δ 1.49 (t, J = 7 Hz, 3 H), Me, 2.05 (quin, J = 7 Hz, 2 H) CH_2, 2.68 (s, 3 H) NMe, 2.97 (t, J = 7 Hz, 2 H) CH_2, 3.05 (t, J = 7 Hz, 2 H) CH_2, 3.89 (s, 3 H) N(im)Me (gave a NOE with the signal at 7.70 ppm), 3.91 (s, 3 H) OMe (gave a NOE with the signal at 7.18 ppm), 4.38 (q, J = 7 Hz, 2 H), CH_2, 7.18 (d, J = 9 Hz, 2 H) C_6H_4, 7.70 (d, J = 9 Hz, 2 H) C_6H_4; ^{13}C-NMR (DMSO-d_6) δ 14.1, 24.6, 25.7, 32.4, 34.6, 48.0, 55.3, 60.0, 113.9, 119.4, 121.5, 130.6, 140.6, 150.2, 159.9, 160.2; MS m/e (relative intensity) 331 (M^+ – HI, 2) 287 (16), 274 (67), 215 (56), 202 (100), 134 (14). Anal. Calcd for $C_{18}H_{26}IN_3O_3$: C, 47.06; H, 5.70; N, 9.15. Found: C, 46.86; H, 5.83; N, 8.83.

Benzyl 2-(4-methoxyphenyl)-4-[3-(methylamino)propyl]-imidazole-5-carboxylate tosylate (5c): yield 78%; mp 149–51 °C (EtOH); ^{1}H-NMR (DMSO-d_6) δ 2.11 (m, 2 H) CH_2, 2.38 (s, 3 H) Me, 2.74 (s, 3 H) NMe, 3.11 (m, 4 H) 2 CH_2, 3.98 (s, 3 H) OMe, 5.55 (s, 2 H) CH_2, 7.14–8.02 (m, 13 H) 2 C_6H_4, C_6H_5. Anal. Calcd for $C_{29}H_{33}N_3O_6S$: C, 63.14; H, 6.03; N, 7.62; S, 5.81. Found: C, 62.77; H, 6.25; N, 7.48; S, 5.86.

Ethyl 4-[3-(methylamino)propyl]-2-(thien-2-yl)-imidazole-5-carboxylate (5d): yield 76%; mp 177–8 °C (EtOH); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.31 (t, J = 6 Hz, 3 H) CH_3, 1.75 (quint, J = 7 Hz, 2 H) CH_2, 2.30 (s, 3 H) NCH_3, 2.50 (t, J = 7 Hz, 2 H) CH_2, 2.90 (t, J = 7 Hz, 2 H) CH_2, 4.25 (q, J = 6 Hz, 2 H) CH_2, 4.65 (br, 1 H) NH, 7.12 (dd, $J_{4'5'}$ = 6 Hz, $J_{3'4'}$ = 4 Hz, 1 H) 4'-H, 7.55 (dd, $J_{3'4'}$ = 4 Hz, $J_{3'5'}$ = 1 Hz, 1 H) 3'-H, 7.65 (dd, $J_{4'5'}$ = 6 Hz, $J_{3'5'}$ = 1 Hz, 1H) 5'-H; ^{13}C-NMR (DMSO-d_6) δ 14.3, 24.3, 28.6, 35.7, 50.9, 59.3, 124.4, 124.7, 126.6, 127.8, 133.8, 141.8, 144.4, 162.1; MS m/e (relative intensity) 293 (M^+ – HI, 11), 236 (99), 203 (49), 190 (100), 176 (21), 162 (47), 110 (48), 44 (62). Anal. Calcd for $C_{14}H_{19}N_2SO_2$: C, 57.34; H, 6.48; N, 14.34; S, 10.92. Found: C, 57.25; H, 6.65; N, 14.39; S, 10.88.

2-(4-Methoxyphenyl)-5-(4-nitrophenyl)-4-[3-(methylamino)propyl]imidazole hydroiodide/hydrochloride (5e): mp 157–8 °C; ^{1}H-NMR (DMSO-d_6) δ 2.05 (m, 4 H) 2 CH_2, 2.52 (s, 3 H) NMe, 3.05 (m, 2 H), CH_2, 4.02 (s, 3 H) OMe, 4.57 (br, 2 H) 2 NH, 7.14 (d, J = 8 Hz, 2 H) C_6H_4, 8.18 (m, 6 H) C_6H_4.

