

Preparation of trans-octaethylchlorin-d₂(α,β), -d₂(γ,δ), and -d₄ as well as octaethylporphyrin-d₂ using acid-catalyzed exchange reaction

Asaad Salehi, Harold N. Fonda, Anthony W. Oertling, Gerald T. Babcock* and Chi K. Chang*

Department of Chemistry
Michigan State University
East Lansing, Michigan 48824-1322

SUMMARY

Preparation of three forms of selectively deuterated trans-octaethylchlorin (t-OEC) and octaethylporphyrin-d₂ (OEP-d₂) with high isotopic purity using acid catalyzed hydrogen-deuterium exchange reaction is described. Deuterated t-OEC labeled at γ,δ -methine carbons was prepared directly by equilibrating t-OEC in D₂SO₄:D₂O (6:1, v/v) at room temperature for 20 hours. t-OEC labeled at all four methine carbons was prepared as above in 72 hours. And t-OEC labeled at α,β -positions was obtained by "back-exchange" of t-OEC-d₄ under the protio condition, H₂SO₄:H₂O (6:1, v/v), in 18 hours. The DDQ dehydrogenation of either dideuteriochlorin species resulted in the formation of OEP-d₂. The isotopic purities of all deuterated compounds were over 98 percent except for t-OEC-d₂(α,β) which was estimated to be ~ 90 percent by proton NMR spectroscopy.

Key words: trans-octaethylchlorin; octaethylporphyrin; $\alpha,\beta,\gamma,\delta$ -methine carbons; deuterium labeling; sulfuric acid-d₂; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

INTRODUCTION

Deuteration of the methine (meso) bridges of tetrapyrrolic macrocycles has contributed to a better understanding of the hemoproteins' electronic and vibrational characteristics by utilizing methods such as ESR(1,2), ENDDOR (3,4), NMR (5,6), IR(7,8) and resonance Raman (9,10) spectroscopy. The relative reactivities of the four methine carbons for hydrogen-deuterium (H/D) exchange result primarily from the ease of electrophilic substitution at these sites which, in turn, depends upon the nature of the substituents on the adjacent pyrrole rings (11,12,13). For example, it has been shown that trans-octaethylchlorin (t-OEC) undergoes facile H/D exchange at γ,δ -meso carbons in refluxing acetic acid-d₁; whereas, α,β -bridges are not affected (14). The exchange reactions, carried out on metal free systems,

are generally acid-catalyzed and a number of acidic media have been reported, including D_2SO_4 - D_2O (11), toluenesulfonic acid- d_1 (15), TFA- d_1 (12), and acetic acid- d_1 (16). The D_2SO_4 - D_2O method represents a strong acidic condition which is routinely used to induce H/D exchange reaction at all four methine carbons in symmetrically substituted ring systems (12). In one instance, however, it has been applied to the oxoporphyrin complexes in which deuteration occurs predominantly at two bridging carbons and the other two sites undergo minimal exchange (17). The D_2SO_4 - D_2O method is usually carried out at ambient temperature in contrast with the refluxing and/or anaerobic condition required by other methods.

We report here a modification of the original D_2SO_4 - D_2O reaction condition (11) which may be used for the preparation of three forms of selectively deuterated trans-octaethylchlorin(t -OEC- $d_2(\alpha,\beta)$ -, $d_2(\gamma,\delta)$ -, and $-d_4$), Figure 1a. The dideuterated chlorin species may then be oxidized to the corresponding octaethylporphyrin- d_2 , Figure 1b, which would otherwise be difficult to prepare and may reveal interesting spectroscopic properties.

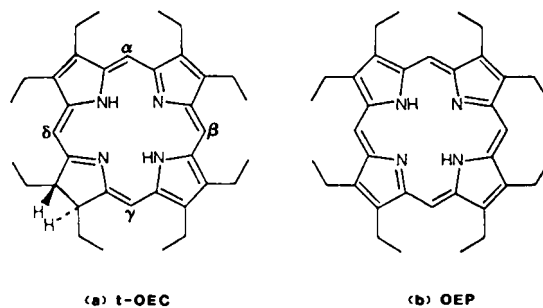


Figure 1: Chemical Structures.

