

Research Article

An improvement to the synthesis of deuterated meso-tetraphenylporphyrins

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Summary

An improved method for the synthesis of deuterated tetraphenylporphyrins (TPPs) is reported. In this method, deuterium labelling at the pyrrole- β -position is increased to more than 95 at%. TPP is the most widely used synthetic porphyrin and high deuterium incorporation is essential for spectroscopic studies and kinetic studies involving relaxation processes. Copyright © 2006 John Wiley & Sons, Ltd.

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Introduction

Porphyrins play essential roles in nature, especially as an active site in hemoproteins such as haemoglobin and cytochrome c.¹ meso-Tetraphenylporphyrin (TPP) is the most popular synthetic porphyrin and its metal-complexes have been used widely not only as model compounds but also interesting materials due to their characteristic properties. Thus, the structures, redox behaviours and photo-physical properties of free base TPP (TPPH₂) and its metal complexes extensively have been studied using various techniques.

Generally partial and/or full deuteration of compounds is a very powerful and indispensable technique not only in molecular spectroscopy but also in

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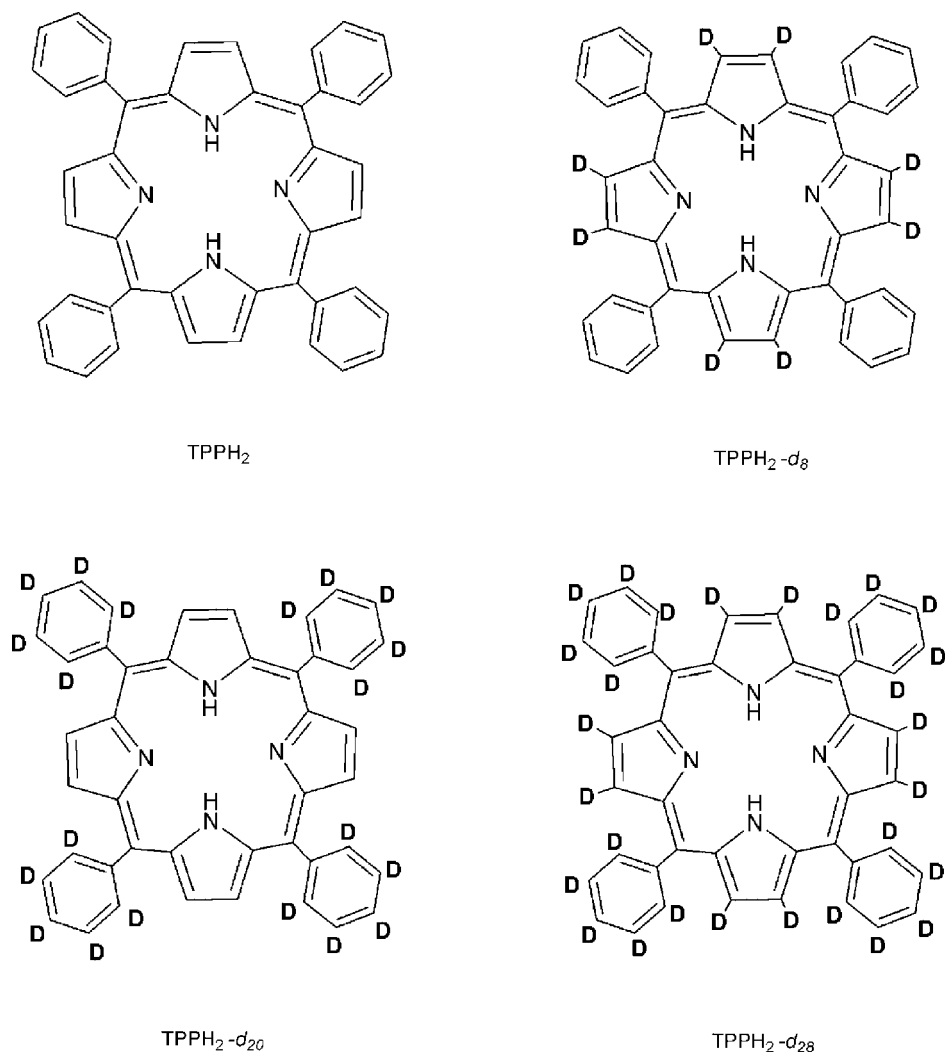