Methyl 2-(4-chlorophenyl)-4-[4-(ethylamino)butyl]-imidazole-5-carboxylate hydroiodide (5f): yield 61%; mp 217–9 °C (EtOH); ^{1}H-NMR (DMSO-d_6) δ 1.24 (t, J = 7 Hz, 3 H) Me, 1.62 (m, 4 H) 2 CH_2, 2.77 (m, 6 H) 3 CH_2, 3.79 (s, 3 H) OMe, 7.52 (d, J = 9 Hz, 2 H) C_6H_4, 7.91 (d, J = 9 Hz, 2 H) C_6H_4; MS m/e 335 (M^+, 16), 278 (10), 250 (100), 218 (58), 138 (46), 58 (96). Anal. Calcd for $C_{17}H_{23}ClIN_3O_2$: C, 44.03; H, 4.99; N, 9.06. Found: C, 44.15; H, 4.87; N, 9.05.

Methyl 2-(4-chlorophenyl)-4-[5-(methylamino)pentyl]-imidazole-5-carboxylate hydroiodide (5g): yield 63%; mp 158–60 °C (i-PrOH); ^{1}H-NMR (DMSO-d_6) δ 1.82 (m, 6 H) 3 CH_2, 2.75 (s, 3 H) NMe, 3.09 (m, 4 H) 2 CH_2, 4.02 (s, 3 H) OMe, 7.73 (d, J = 8 Hz, 2H) C_6H_4, 8.32 (d, J = 8 Hz, 2 H) C_6H_4; MS m/e 335 (M^+, 2), 233 (28), 139 (25), 114 (14), 44 (100). Anal. Calcd for $C_{17}H_{23}ClIN_3O_2$: C, 44.03; H, 4.99; N, 9.06. Found: C, 43.76; H, 5.04; N, 9.23.

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Registry No. **1a**, 126336-72-9; **1d**, 138434-96-5; **1f**, 134471-61-7; **1g**, 126336-74-1; **2a**, 459-73-4; **2b**, 13200-60-7; **2c**, 1738-68-7; **2e**, 7409-30-5; **2f**, 616-34-2; **5a**, 138434-90-9; **5b**, 138434-91-0; **5c**, 138434-93-2; **5d**, 138434-94-3; **5e**, 138434-95-4; **5f**, 134471-58-2; **5g**, 134471-59-3.

Direct Observation of Tautomeric Forms of Deuteroporphyrin Derivatives by ^{1}H NMR Spectroscopy: Substituent Effects and Structure Implications

Maxwell J. Crossley,* Margaret M. Harding, and Sever Sternhell

Department of Organic Chemistry, The University of Sydney, N.S.W. 2006, Australia

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A study of the position of tautomeric equilibrium in deuteroporphyrin IX methyl ester (**3**) and monosubstituted derivatives **4–7** using variable-temperature studies on the N,N-dideuteriated derivatives **8–12** is reported. The kinetic isotope effect on the prototropic exchange process is sufficiently large to allow the convenient observation of the individual tautomers by ^{1}H NMR spectroscopy. As in the case of 2-substituted 5,10,15,20-tetraphenylporphyrins **1**, the position of the tautomeric equilibrium in deuteroporphyrin derivatives is dependent on the substituent pattern on the porphyrin outer periphery. For the isomeric acetylporphyrins, 8-acetyldeuteroporphyrin IX dimethyl ester (**9**) and 3-acetyldeuteroporphyrin IX dimethyl ester (**10**), the acetyl group is the major influence in determining tautomer stability, i.e., both porphyrins are essentially one tautomer (>85% at 298 K) in which the acetyl group is not involved in the aromatic delocalization pathway. The more stable tautomer (59% at 298 K) of 3-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**11**) is that in which the hydroxyethyl substituent is directly substituted on the aromatic pathway. The vinylporphyrin (**12**) exists predominantly (56% at 298 K) as the tautomer in which the vinyl group is substituted on the β–β pyrrolic bond remote from the aromatic delocalization pathway. Conjugation of the vinyl group in **12** and the carbonyl group in the acetylporphyrins **9** and **10** with the β–β pyrrolic double bond probably contributes to the overall stability of the major tautomer of these porphyrins. This work serves to further emphasize that all nonsymmetric free-base porphyrins are necessarily a mixture of two tautomers of different energies which should be taken into account in interpreting the physical and chemical properties of these systems.

The fact that the symmetrically-substituted free-base porphyrin, 5,10,15,20-tetraphenylporphyrin, undergoes prototropic tautomerism between two equivalent forms (**1a** and **1b**, R = H) was shown by the ^{1}H NMR spectroscopy variable temperature studies of Storm and his co-workers.[1] The exchange process was conveniently observed and quantified in the temperature range 220–300 K, and the tautomerism was shown to involve a large kinetic isotope effect consistent with the coupled transfer of the two protons.[1,2]

This tautomeric process is a fundamental property of all free-base porphyrins. Indeed, all nonsymmetric free-base porphyrins are in fact a mixture of two tautomers whose populations depend on the substituents on the porphyrin outer periphery. In recent studies on 2-sub-

(1) (a) Storm, C. B.; Teklu, Y. *J. Am. Chem. Soc.* **1972**, *94*, 1745. (b) Storm, C. B.; Teklu, Y.; Sokoloski, E. A. *Ann. N.Y. Acad. Sci.* **1973**, *206*, 631.