EXPERIMENTAL

OEP and t -OEC were synthesized according to the published methods (18, 19). Proton NMR spectra were obtained at 250 MHz on a Bruker spectrometer in deuterated chloroform with the solvent signal as an internal standard. Chloroform- d_1 (99.8 atom percent D), D_2O (99.8 atom percent D) and 98 percent sulfuric acid- d_2 in D_2O (99.5 atom percent D) were obtained from Aldrich Chemical Co. Dichloromethane was freshly distilled from CaH_2 . All other solvents were reagent grade and were used without further purification. The extent of deuteration was estimated by integration of the proton NMR spectra. Column chromatography was performed on Alcoa basic alumina (type F-20).

trans-octaethylchlorin-d₂(γ,δ)

In a typical experiment, 10 mg of t-OEC was equilibrated in 2.1 ml of D₂SO₄:D₂O (6:1,v/v) and allowed to sit at room temperature in a desiccator for 20 hours. The solution was then quenched with ice water and extracted with dichloromethane. The extract was washed with sodium bicarbonate and with water and dried over anhydrous sodium sulfate. At this point, the sample may contain about 2-3 percent OEP which results from oxidation of t-OEC. This was demonstrated by t.l.c. and by proton NMR spectrum (OEP meso-proton peak at δ 10.2). Purification was carried out on alumina with benzene as eluant. Quantitative deuteration was established by the disappearance of the γ,δ - proton signal at 8.9 ppm, Figure 2c. MS: m/e 538(M⁺), 509(M⁺-29), 269(M⁺⁺); m.p. 231-232°C.

trans-octaethylchlorin-d₄

The tetradeuterated species was prepared by the same method as described above; however, the sample was permitted to sit at room temperature for ~ 72 hours. One hundred percent deuteration was established by the disappearance of proton NMR signals at 8.9 and 9.7 ppm due to γ,δ - and α,β - protons, respectively, Figure 2d.

trans-octaethylchlorin-d₂(α,β)

t-OEC-d₄ (10 mg) was subject to "back-exchange" in 2.1 ml of H₂SO₄(96.4 percent):H₂O(6:1, v/v) followed by the same work-up as mentioned above. This method gave ~ 90 percent deuteration at α,β - position and complete proton recovery at the γ,δ - sites, Figure 2b.

octaethylporphyrin-d₂

To a refluxing dichloromethane solution of dideuterochlorin was added a solution of DDQ (excess) in benzene according to the published methods (20,21). The green color of the chlorin solution turned red almost instantaneously. After refluxing for an additional 0.5 h, the solution was evaporated to dryness and chromatographed on alumina with chloroform. The visible absorption spectrum and the proton NMR signal at δ 10.2 showed the characteristic OEP spectrum. MS: m/e 536(M⁺), 507(M⁺-29), and 268(M⁺⁺); m.p. 322-324°C.

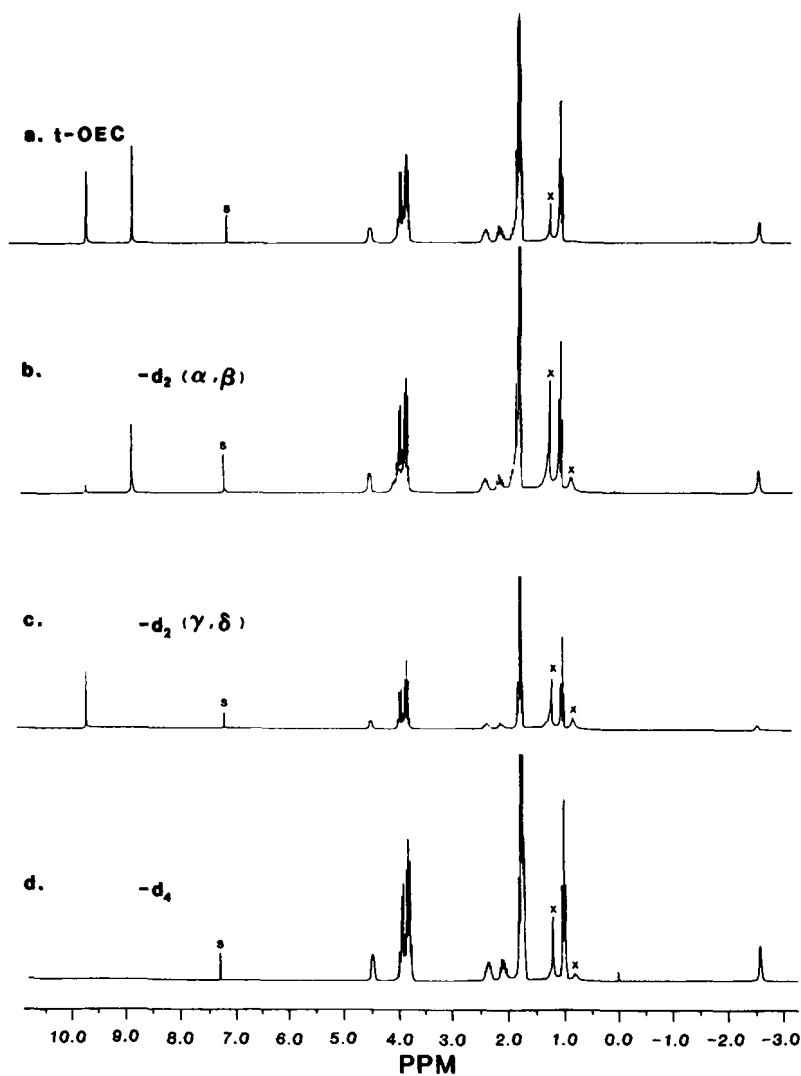


Figure 2: 250-MHZ proton NMR spectra of t-OEC and its deuterium labeled derivatives in CDCl_3 . S indicates residual undeuterated solvent and X represents other impurities.