Figure 1. Molecular structure of normal TPP and its deuterated derivatives

reaction and relaxation dynamics. In the case of TPP, three deuterated derivatives are well known as shown in Figure 1. Deuterium labelling of phenyl groups can be achieved with nearly 100% incorporation² but deuterium labelling at the pyrrole- β -position has been reported to be, at most 90%.³ The practical values of '85–90%' deuterium incorporation are sometimes not good enough for studying deuterium isotope effects. In particular, the remaining protons disturb accurate measurements such as electron paramagnetic resonance (EPR) relaxation times due to large nuclear magnetic moments. Here, we present an improved method for the synthesis of pyrrole-deuterated and fully deuterated TPPs. In this method, deuterium incorporation for pyrrole hydrogens in d_8 and d_{28} derivatives of greater than

95 at% is achieved, which is sufficiently high for most of spectroscopic measurements.

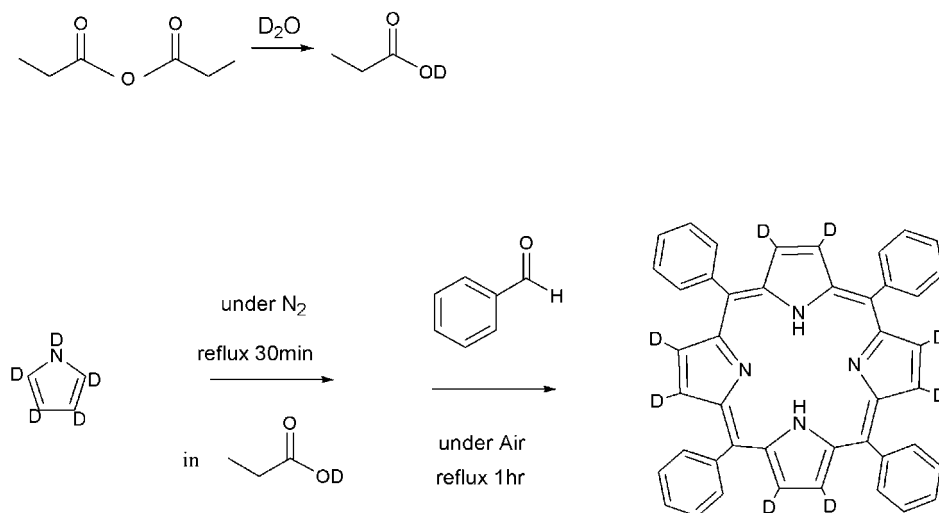
Results and discussion

There are two general methods for the synthesis of normal tetraphenylporphyrin: one is by Adler *et al.*⁴ and the other is by Lindsey *et al.*^{5,6} While the Lindsey's method gives much higher yield and allows the synthesis of various derivatives such as tetramesitylporphyrin,⁷⁻⁹ Adler's method is more convenient for the case of TPP. Phenyl-deuteration of TPP has been established principally by using benzaldehyde-*d*₅ or benzaldehyde-*d*₆ instead of unlabelled benzaldehyde,² as in Adler's method. On the other hand, pyrrole deuteration cannot be achieved simply by replacing normal pyrrole with deuterated pyrrole in the above method.³ During reflux in propionic acid, β -hydrogen atoms of pyrrole can be exchanged with the acidic hydrogen of propionic acid. Shirazi and Goff reported a convenient method for synthesis of pyrrole-deuterated TPP with 90 at% deuterium incorporation.³ They prepared deuterated pyrrole in propionic acid-*d*₁ from normal pyrrole and then reacted it with benzaldehyde as a one-pot reaction. Since the propionic acid-*d*₁ is prepared from propionic anhydride and D₂O (99.9%), a nearly quantitative incorporation might be expected. We suspect that the source of the proton which is partially involved at the pyrrole- β -position in the porphyrin must be due to the protons of the unlabelled pyrrole as the reactants.

