Variable-Temperature Solid-State ^{15}N Cross-Polarization Magic-Angle Spinning Nuclear Magnetic Resonance Analysis of Octamethylporphyrin

Claudio O. Fernandez,[‡] Marcelo Kogan,[‡]
Aldonia Valasinas,[†] and Benjamin Frydman*[,†]

S'LIL Pharmaceuticals, LLC, 535 Science Drive, Suite C, Madison, Wisconsin 53711-1066, and Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Buenos Aires, Argentina

Received February 9, 1998

Free-base porphyrins possess two central hydrogens that may bind to any of the four inner nitrogens in the molecule. Exchange among the different possible arrangements results in a tautomeric process (Figure 1) that has been extensively studied by variable-temperature solution[1−8] and solid-state[9−14] NMR. The latter analysis showed that crystal packing forces may disturb the equilibrium constant of the tautomerism, yielding exchange processes between nondegenerate states even in the case of symmetrically substituted molecules. It was possible to understand the difference between the solution, where exchange in symmetrically substituted porphyrins takes place between two equally populated isomers, and the solid-state behavior of N−H tautomerism in terms of intermolecular packing interactions which may stabilize one tautomeric isomer of an exchanging porphyrin with respect to the other isomer. The presence of two unequal populations of porphyrin tautomers in the solid state is of interest for performing data storage in the frequency domain (FDOS) by means of photochemical hole burning (PHB).[15] The alkyl-substituted porphyrins possess the smallest electron−phonon coupling strength among organic dyes and pigments and allow the creation of the most deep and narrow spectral holes.[16] Octamethylporphyrin **1** possesses the steric and electronic requirements necessary for hole burning; its use has not been explored however, probably due to the lack of a simple and clean synthetic procedure. Recently, a facile synthesis of **1** and of its $^{15}N_4$-enriched isomer has been developed[17] and made possible an analysis in the solid state of the **1a** ⇌ **1b** tautomeric equilibrium (Figure 1).

The analysis of NH tautomerism using solid-state ^{13}C CPMAS NMR spectra of a β-octasubstituted porphyrin such as octamethylporphyrin **1** is more cumbersome than of a meso- or β-tetrasubstituted porphyrin. In the solid state, phase assignments of ^{13}C chemical shifts can be assisted either by the pulse sequence devised by Opella and Frey,[18] where resonances from quaternary or methyl carbons are identified by introducing short delays (ca. 50 μs) prior to the acquisition, or by using short contact times (ca. 50 μs). In the former case, only signals with strong dipolar couplings to protons decay; in the latter case, only carbons with strong dipolar couplings to protons (short T_{CH}) are allowed to cross-polarize (CH and CH_2). In a β-octasubstituted porphyrin there are no nuclear CH residues except in the meso bridges; therefore its ^{13}C CPMAS spectra are more difficult to analyze due to the severe peak overlaps in the pyrrole carbon region. An exhaustive ^{13}C CPMAS NMR analysis carried out on solid octaethylporphyrin[11] led us to propose that its N−H tautomerism was not quenched at room temperature (as proposed in an earlier study[19]), and although the absence of β-hydrogens precluded a simplification of the pyrrole carbon region of the CPMAS spectra, the N−H exchange could be partially analyzed in the range from slow to fast exchange. We report below on the ^{15}N CPMAS NMR analysis of octamethylporphyrin **1**.

Results and Discussion

The ^{15}N CPMAS spectrum of **1** at variable temperature is shown in Figure 2. At 293 K the peak at 206.3 ppm was assigned to the pyrrolenine nitrogens (=N−) while the peak at 118.1 ppm was assigned to the pyrrole nitrogens (−NH−), following the criteria that we used for the assignments of the ^{13}C chemical shifts of the carbons in the pyrrole and pyrrolenine rings of porphyrins.[11] The presence of two nitrogen peaks in the solid-state spectrum of **1** could be attributed either to a quenching of the N−H tautomerism process shown in Figure 1, where the exchange takes place between two equally populated tautomers but at a slower rate than the NMR time scale, or to a fast tautomeric process in the solid, where asymmetric packing forces led to the presence of two unequally populated tautomers.[9,11] A variable-temperature ^{15}N CPMAS NMR analysis performed on isotopically enriched *meso*-tetraphenylporphyrin and *meso*-tetratolylporphyrin[9] revealed that in the former tautomerism was influenced by the crystalline packing forces, while in the latter the effect of crystal packing forces on the tautomeric behavior of the porphy-

---

* Corresponding author: Dr. Benjamin Frydman. Phone: 608-231-3854. Fax: 608-231-3892. E-mail: bjf@mail.slil.wisc.edu.