(2) Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 1601.

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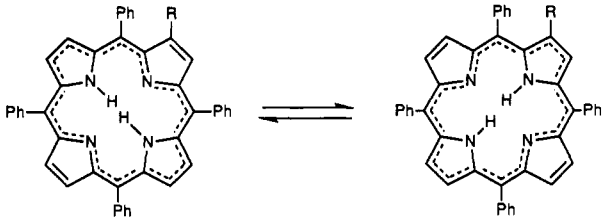
stituted 5,10,15,20-tetraphenylporphyrins, we have shown that the position of the tautomeric equilibrium is highly substituent dependent.[3,4] By appropriate substitution, the porphyrin may exist almost exclusively in one tautomeric form. For example, 2-nitro-5,10,15,20-tetraphenylporphyrin 1 (R = NO_2) exists more than 98% in form **1a**.[3] Hence, the electron distribution in the porphyrin is dramatically altered compared to 5,10,15,20-tetraphenylporphyrin 1 (R = H), and the structure of 1 (R = NO_2) may be regarded as containing essentially two localized β–β pyrrolic bonds and two aromatic β–β pyrrolic bonds. In the series 1, the influence of the substituents on the position of the tautomeric equilibrium is not straightforward, most probably as a result of a combination of steric and electronic effects.[3]



1a 1b

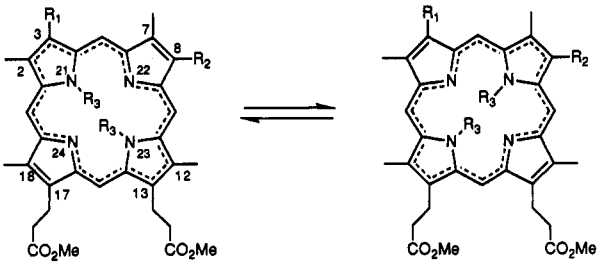
In contrast to the 2-substituted 5,10,15,20-tetraphenylporphyrins, there is comparatively limited data available on the effect of β-pyrrolic substituents on the position of the tautomeric equilibrium in other porphyrin systems and in particular in the naturally-occurring porphyrins and their derivatives and other per-β-substituted porphyrins. These porphyrins contain, in general, six to eight β-pyrrolic substituents and are unsubstituted in the *meso* positions and, thus, are sterically and electronically different from the 2-substituted *meso*-tetraarylporphyrins. The tautomeric process in *meso*-unsubstituted porphyrins is faster than in *meso*-tetraarylporphyrins, the exchange of the inner hydrogens still being fast at 200 K on the NMR timescale,[5] thereby precluding a direct measurement of the tautomer ratio by ^{1}H NMR.

In a 1973 paper on porphyrin tautomerism, Storm and his co-workers[1a] reported low-temperature 60-MHz ^{1}H NMR spectroscopic studies of N,N-dideuteriated deuteroporphyrin IX dimethyl ester which showed signals due to the two β-pyrrolic protons reaching a coalescence point at about 200 K. This observation suggests that the exchange process in related systems might similarly be accessible to study by ^{1}H NMR spectroscopy of the appropriate N,N-dideuteriated porphyrins; this would be a considerably easier approach than recent tautomeric studies by other groups which have focused on the study of specially synthesized ^{15}N-labeled porphyrins by NMR spectroscopy.[6,7]

We now report a study of the position of tautomeric equilibrium in deuteroporphyrin IX methyl ester (**3**) and monosubstituted derivatives **4–7** using variable-temperature studies on the N,N-dideuteriated derivatives **8–12**. The kinetic isotope effect on the prototropic exchange process is sufficiently large to allow the convenient observation of the individual tautomers of porphyrins **8–12** by ^{1}H NMR spectroscopy. As in the case of 2-substituted 5,10,15,20-tetraphenylporphyrins **1**, the position of the tautomeric equilibrium in deuteroporphyrin derivatives is dependent on the substituent pattern on the porphyrin outer periphery.