In the solution where propionic acid-*d*₁ and unlabelled pyrrole are mixed under the condition of Shirazi and Goff,³ the ratio of deuterium versus proton that can be exchanged with deuterium is calculated as 8:92. This value is almost coincident with the reported value for deuterium labelling by Shirazi and Goff. Here the use of pyrrole-*d*₅ as the starting material gives theoretically 98% incorporation, and thus this strategy is expected to increase the deuterium content in the final product.

By replacing pyrrole-*d*₅ instead of unlabelled pyrrole in the Shirazi and Goff method, we have improved the deuterium incorporation at the pyrrole- β -position for the *d*₈ and *d*₂₈ compounds according to Scheme 1.

Since the deuterium incorporation is quite high, it is difficult to estimate the accurate deuterium content from the ¹H-NMR data as in the literature. Thus we evaluated the deuterium content by use of simulated FAB-mass spectra. Figure 2 shows the observed FAB-mass spectra and their simulations for TPPH₂-*d*₈, TPPH₂-*d*₂₀ and TPPH₂-*d*₂₈. For the simulation, the normal TPPH₂ spectrum was used as the reference. In both the *d*₈ and *d*₂₈ compounds, deuterium content of the 95–96 at% D at pyrrole- β -hydrogen reproduce the observed mass spectra. In Figure 2, simulations for the deuterium content of 95% for the pyrrole- β -hydrogens are presented. On the other hand, for the *d*₂₀



Scheme 1. Synthetic route of pyrrole deuterated TPPs

compound, the simulation spectrum with 100% deuterium incorporation of the phenyl groups reproduces the observed mass spectrum very well.

In the three kinds of the deuterated products, elemental analysis data match calculated values ranging from 90 to 100% as the deuterium content of pyrrole hydrogens. Thus we could not conclude the deuterium incorporation from the elemental analysis accurately. Results of the elemental analysis are presented in Table 1, together with calculated values for 95at% deuterium labelling at the pyrrole- β -position.

During procedures for metalation of the free base porphyrins, the deuterium contents are maintained in zinc(II) and copper(II) complexes. The mass spectra of zinc and copper TPP- d_8 , TPP- d_{20} and TPP- d_{28} complexes show exactly the same deuteration incorporation as those of the corresponding free bases.

Experimental

General

Pyrrole and benzaldehyde were distilled prior to use. *Normal* propionic anhydride was distilled under the reduced pressure. Pyrrole- d_5 was purchased from Aldrich and used just as received. Benzaldehyde- d_6 was prepared according to the literature.² 1H -NMR and 2H -NMR measurements were carried out on an NMR spectrometer Model Bruker DRX, by using 1H (500 MHz) and 2H (75 MHz) probes, respectively. FAB mass spectra were measured on a JEOL mass spectrometer Model JMS-700.