[†] S'LIL Pharmaceuticals.

[‡] Universidad de Buenos Aires.

[1] Storm, C. B.; Teklu, Y. *J. Am. Chem. Soc.* **1972**, *94*, 1745.

[2] Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 3637.

[3] Abraham, R. J.; Hawkes, G.; Smith, K. M. *Tetrahedron Lett.* **1974**, *16*, 1483.

[4] Hennig, J.; Limbach, H. H. *J. Am. Chem. Soc.* **1984**, *106*, 292.

[5] Gust, D.; Roberts, J. D. *J. Am. Chem. Soc.*, **1977**, *99*, 3637.

[6] Yeh, H. J.; Sato, M.; Morishima, I. *J. Magn. Res.* **1977**, *26*, 365.

[7] (a) Stilbs, P.; Moseley, M. E. *J. Chem. Soc., Faraday Trans. 2* **1980**, *76*, 729. (b) Stilbs, P. *J. Magn. Reson.* **1984**, *58*, 152.

[8] (a) Crossley, M. J.; Harding, M. M.; Sternhell, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 3608. (b) Crossley, M. J.; Field, L. D.; Harding, M. M.; Sternhell, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2335.

[9] Limbach, H. H.; Hennig, J.; Kendrick, R.; Yannoni, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 4059.

[10] Frydman, L.; Olivieri, A. C.; Diaz, L. E.; Frydman, B.; Morin, F. G.; Mayne, C. L.; Grant, D. M.; Adler, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 336.

[11] Frydman, L.; Olivieri, A. C.; Diaz, L. E.; Valasinas, A.; Frydman, B. *J. Am. Chem. Soc.* **1988**, *110*, 5856.

[12] Frydman, L.; Olivieri, A. C.; Diaz, L. E.; Frydman, B.; Kustanovich, I.; Vega, S. *J. Am. Chem. Soc.* **1989**, *111*, 7001.

[13] Frydman, L.; Rossomando, P. C.; Sambrotta, L.; Frydman, B. *J. Phys. Chem.* **1992**, *96*, 4753.

[14] Braun, J.; Schwesinger, R.; Williams, P. G.; Morimoto, H.; Wemmer, D. E.; Limbach, H. H. *J. Am. Chem. Soc.* **1996**, *118*, 11101.

[15] Renge, I.; Wolleb, H.; Spahni, H.; Wild, U. P. *J. Phys. Chem.* **1997**, *101*, 6202 and references therein.

[16] Renge, I. *J. Opt. Soc. Am. B* **1992**, *9*, 719.

[17] Kogan, M.; Valasinas, A. *J. Labeled Compd. Radiopharm.* **1994**, *34*, 943.

[18] Opella, S. J.; Frey, M. H. *J. Am. Chem. Soc.* **1979**, *101*, 5855.

[19] Okazaki, M.; McDowell, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 3185.

[20] Wehrle, B.; Limbach, H. H.; Köcher, M.; Ermer, O.; Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 934.