Results

The tautomeric equilibrium **2a** ⇄ **2b** for a range of deuteroporphyrin derivatives was investigated by variable-temperature NMR spectroscopy in an analogous way to that previously described for 2-substituted tetraphenylporphyrins **1**.[3,4] However, initial studies on **4**



2a **2b**

	R_1	R_2	R_3
3	H	H	H
4	H	$COCH_3$	H
5	$COCH_3$	H	H
6	$CH(OH)CH_3$	H	H
7	$CH=CH_2$	H	H
8	H	H	D
9	H	$COCH_3$	D
10	$COCH_3$	H	D
11	$CH(OH)CH_3$	H	D
12	$CH=CH_2$	H	D
13	$CH=CH_2$	$CH=CH_2$	H
14	$(CH_2)_2CO_2Me$	$(CH_2)_2CO_2Me$	H
15	$(CH_2)_2CO_2Me$	$COCH_3$	H

showed that, even at 175 K in CD_2Cl_2, the tautomeric exchange **4a** ⇄ **4b** was still rapid on the NMR scale and only exchange broadened spectra were observed. To overcome this problem, the inner hydrogens of all porphyrins studied in this work, **4–7**, were exchanged for deuterons thus making use of the large isotope effect in porphyrins ($k_{NH/ND}$ ca. 30).[2,5] Variable-temperature analysis of the N,N-dideuteriated derivatives **8–12** showed that the tautomeric equilibrium **2a** ⇄ **2b** was slow on the NMR time scale in the temperature range 200–220 K, and analysis of low temperature spectra of **8–12** showed distinct signals which were assigned to the two tautomeric forms of the porphyrin.

Integration of the β-pyrrolic and in some cases side-chain resonances allowed the relative tautomeric populations to be calculated (Table I, Figures 1 and 2). This method of determining relative populations is justified by the concordance of the results obtained by integration and by line-shape analysis in our previous studies.[3a,4] Extrapolation of the low-temperature equilibrium populations to higher temperature follows the expression $\Delta G = -RT \ln K = -RT \ln (P_1/P_2)$ derived from the van't Hoff equation; populations were extrapolated with temperature assuming ΔS to be negligible, an assumption that we found to be justified in earlier work by independently measuring populations by line-shape analysis and by extracting the activation parameters.[4]

In the case of *N,N*-dideuteriodeuteroporphyrin IX dimethyl ester (**8**), when the exchange **8a** ⇄ **8b** is slow on

(3) (a) Crossley, M. J.; Harding, M. M.; Sternhell, S. *J. Am. Chem. Soc.* **1986**, *108*, 3608. (b) Crossley, M. J.; Harding, M. M.; Sternhell, S. *J. Org. Chem.* **1988**, *53*, 113.

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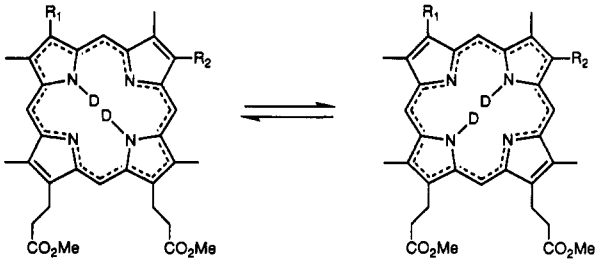
(5) Abraham, R. J.; Hawkes, G. E.; Hudson, M. F.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 2* **1975**, 204.

(6) Goldbeck, R. A.; Bo-Ragner, T.; Wee, A. G. H.; Shu, A. Y. L.; Records, R.; Bunnenberg, E.; Djerassi, C. *J. Am. Chem. Soc.* **1986**, *108*, 6449.

(7) Irving, C. S.; Lapidot, A. *J. Chem. Soc., Chem. Commun.* **1977**, 184.

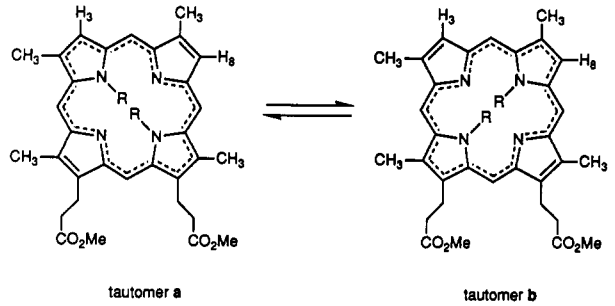
Table I. Relative Tautomeric Populations ± 5% of 2a and 2b in CD_2Cl_2 at 298 K



2a ⇌ 2b

	R_1	R_2	relative populations[a] 2a	2b
8	H	H	50	50
9	H	$COCH_3$	87	13
10	$COCH_3$	H	14	86
11	$CH(OH)CH_3$	H	59	41
12	$CH{=}CH_2$	H	44	56

[a] Determined by integration of low-temperature spectra; values extrapolated to 298 K by application of the van't Hoff equation—see text.