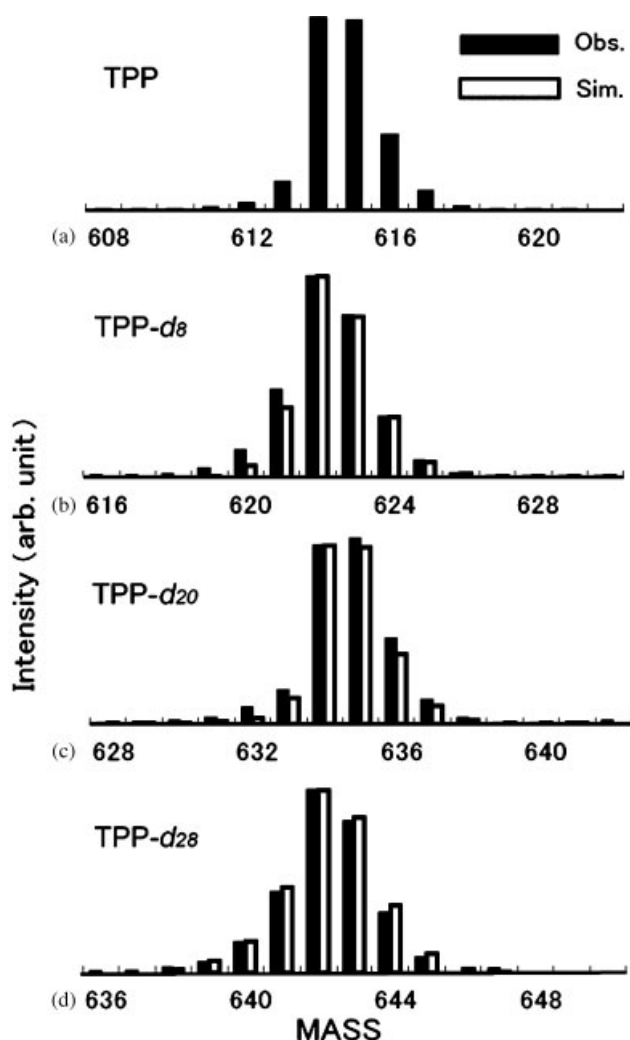


Figure 2. FAB mass spectra of TPPs and their simulations

5,10,15,20-TPP-d₈. To propionic anhydride (62.5 ml, 0.49 mol) (Wako Pure Chemical Industries, Ltd) was added D₂O (8.55 ml, 0.49 mol) (99.9%, Aldrich) under nitrogen, and the mixture was heated under reflux for 30 min to give propionic acid-*d*₁. To this solution, pyrrole-*d*₅ (1 g) was added dropwise and the mixture was heated under reflux for 1 h. After introducing air to the reaction vessel, benzaldehyde (1.47 g) was added to the mixture, and this was then heated under reflux for a further 1 h. After cooling the reaction mixture overnight, the resulting participate, which consists of crude TPP-*d*₈, was collected and purified as described below. Separately, propionic acid in the filtrate was distilled off under the reduced pressure. The residue of the distillation was applied to silica gel column chromatography (dichloromethane),

Table 1. Elemental analysis data for deuterated TPPs

		C	H	N
TPPH ₂	Found	85.93	4.69	9.02
C ₄₄ H ₃₀ N ₄	Calcd.	85.97	4.92	9.11
TPP- <i>d</i> ₈	Found	84.74	4.77	8.85
C ₄₄ H ₂₂ D ₈ N ₄ (95%) ^a	Calcd.	84.92	4.86	9.00
TPPH ₂ - <i>d</i> ₂₀	Found	83.53	4.82	8.66
C ₄₄ H ₁₀ D ₂₀ N ₄	Calcd.	83.24	4.76	8.83
TPPH ₂ - <i>d</i> ₂₈	Found	81.96	4.69	8.58
C ₄₄ H ₂ D ₂₈ N ₄ (95%) ^a	Calcd.	82.26	4.71	8.72

^aDeuterium content 95 at% is used only for the pyrrole- β -hydrogens.

and the eluent was evaporated into solid, which was washed with methanol to give another portion of crude TPP-*d*₈. The two portions of crude products were then treated with DDQ.¹⁰ The chlorine-free pyrrole-deuterated porphyrin was purified by column chromatography (silica gel/dichloromethane, toluene : dichloromethane = 8 : 2) and recrystallization from chloroform/methanol. The final products were identified by ¹H-NMR, ²H-NMR, elemental analysis (Table 1) and mass spectrometry (Figure 2). The deuterium incorporation is evaluated from mass simulation as more than 95%. Details of the deuterium content is described in the 'Results and discussion' section.

*5,10,15,20-TPP-d*₂₈. It is noted that for the *d*₂₈ derivative, benzaldehyde-*d*₆ should be used since the hydrogen atoms of the aldehyde can be released in solution during the reflux. All the other procedures were the same as those of the *d*₈ derivative.

Conclusion

The deuterium labelling at the pyrrole- β -position is slightly lower than that expected theoretically and at the moment the reason is not clear. We have also examined the mass spectra of the compounds which were prepared by the original Shirazi and Goff method. The best fit for the mass spectra were given with the deuterium contents of 86–88%. The method described improves the deuterium incorporation significantly for spectroscopic studies and this helps in elucidating the properties of these porphyrins.

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