **11** and **12**, the  ${}^4J_{\text{Me,H}}$  values indicate the presence of unequally populated tautomers (a value of  ${}^4J_{\text{Me,H}}$  1.25 Hz is predicted if the tautomers are degenerate), while the value in the hydroxyethylporphyrin, **13**, indicated that the energy of the two tautomers is similar. The data agree with the measured tautomeric populations,<sup>3d</sup> and in all cases the predicted and calculated values agree well within experimental area. However, it should be noted that due to the quite small difference in  ${}^4J_{\text{Me,H}}$  in the two extreme cases (0.4 Hz), the parameter is quite sensitive to the tautomeric populations extrapolated from low temperatures. The estimated errors allow for uncertainty in extrapolation of populations to 298 K and the integrals obtained from low-temperature spectra. When the errors are considered, the difference in bond order of the four  $\beta$ - $\beta'$  pyrrolic bonds is not large compared to other aromatic and vinylic systems, and hence accurate measurements of coupling constants are required in order to be of significance.

There is one previous report of the study of bond orders in porphyrins by measurement of  ${}^4J_{\text{Me,H}}$ .<sup>19</sup> However, the study assumed that the position of the tautomeric equilibrium is inde-

(19) (a) Clezy, P. S.; Fookes, P.; Sternhell, S. *Aust. J. Chem.* **1978**, *31*, 639. (b) Chakraborty, S.; Clezy, P. S.; Sternhell, S.; van Thuc, L. *Aust. J. Chem.* **1982**, *35*, 2315.

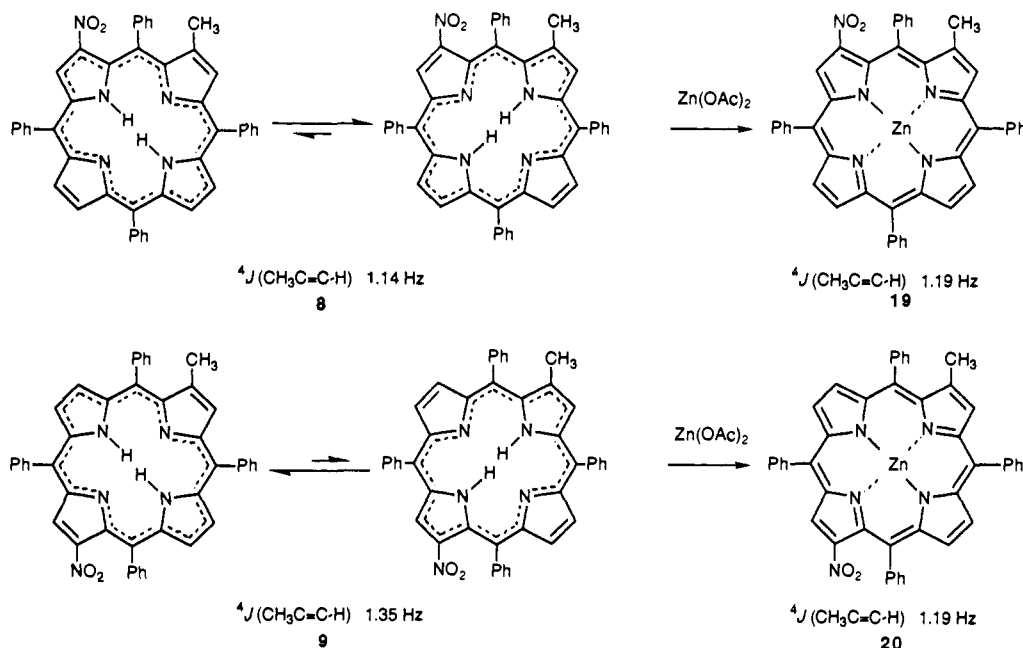
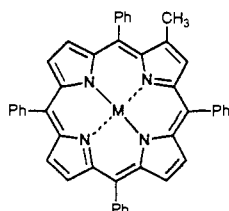


Figure 4. Measured values of  ${}^4J_{\text{Me,H}}$  in free-base methylnitroporphyrins at room temperature undergoing rapid tautomerism and the values in the corresponding zinc(II) chelates.

pendent of the substituent pattern on the porphyrin periphery. Using the values obtained in this work, this data reported for deuterioporphyrin III diethyl ester was re-evaluated using the model values proposed above. The two tautomers in this porphyrin are degenerate and so equally populated. Rapid tautomerism at room temperature leads to a predicted value of 1.21 Hz, which agrees well with the reported value of  $1.19 \pm 0.02$  Hz. The apparent consistency between the model values and the experimental results in the work of Clezy et al.<sup>19</sup> was a result of overestimation of the upper limit of  ${}^4J_{\text{Me,H}}$  (1.6 Hz) and underestimation of the lower limit (0.8 Hz).