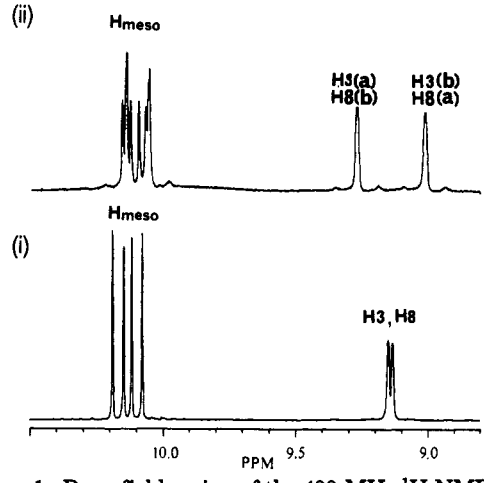


Figure 1. Downfield region of the 400-MHz ^1H NMR spectrum of deuteroporphyrin IX dimethyl ester in CD_2Cl_2: (i) R = H, **3**, 295 K; (ii) R = D, **8**, 225 K.

the NMR time scale, the NMR spectrum should contain, in principle, four β-pyrrolic resonances and eight meso resonances. The protons H3 and H8 in tautomer **8a** should give rise to two distinct singlets, and similarly, the corresponding protons in tautomer **8b** should give rise to two distinct singlets. Each tautomer contains four *meso* ring protons. Clear evidence for the presence of the two tautomers is apparent from analysis of the *meso*-proton region of the spectrum. The four *meso* resonances present at 298 K collapse to give eight overlapping resonances at low temperature, an observation which is entirely consistent

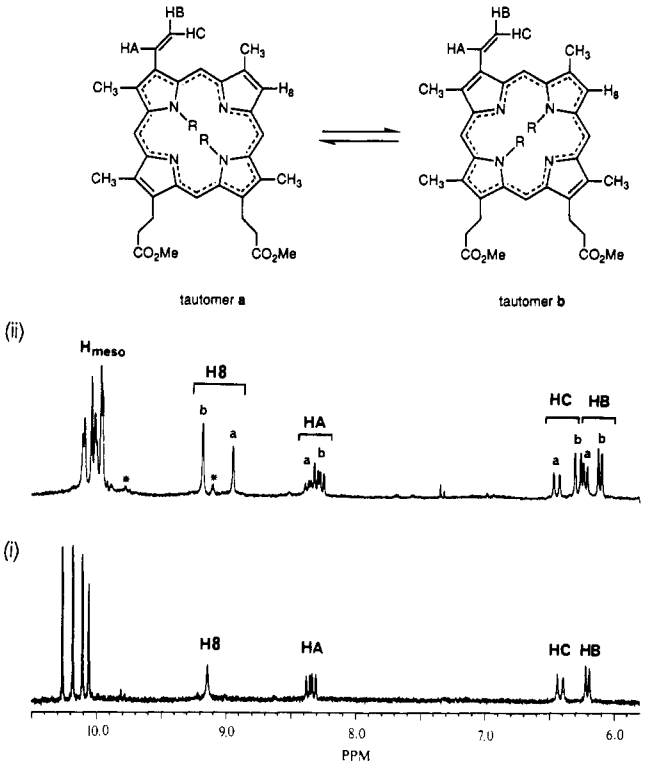


Figure 2. Downfield region of the 400-MHz ^1H NMR spectrum of 3-vinyldeuteroporphyrin IX dimethyl ester in CD_2Cl_2: (i) R = H, **7**, 295 K; (ii) R = D, **12**, 225 K; an asterisk (*) denotes peaks arising from minor impurity.

with the slow tautomeric exchange **8a** ⇄ **8b** on the NMR time scale. The observed signal intensities (Figure 1) can only be explained by the presence of two approximately equally populated tautomers. The β-pyrrolic region of the spectrum, in the temperature range 220–240 K, contained only two broadened signals which were assigned to two sets of overlapping singlets (Figure 1). The similar chemical shifts of H3(a)/H8(b) and H8(a)/H3(b) are a result of the very similar structures of the two tautomers (Figure 1).

For the other porphyrins studied, **9–12**, the tautomerism was conveniently monitored by the intensity of the resonance arising from the β-pyrrolic proton at the unsubstituted position, i.e., H8 for **10–12** and H3 for **9**. This resonance appeared as a singlet at room temperature and broadened to two singlets of unequal intensity at low temperature. Assignment of the major tautomer was on the basis of the chemical shift of the β-pyrrolic proton. For example, H8 in tautomer **2b**, being an aromatic-type proton, should resonate downfield of H8 in tautomer **2a**, which is essentially olefinic.[3] This method of assignment of the tautomers on the basis of chemical shift is justified by the large amount of chemical shift data obtained in the assignment of the tautomers of 2-substituted 5,10,15,20-tetraphenylporphyrins **1**. In that study, independent confirmation of the chemical shift assignments was possible by decoupling of the porphyrin N-H protons at low temperature.[3] For all 16 2-substituted porphyrins studied, the assignment of the two tautomers on the basis of the chemical shift of H3, the β-pyrrolic proton adjacent to the substituent, gave the same result as the decoupling experiments, i.e., resonances arising from β-protons substituted on the aromatic delocalization pathway resonate downfield of resonances arising from β-protons substituted on double bonds.