S0022-3263(98)00231-X CCC: $15.00

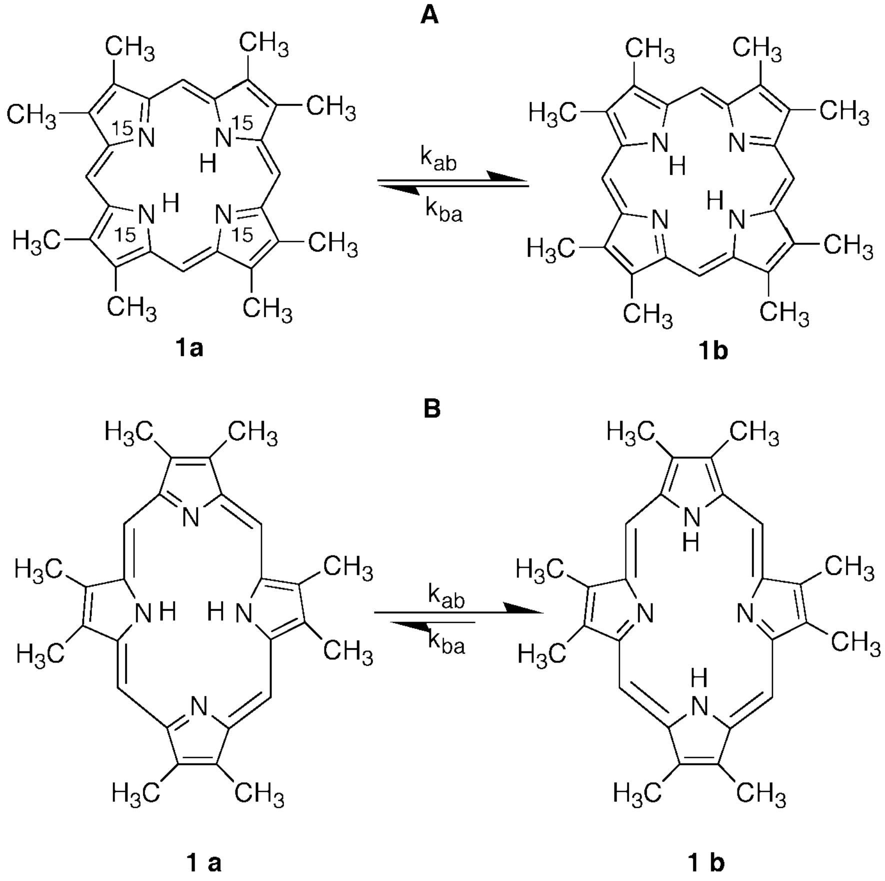

Figure 1. N−H tautomerism in [$^{15}N_4$]octamethylporphyrin **1**. (A) The hydrogens are localized in opposite pyrrole rings and tautomerism proceeds without distortion of the porphyrin ring. (B) Tautomerism proceeds with distortion of the porphyrin ring, and crystal packing forces stabilize one tautomeric isomer with respect to the other, inducing an exchange process between nondegenerate states. Note that the molecular distortions were exaggerated to help visualize the net effect of crystal packing forces.

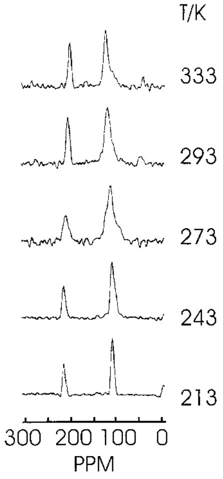

Figure 2. Experimental ^{15}N CPMAS NMR spectra of [$^{15}N_4$]octamethylporphyrin **1** recorded at 30.42 MHz and variable temperatures. Spectral parameters were as given in the Experimental Section.

rin, if present, was very small. This was also the case of porphine, where both ^{15}N CPMAS NMR[20] and ^{13}C CP-MAS NMR[12] variable-temperature analyses revealed that a solution-type tautomerism also takes place in the solid; i.e., in the ^{15}N CPMAS spectrum both ^{15}N peaks coalesce into a single peak on heating, and the same happened with the double ^{13}C peaks of the ^{13}C CPMAS spectrum.

To decide which explanation better fits the experimental data shown in Figure 2 at 293 K, a variable-temperature analysis was carried out. It was evident that across the temperature range used, the two resonances are in the slow exchange limit. As temperature increased the lines broadened, moved toward each other, and then narrowed again. This variable-temperature display (shown in Figure 2) does not support the presence in the solid of a quenching of N−H tautomerism, with lines coalescing in a single peak. Rather, the spectra suggest the existence of crystal packing forces that affect the migration of the central protons. This model has already been discussed by us[11] and by others[9] for several alkyl-substituted porphyrins. The model proposes that the observed dynamic process reflects an overlapping of two exchange processes among two unequally populated sites. Each site possesses its own transverse relaxation time, its own equilibrium magnetization value M_o, and its own Larmor frequency, and both sites share the same exchange constants k_{ab} and k_{ba}. For the purpose of spectra simulation, there is no need to measure the two independent kinetic constants; it suffices to state the problem in terms of an independent kinetic constant which is the equilibrium constant of the process $K = k_{ab}/k_{ba}$ (see Figure 1). Thus, a difference Δ can be measured between the chemical shifts of the pyrrolenine (δ_1) and the pyrrole (δ_2) nitrogens:

$$\Delta = \delta_1 - \delta_2 = \Delta_o(1 - K)/(1 + K) \qquad (1)$$

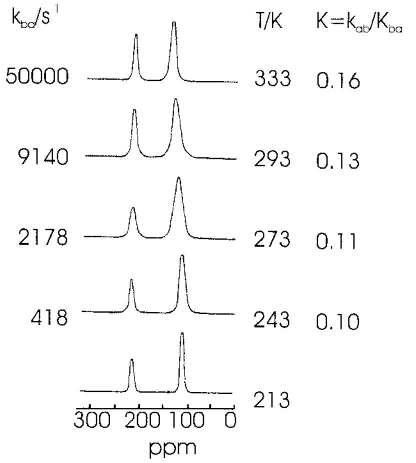

Figure 3. Calculated 30.42 MHz ^{15}N CPMAS NMR spectra of [$^{15}N_4$]octamethylporphyrin **1** at variable temperatures. Parameters used in the simulations are given in the figure.