**Metalloporphyrins.** (a) **Effect of the Central Metal Ion.** In order to investigate the effect of the central metal ion on the  $\pi$ -bond order of the  $\beta$ - $\beta'$  pyrrolic bonds in porphyrins, metal complexes **15**–**18** were prepared from 2-methyl-5,10,15,20-



- 2 M = 2H  
 15 M = Pd  
 16 M = Ni  
 17 M = Zn  
 18 M = Mg

tetraphenylporphyrin (**2**). The four metals were chosen to span a range of electronegativities. The  ${}^4J_{\text{Me,H}}$  values in the complexes (Table III) range between 1.14 and 1.22 Hz and within experimental error are essentially identical. This result is particularly significant as it shows that the  $\pi$ -bond order of the four  $\beta$ - $\beta'$  pyrrolic bonds in metalloporphyrins is very similar regardless of the electronegativity of the central metal ion. Furthermore, the average (on the NMR time scale) electron distribution in unsubstituted free-base porphyrins and the corresponding metalloporphyrins is similar. This is consistent with the representation of the metalloporphyrin as the sum of the two valence bond contributors **3e** and **3f**, but could equally well be a result of averaging over all canonical forms (Figure 2).

The results argue strongly against the representation of the magnesium(II) porphyrin as a [16]annulene dianion (Figure 3). In such a dianion structure, the porphyrin contains four localized  $\beta$ - $\beta'$  pyrrolic double bonds, and hence, in the corresponding methylporphyrins, a  ${}^4J_{\text{Me,H}}$  value of 1.5 Hz would be predicted. This value is significantly higher than the observed value and is well outside the experimental uncertainty in the measurements made in this work.

(b) **Effect of  $\beta$ -Substituents.** In free-base porphyrins **8** and **9**, the nitro group overrides the substituent effect of the methyl group on the position of the tautomeric equilibrium,<sup>3c</sup> and both **8** and **9** exist almost exclusively as the one tautomeric form (Figure 4). Substitution of the nitro group on the isolated double bond outside the aromatic delocalization pathway results in a decrease in bond order of the allylic fragment in **8** ( ${}^4J_{\text{Me,H}}$  1.15 Hz) and an increase in the bond order of the allylic fragment in **9** ( ${}^4J_{\text{Me,H}}$  1.35 Hz) (Table I).

In order to see if the substituent effect of the nitro group was also present in metalloporphyrins, zinc complexes **19** and **20** were prepared. In both cases, complexation of the free-base porphyrin resulted in the allylic coupling constant changing to 1.19 Hz (Figure 4). Since the values in 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) and its zinc(II) complex (**17**) are effectively identical, this result shows clearly that while, in free-base porphyrins, the nitro group effects a high degree of bond fixation on the porphyrin periphery, the nitro group does not alter the bond order in the corresponding zinc porphyrins. Thus, there are significant structural differences between the free-base porphyrins and metalloporphyrins, which are reflected in the bond order of the four  $\beta$ - $\beta'$  pyrrolic positions.

While this result was demonstrated only for one substituent, the nitro group, it should be noted that in studies of the thermodynamic stability of 18 2-substituted porphyrins, the nitro and cyano groups induce the greatest degree of bond fixation on the porphyrin periphery, and these porphyrins exist as essentially one tautomer.<sup>3a</sup> Given that in the corresponding metallomethylporphyrin, no corresponding bond fixation was observed, it is reasonable to assume (although not conclusive) that other substituents would not induce changes in bond order in metalloporphyrins.

### Conclusions

The allylic interproton spin-spin coupling constant,  ${}^4J_{\text{Me,H}}$  ( ${}^4J_{\text{CH}_3\text{C}=\text{CH}}$ ), which has previously been established as a sensitive probe of bond order, was measured in a range of

free-base porphyrins and metallo-2-methylporphyrins. The best estimate of the allylic coupling constant across the fully delocalized  $\beta$ - $\beta'$  porphyrin bond (1.00 Hz) was obtained from low-temperature spectra of the  $N,N'$ -dideuteriated [ $N,N'$ -D<sub>2</sub>]-methylporphyrin **2** and was confirmed by measurement of  $^4J_{Me,H}$  in the methylbacteriochlorin **4**. The best estimate for the allylic coupling constant across the fully localized  $\beta$ - $\beta'$  bond that is not involved in the  $\pi$ -electron delocalization pathway was found to be 1.50 Hz. This value was obtained from low-temperature studies on methylnitroporphyrins in which individual tautomers were directly detected. The measured room-temperature  $^4J_{Me,H}$  values in a range of substituted porphyrins ((1.02–1.45)  $\pm$  0.03 Hz) were correlated to the  $\pi$ -bond order of the four  $\beta$ - $\beta'$  pyrrolic linkages of the porphyrins. In 2-methyl-5,10,15,20-tetraphenylporphyrin (**2**) ( $^4J_{Me,H}$  1.19  $\pm$  0.03 Hz), the bond order across the two  $\beta$ - $\beta'$  pyrrolic bonds involved in the aromatic delocalization pathway in each of the isolated tautomers, **2a** and **2b**, is considerably higher than the bond order in toluene and pyrrole and corresponds to a Pauling bond order of ca. 0.76 or an SCF bond order of ca. 0.66. The bond order across the two  $\beta$ - $\beta'$  pyrrolic bonds not involved in the delocalization pathway is similar to that found in "pure" double bonds, and these bonds may be regarded as essentially fully localized carbon-carbon double bonds. A similar result was found for a series of deuterioporphyrin dimethyl ester derivatives.