Supporting evidence for the assignments were obtained by the chemical shifts of side-chain resonances, e.g., the vinyl side-chain protons in **12** (Figure 2). As in the case

of the deuteroporphyrin 8, the *meso* region of the spectra of **9–12** at low temperature contained multiple signals which were assigned to eight overlapping singlets arising from the two tautomers **2a** and **2b**.

Discussion

The relative tautomeric populations of porphyrins **8–12** are summarized in Table I. The analysis of tautomer populations carried out in this work follows procedures previously published for the detailed analysis of the kinetics and thermodynamics of tautomerism in nonsymmetric 5,10,15,20-tetraphenylporphyrins.[3a,4]

In the case of deuteroporphyrin IX dimethyl ester (**8**), the ^{1}H NMR spectra are consistent with the presence of two tautomers of approximately equal energy. While integration of distinct β-pyrrolic signals assignable to each tautomer was not possible, the intensities of the eight overlapped *meso* resonances (Figure 1) are clear evidence the tautomers are present in approximately equal amounts. This is not unreasonable as the tautomers **8a** and **8b**, while nondegenerate, each have the same substituents, although in a different sequence, on their isolated β–β pyrrolic double bonds and the macrocyclic aromatic ring. Thus, to a first approximation, any substituent effects on the tautomeric equilibrium of **8** would be expected to stabilize each tautomer equally.

Introduction of an acetyl substituent in the β-pyrrolic position (porphyrins **9**, **10**) results in the relative population of the major tautomer as 94% at 220 K. Despite the fact that there are seven β-pyrrolic substituents, each of which will play a role in determining tautomer stability, the results show clearly that for the isomeric acetylporphyrins, 8-acetyldeuteroporphyrin IX dimethyl ester (**9**) and 3-acetyldeuteroporphyrin IX dimethyl ester (**10**), the acetyl group is the major influence in determining tautomer stability. For porphyrin **9**, the major tautomer has structure **9a**, while for the isomeric porphyrin **10**, the major tautomer is **10b**, i.e., both porphyrins exists predominantly as the tautomer in which the acetyl group is not involved in the aromatic delocalization pathway. Studies on the 3-vinylporphyrin (**12**) also indicated stabilization of the tautomer in which the vinyl group is substituted on the β–β pyrrolic bond remote from the aromatic delocalization pathway, **12b**, although the energy difference between the tautomers is less pronounced than in the case of the acetylporphyrins **9** and **10**. While several conformations of the vinyl side chain in tautomers **12a** and **12b** are possible, it is highly likely that the s-trans conformation shown for **12b** (Figure 2) is significantly populated. Conjugation of the vinyl group in **12b** and the carbonyl group in the acetylporphyrin tautomers **9a** and **10b** with the β–β pyrrolic double bond probably contributes to the overall stability of the major tautomer of these porphyrins. In contrast, the major tautomeric form of 3-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**11**) is **11a**, i.e., the more stable tautomer is that in which the hydroxyethyl substituent is directly substituted on the aromatic pathway.

Comparison of the results obtained in this study with the results obtained in similar porphyrins in the tetraphenylporphyrin series **1** (R = CHO, CH_2OH, $CH{=}CH_2$)[3] is informative. In the tetraphenylporphyrin system **1**, all electron-withdrawing groups stabilized tautomer **1a**, while alkyl substituents stabilized **1b**.[3] Thus, both the tautomer structure and stability of the acetylporphyrins **4** and **5** and the (hydroxyethyl)porphyrin **6** are exactly what one would have predicted from the results obtained for the 2-substituted 5,10,15,20-tetraphenylporphyrins **1**. In contrast, the vinyl group preferentially resides on the aromatic delocalization pathway in **1** (R = $CH{=}CH_2$),[3a] whereas in the present study, the more stable tautomeric form is **10a** in which the vinyl group is remote from the aromatic delocalization pathway. In both cases the energy differences between the tautomers are small. The observed difference in substituent effect of the vinyl group is readily explained in terms of steric interactions. In the case of 2-vinyl-5,10,15,20-tetraphenylporphyrin (**1**) (R = $CH{=}CH_2$), examination of molecular models show that there is appreciable steric interaction between the vinyl group and the *peri* phenyl ring when the vinyl group is held in the plane of the porphyrin ring. It is likely that this interaction causes the vinyl group to preferentially adopt an out-of-plane conformation, thereby lowering any stabilization arising through conjugation of the vinyl group with the β–β pyrrolic bond in **1a**.