CONCLUSION

The original procedure reported for the tetradeuteration of OEP (80 mg in $\text{D}_2\text{SO}_4:\text{D}_2\text{O}$, 2 ml; 9:1, w/v) has been modified to prepare three forms of selectively deuterated trans-octaethylchlorin; namely, $-\text{d}_2(\alpha,\beta)$, $-\text{d}_2(\gamma,\delta)$, and $-\text{d}_4$ derivatives. This method offers an alternative approach to that of acetic acid- d_1 for H/D exchange at ambient temperature in unsymmetrically substituted tetrapyrrolic macrocycles. It is also particularly attractive for

deuterium labeling in systems where prolonged refluxing conditions are not desirable. The partially-deuterated porphyrin and chlorin complexes are currently being utilized to verify the proposed "quadrant-localized" vibrational modes in the chlorin macrocycles²², by means of IR and resonance Raman spectroscopy.

REFERENCES

1. Fajer, J., Borg, D.C., Forman, A., Dolphin, D. - *J. Am. Chem. Soc.*, **42**: 3451 (1970).
2. Mengersen, C., Subramanian, J., Fuhrhop, J.W., Smith, K. M. - *Z. Naturforsch.*, **29a**: 1827 (1974).
3. Norris, J. R., Scheer, H., Druyan, M.E., Katz, J.J. - *Natl. Acad. Sci. USA*, **71**: 4897 (1974).
4. Feher, G., Hoff, A.J., Isaacson, R.A., Ackerson, L.C. - *Ann. N. Y. Acad. Sci.*, **244**: 239 (1975).
5. Morishima, I., Takamuki, Y., Shiro, Y. - *J. Am. Chem. Soc.*, **106**: 7666 (1984).
6. Godziela, G.M., Goff, H.M. *J. Am. Chem. Soc.*, **108**: 2237 (1986).
7. Urban, M. W., Nakamoto, K., Kincaid, J. - *Inorg. Chim. Acta*, **61**: 77 (1982).
8. Kincaid, J. R., Urban, M. W., Watanabe, T., Nakamoto, K. - *J. Phys. Chem.* **87**: 3096 (1983).
9. Ozaki, Y., Kitagawa, T., Ogoshi, H. - *Inorg. Chem.*, **18**: 1772 (1979).
10. Andersson, L. A., Sotiriou, C., Chang, C. K., Loehr, T. M. - *J. Am. Chem. Soc.*, **109**: 258 (1987).
11. Bonnett, R., Stephenson, G.F. - *Proc. Chem. Soc.*, 291 (1964).
12. Bonnett, R.; Gale, I. A. D., Stephenson, G. F. - *J. Chem. Soc. (c)*, 1168 (1967).
13. Smith, K. M., Langry, K. C., deRopp, J. S. - *J. Chem. Soc. Chem. Comm.*, 1001 (1979).
14. Cavaleiro, J. A. S., Smith, K. M. - *J. Chem. Soc., Perkin Trans. 1*, 2149 (1973).
15. Hickman, D.L., Goff, H.M. - *J. Am. Chem. Soc.*, **106**: 5013 (1984).
16. Woodward, R. B., Skaric, V. - *J. Am. Chem. Soc.*, **83**: 4676 (1961).
17. Stolzenberg, A. M., Laliberte, M. A. - *J. Org. Chem.*, **52**: 1022 (1987).
18. Wang, C. B., Chang, C. K. - *Synthesis*, 548 (1979).
19. Whitlock, Jr., H. W., Hanauer, R., Oester, M. Y., Bower, B. K. - *J. Am. Chem. Soc.*, **91**: 7485 (1969).
20. Eisner, V., Linstead, R. P. - *J.*, 3749 (1955).
21. Barnett, G. H., Hudson, M. F., Smith, K. M. - *Tet. Lett.*, 2887 (1973).
22. Boldt, N. J., Donohoe, R. J., Birge, R. R., Bocian, D. - *J. Am. Chem. Soc.*, **109**: 2284 (1987).