The relatively high bond order between the  $\beta$ - $\beta'$  pyrrolic carbon atoms within the [18]annulene system is not unreasonable as most aromatic systems other than benzene (e.g., naphthalene) exhibit a range of bond orders. The parameter  $^4J_{Me,H}$  also provides an approximate indication of the position of the tautomeric equilibrium. In more complex systems, where coupling information from the inner N-H protons is not available, disturbance of the

tautomeric equilibrium can be detected from one measurement at room temperature, which otherwise can only be determined from low-temperature spectra.

The room-temperature  $^4J_{Me,H}$  values in methylnitroporphyrins **5–10** range from 1.12 to 1.45 Hz and confirm the values previously obtained for tautomer populations at low temperature, i.e., the nitro group significantly alters the thermodynamic stability of the tautomers. With the establishment of the two extreme values of  $^4J_{Me,H}$  in free-base porphyrins, this approach was used to obtain ground-state structural information about bond delocalization between the  $\beta$ - $\beta'$  pyrrolic positions of metalloporphyrins. For the series of 2-methylporphyrins **15–18** (M = Mg, Zn, Pd, Ni) the  $^4J_{Me,H}$  values lie in the range 1.14–1.21 Hz, i.e., a Pauling bond order of ca. 0.76. This finding clearly rules out the possibility that a 16-atom dianion structure with localized double bonds at the four  $\beta$ - $\beta'$  pyrrolic positions as has been previously proposed.<sup>8</sup> In order to determine whether the metalloporphyrin structure is best considered as equilibrating 18 $\pi$ -electron tautomers or involves a fully delocalized system, the bond order in two methyl-nitro porphyrins was determined on the free-base and corresponding zinc porphyrins. While  $\beta$ -substitution with the nitro group effects a high degree of bond fixation in free-base porphyrins **8** and **9** by altering the position of the tautomeric equilibrium, no evidence for a parallel result was found in the corresponding zinc(II) metalloporphyrins, **19** and **20**. This result implies that metalloporphyrins are completely delocalized on the NMR time scale; valence bond tautomerism, if present, must involve a very low energy barrier between tautomers.

**Acknowledgment.** We thank the Australian Research Council for financial support.

## Determination of Conformation and Relative Configuration of a Small, Rapidly Tumbling Molecule in Solution by Combined Application of NOESY and Restrained MD Calculations

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**Abstract:** The conformation and relative configuration of seven stereogenic centers in a small, rapidly tumbling molecule have been determined simultaneously in CDCl<sub>3</sub> by 2D NOE spectroscopy and restrained MD calculations. Two different methods of evaluating interproton distances from NOESY data were applied and their merits and drawbacks are discussed. The usefulness of the proton detected heteronuclear long range correlation experiment (HMBC) for the assignment of diastereotopic protons is demonstrated. A new approach for the determination of the relative configuration is introduced. By utilizing NOE restraints within molecular dynamic simulations that are larger than the energetic terms responsible for maintaining chirality, the chiral centers can switch and adopt the configuration consistent with the experimental measurements. This approach is illustrated here with the title compound **1** which is extremely well determined by the experimental constraints (58 distance restraints). It adopts a single conformation in CDCl<sub>3</sub> solution with structural features similar to corresponding molecular fragments of X-ray structures from similar molecules.

### 1. Introduction

The determination of the relative and absolute configuration of stereogenic elements in synthetic intermediates, as well as the study of their conformational preferences, is of major importance for both natural product synthesis and the development of new synthetic methods. A deeper insight into the structure and conformation of the species under study is a precondition to predict

and optimize the stereochemical outcome of further synthetic transformations.

X-ray crystallographic analysis is without doubt the most secure method to solve the structural problem, but it suffers from the well-known problem of requiring single crystals. Furthermore, the method is principally not suited to analyze conformational preferences of the system *in solution*, which in turn builds the basis for the rational design of new stereoselective transformations.

The method of choice to simultaneously determine configuration and conformation of molecules in solution is obviously NMR spectroscopy, whose capability in this field has been thoroughly

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