The results of the present work suggest that in the case of deuteroporphyrins, conjugation between the β-pyrrolic substituent (acetyl, vinyl) and the β–β pyrrolic bond outside the aromatic delocalization pathway contributes to the overall stability of major tautomer. While it was not our intention in the present work to analyze how given substituents actually control the position of the tautomeric equilibrium, we have observed previously that several factors including the steric and electronic nature of the substituent, the basicity of the inner nitrogens, and the nature of the transition state and activation parameters for tautomerism are implicated.[3,4] Further studies on related porphyrins will help unravel the relative importance of each of these factors.[8]

The two reported NMR studies of tautomerism in related porphyrins both involved the use of ^{15}N-labeled porphyrins.[6,7] NMR studies on [$^{15}N_4$]protoporphyrin IX dimethyl ester (**13**) and [$^{15}N_4$]coproporphyrin III tetramethyl ester (**14**) did not report unequally populated tautomers.[7] This is not surprising as the two tautomers of each compound, while different, each have the same substituents on their isolated β–β pyrrolic double bonds and the macrocyclic aromatic ring. The result thus parallels the results obtained for deuteriated deuteroporphyrin IX dimethyl ester **8** in the present study.

Djerassi et al.[6] reported preliminary kinetic and thermodynamic data for tautomerism in a nonsymmetric monoacetylporphyrin derivative, porphyrin **15**, in which significant perturbation of the tautomeric equilibrium was observed. Assignment of the major tautomer (90% at 200 K) was based on magnetic circular dichroism (MCD) studies.[9] In the $^{15}N_4$-labeled acetylporphyrin **15**, the tautomeric equilibrium lies heavily in favor of tautomer **15a** which is stabilized by substitution of the acetyl group on the isolated double bond and the alkyl group on the aromatic delocalization pathway. This result is exactly what is predicted from the substituent effects observed in the present study. Furthermore, carrying out a ^{1}H NMR study on the N,N-dideuterated derivative of **15** would allow direct assignment of the tautomers and thus avoid the need to invoke MCD, which is not fully understood. While extensive MCD studies have been carried out on a range

(8) A reviewer has pointed out that the thermodynamic stability of 2-substituted 5,10,15,20-tetraphenylporphyrin correlates well with the pK_a's of 3-substituted pyridines, suggesting that relative basicity of the inner nitrogens may be the dominant factor in determining tautomer populations.

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of substituted porphyrins, interpretation of the data is not straightforward,[6,9] in particular the influence of N-H tautomerism on the side-chain conformation and thus the sign of the MCD.[6] Thus, at the present time, MCD cannot be considered a definitive technique for the assignment of tautomer structure in porphyrin systems.

The results of this work have considerable implications for the interpretation of physical and chemical properties of the naturally-occurring free-base porphyrins and derivatives. Even though the energy differences between tautomers are small, the disturbed electron distribution in the macrocycle must be taken into account when considering reactivity and the electron density at various positions on the porphyrin periphery. This is particularly the case when properties under thermodynamic control are considered. There are many physical and chemical properties of free-base porphyrins which probably should be reexamined in light of the present work which gives an insight into the thermodynamics and kinetics[4] of free-base porphyrins on the NMR time scale. A couple of examples suffice to illustrate this point.

Correlations have been noted to occur between the nature of side chains on porphyrins and the positions and intensities of their absorption bands.[10] It has been noted that a single carbonyl (aldehyde or ketone), a carboxylic acid, an ester, or an acrylic acid side chain modulates the visible spectrum of free-base naturally occurring porphyrins so that band III becomes more intense than band IV, the reverse of the normal situation (and that which occurs when the single substituent is a vinyl), affording a "rhodo-spectrum".[10] However, when two of these "rhodofying" groups are on adjacent pyrrolic rings the effect is cancelled out. It is of interest to note that the strongly electron-withdrawing groups, as distinct from the vinyl group, are also those substituents which our work suggests would strongly polarize the position of the tautomeric equilibrium in the system when there is one such substituent (or more when they are on the same or the antipodal pyrrolic rings) leading to a high proportion of one of the tautomers in the equilibrium mixture. This would give rise to a system which on a time-average is substantially a localized one of D_{2h} symmetry, thereby resulting in a very substantial difference in the relative contribution of the two tautomers and hence in the magnitudes of electric transition dipoles in the x and y directions. In contrast, when two such groups are in adjacent pyrrolic rings cancelling the effect of each other, or when there is a single vinyl substituent, approximately equal amounts of the two tautomers will exist in the equilibrium mixture, leading to a system which approximates D_{4h} symmetry on a time-average and in which the contribution of the two tautomers to the spectrum are much closer in magnitude. On this basis, it is not surprizing that there are considerable differences observed in the visible spectra of porphyrin systems with different substitution patterns.