where $\Delta_o = \delta_{=N-} - \delta_{-NH}$ is the difference in the chemical shifts in the absence of exchange. Equation 1 allowed the determination of the equilibrium constant K for the spectra at higher temperatures. The values of K could then be extrapolated to the slower exchange region assuming that K has an exponential temperature dependence: $K = A\ \exp(-E/RT)$. The process shown in Figure 1 can therefore be analyzed by the variation of only the rate constant k_{ab}. The simulated spectra corresponding to the data obtained from the ^{15}N CPMAS NMR of **1** at variable temperature are shown in Figure 3 together with the parameters used for the simulations. The good fit between the experimental data and the simulations lends support to the suggestion that in the solid the tautomeric equilibrium in **1** is affected by crystal packing forces, as was the case with octaethylporphyrin.[11] These forces break the degeneracy observed in the solution spectra and result in the presence in the crystal of two unequally populated tautomers.

As suggested by our previous work,[10,11] these forces may operate by two different mechanisms depending on whether the hydrogen migration is coupled to a skeletal rearrangement. If it is assumed that tautomerism may proceed without a skeletal rearrangement (as in Figure 1A), the perturbations of the solid-state reaction will depend on the static configuration that crystal packing forces induce on the porphyrin molecules. If, however, tautomerism requires a skeletal rearrangement,[21] then the crystal packing forces will perturb the reaction by precluding the rearrangement, thereby favoring the presence of one tautomer over the other (as outlined in Figure 1B). It was possible to measure rate constants for the migration of the central hydrogens and to obtain the energetic parameters involved in the solid-phase reaction (Table 1). This energy profile of the hydrogen transfer in solid porphyrins[9,20] should be considered as the sum of a solution contribution (a symmetrical double minimum potential) plus the contribution of the packing energy at each point of the reaction coordinate. Whether this migration is coupled to a reorientation of the macrocycle as is the case in porphine[13] has yet to be determined.

Table 1. Relevant Parameters for the N−H Tautomerism of Octamethylporphyrin 1 in the Solid Phase

parameter	1
ΔH (kcal/mol)[a]	1.5 ± 0.1
ΔS (eu)[a]	0 ± 1
E_a (kcal/mol)[b]	9.1 ± 1.0

[a] From the equation $K = k_{ab}/k_{ba} = e^{\Delta S/R}\ e^{-\Delta H/RT}$. [b] From the equation $k_{ab} = A\ \exp(-E_a/RT)$.

Conclusion

The N−H tautomerism of [$^{15}N_4$]octamethylporphyrin **1** was studied by high-resolution ^{15}N CPMAS NMR in the solid state. Spectra were recorded at different temperatures and indicated that the N−H tautomerization process was not quenched at room temperature. The N−H exchange could be analyzed in the range from slow to fast exchange, and it was shown that in the solid crystal packing forces lead to the presence of two unequally populated tautomers.

Experimental Section

Synthesis of [$^{15}N_4$]octamethylporphyrin **1** was carried out as described elsewhere.[17] ^{15}N CPMAS NMR spectra were obtained at 30.42 MHz over 4000 scans, pulse interval of 3 s, contact time of 10 ms, rotor speed of 2.5 kHz, spectral width of 25 000 Hz, Fourier number equal to 4096. The spectra were recorded on a Bruker MSL-300 spectrometer equipped for variable-temperature work. Rotors used were of 4 mm. Simulation of spectra was carried out using an Exchange program designed for calculation of chemical exchange between four isotropic resonances affected by two simultaneous reactions as present in a system of two unequally populated tautomers.

Acknowledgment. This research was supported in part by the Consejo Nacional de Investigaciones Cientificas y Tecnicas (Argentina).

JO980231C

---

(21) Sarai, A. *Chem. Phys. Lett.* **1981**, *83*, 50; *J. Chem. Phys.* **1982**, *76*, 5554; **1984**, *80*, 5341.