Hambright and his colleagues have reported electrochemical studies of a range of per-β-substituted porphyrins and have proposed a range of substituent effects for calculation of reduction potentials.[11] They observed that for some substituents the effects appeared to be additive, while for others the combined effects were lower than might have been expected. This observation can now be explained by appreciation of the fact that substituents in the same or antipodal β-pyrrolic rings work in concert while those in adjacent β-pyrrolic rings do not.

Further study of related porphyrin systems will further clarify other substituent effects on the structure of the per-β-substituted porphyrins. The present study has been restricted to the synthetically accessible derivatives of deuteroporphyrin and confirms our general conclusions regarding tautomerism in nonsymmetric porphyrins. However, these results serve to emphasize the point that *all nonsymmetric free-base porphyrins exist in solution as a mixture of two distinct forms.* This fact that does not appear to have been widely appreciated; for example, it is not recognized in the recently published IUPAC recommendations on porphyrin nomenclature.[12] More importantly, our observations are pertinent to the interpretation of other physicochemical and purely chemical properties of the porphyrin system.

Experimental Section

NMR Spectra. Proton NMR spectra were recorded on Bruker WM and AMX 400-MHz spectrometers locked on solvent deuterium. Samples were prepared in dideuteriodichloromethane (Aldrich), which had been passed through a short plug of anhydrous K_2CO_3 to remove acidic impurities, as ca. 0.02 M solutions, and were degassed. Temperature was calibrated by the shift difference in methanol.[13] Deuteriated porphyrins were prepared by four successive equilibrations of a solution of the porphyrin in CD_2Cl_2 with D_2O. The solutions were dried over Na_2SO_4 prior to NMR spectroscopic analysis.

Porphyrins. 8-Acetyldeuteroporphyrin IX methyl ester (**4**), 3-acetyldeuteroporphyrin IX methyl ester (**5**), 3-(1-hydroxyethyl)deuteroporphyrin IX dimethyl ester (**6**), and 3-vinyldeuteroporphyrin IX dimethyl ester (**7**) were prepared by standard literature procedures.[14,15] NMR, **4**: δ −3.95 (bs, NH), 3.25, 3.28 (2 t, J = 7.65, 7.85 Hz, 2 × $CH_2CH_2CO_2CH_3$), 3.28, 3.53, 3.66 (3 s, 3 × CH_3), 3.64 (s, 2 × CO_2CH_3), 3.76, (d, J = 1.17 Hz, CH_3), 4.30, 4.41 (2 t, J = 7.51, 7.74 Hz, 2 × CH_2COCH_3), 9.16 (s, H3), 9.99, 10.10, 10.77 (3 s, H_{meso}). **5**: δ −4.11 (bs, NH), 3.14, 3.28 (2 t, J = 7.59, 7.83 Hz, 2 × $CH_2CH_2CO_2CH_3$), 3.26, 3.53, 3.79 (3 s, 3 × CH_3), 3.65 (s, 2 × CO_2CH_3), 3.72, (d, J = 1.16 Hz, CH_3), 4.28, 4.41 (2 t, J = 7.77, 7.78 Hz, 2 × CH_2COCH_3), 9.12 (s, H8), 9.97, 10.03, 10.71 (3 s, H_{meso}). **6**: δ −4.12 (bs, NH), 1.54 (bs, OH), 2.04 (d, J = 6.62 Hz, $CH(OH)CH_3$), 3.24 (m, 2 × $CH_2CH_2CO_2CH_3$), 3.47, 3.53, 3.55 (3 s, 3 × CH_3), 3.66, 3.70 (2 s, 2 × CO_2CH_3), 3.63, (d, J = 1.24 Hz, CH_3), 4.23 (dt, J = 2.57, 7.72 Hz, 2 × CH_2COCH_3), 6.14 (q, J = 6.62 Hz, $CH(OH)CH_3$), 9.07 (s, H8), 9.90, 9.95, 9.97, 10.02 (4 s, H_{meso}). **7**: δ −3.91 (bs, NH), 3.31 (2 t, J = 7.81 Hz, 2 × $CH_2CH_2CO_2CH_3$), 3.59, 3.65, 3.66, 3.72 (4 s, 4 × CH_3), 3.74, (d, J = 1.24 Hz, CH_3), 8.32, 6.20, 6.41 (AMX system, J_{AM} = 11.5, J_{AX} = 17.8, J_{MX} = 1.6 Hz, CH=CH_2), 4.23 (2 t, J = 7.42 Hz, 2 × CH_2COCH_3), 9.13 (s Hβ), 10.04, 10.15, 10.09, 10.04 (4 s, H_{meso}).

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