A General Reductive Denitration Method for Regiospecific Deuteriation of the Porphyrin Nucleus: Synthesis of [20-$^2H_1$]Mesoporphyrin IX Dimethyl Ester

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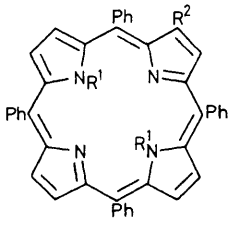
Treatment of *meso*- or β-nitroporphyrins with deuteriated lithium hydroxide and [*N,N,S*-$^2H_3$]2-aminobenzenethiol in dry *N,N*-dimethylformamide results in replacement of the nitro group with deuterium; the regiospecificity of the process is demonstrated by synthesis of [20-$^2H_1$]mesoporphyrin IX dimethyl ester.

Despite a considerable number of physicochemical and biological studies which have used deuterium-labelled porphyrins,[1] no method has been reported previously for the regiospecific mono-deuteriation of the porphyrin nucleus. Deuterium-labelled porphyrins have previously been obtained by synthesis from deuteriated pyrrolic precursors with incorporation of more than one deuterium,[2] by an electrochemical reduction process which resulted in the incorporation of deuterium at all four *meso*-positions,[3] and by catalysed deuterium-exchange processes which resulted either in complete ring deuteriation[4,5] or in the formation of isomeric mixtures of deuteriated compounds.[4,6] We now report a general method for regiospecific mono-deuteriation of the porphyrin nucleus which we have developed from our recent observation that the β-nitroporphyrin (**1**) was reductively denitrated to give the parent porphyrin (**2**) in high yield on treatment with 2-aminobenzenethiol and lithium hydroxide in *N,N*-dimethylformamide (DMF);[7] use of several other thiols in the reaction resulted in the formation of 2-thioporphyrins.[7]

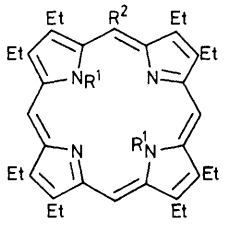
The potential of the reductive denitration process for introduction of a deuterium label to the porphyrin periphery was demonstrated by reaction of (**1**) with deuteriated lithium hydroxide and [*N,N,S*-$^2H_3$]2-aminobenzenethiol in dry DMF for 24 h, which gave the deuteriated porphyrin (**3**) (70 atom %, by ^1H n.m.r. and mass spectral analysis) in 70% yield following an acetic acid quench and chromatographic work-up.

Control experiments indicated that the hydrogens on the inner nitrogens of the porphyrins used in this study were also reactive under these conditions resulting in partial loss of label from the reagents. It was found to be advantageous to exchange these inner hydrogens with deuterium in a two-phase dichloromethane–[$^2H_2$]water system with a catalytic amount of [$^2H_2$]sulphuric acid (two exchanges) prior to reductive denitration.

Treatment of the dideuteriated β-nitroporphyrin (**4**), obtained from (**1**) as above, with deuteriated lithium hydroxide and [*N,N,S*-$^2H_3$]2-aminobenzenethiol in dry DMF for 48 h gave (**3**) (75 atom %) in 80% yield; the inner positions being re-exchanged under the protic work-up conditions.



(1) $R^1 = H$, $R^2 = NO_2$
(2) $R^1 = R^2 = H$
(3) $R^1 = H$, $R^2 = [^2H]$
(4) $R^1 = [^2H]$, $R^2 = NO_2$



(5) $R^1 = [^2H]$ $R^2 = NO_2$
(6) $R^1 = H$, $R^2 = [^2H]$

The *meso*-nitroporphyrin (**5**) gave the deuteriated porphyrin (**6**) (50 atom %) in 55% yield on treatment under the same conditions for 100 h and thus established that the denitration process was also applicable for mono-deuteriation of a *meso*-position on the porphyrin nucleus.

While the above results demonstrate that deuteriated porphyrins can be prepared under these conditions they do not allow determination of whether the process is specific because of symmetry in the products (**3**) and (**6**).

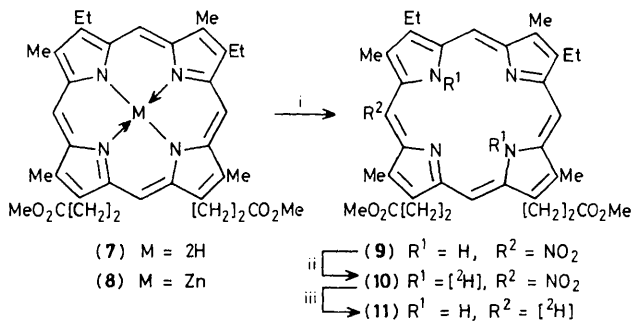
The regiospecificity of the deuteriation process was proven by the specific labelling of one of the four possible *meso*-positions of mesoporphyrin dimethyl ester (**7**) as follows (Scheme 1).

Treatment of the zinc(II) chelate (**8**) with iodine (1 equiv.) and silver nitrite (1 equiv.) in $MeCN–CH_2Cl_2$ gave a mixture of the four possible mono-nitroporphyrins in 93% yield. The mixture was demetallated (99% yield) by treatment with anhydrous hydrogen chloride in CH_2Cl_2, neutralized with base and the isomers separated by chromatography [preparative h.p.l.c.; Whatman Magnum 20 column; $MeCN–C_6H_6$ (3:97)] to give in order of elution, 15-nitro- (6%), 20-nitro- (**9**) (50%) (m.p. 204.5—205.5 °C), 10-nitro- (18%), and 5-nitro-mesoporphyrin IX dimethyl ester (21%).† The structural assignment of the four compounds is based on nuclear Overhauser effects (n.O.e.) and will be described fully elsewhere;[8] the 20-nitro compound (**9**) is, however, the only isomer which exhibits n.O.e. at an adjacent *meso*-proton from each of the methylene groups directly attached to the porphyrin ring and from only two of the ring methyl groups.

The dideuteriated 20-nitromesoporphyrin IX dimethyl ester (**10**), obtained from (**9**) in quantitative yield, was reductively denitrated under standard deuteriation conditions (see above) for 100 h, subjected to protic work-up, and treated with diazomethane to give [20-$^2H_1$]mesoporphyrin IX dimethyl ester (**11**) (70 atom %, by ^1H n.m.r. and mass spectral analysis) in 46% yield.

The specificity of the process was shown by 400 MHz ^1H n.m.r. spectroscopic experiments, the resonances in the spectrum of (**11**) being unequivocally assigned by n.O.e. experiments. In particular, the singlet at δ 10.00 [0.3(0) H] was assigned to H-20 since it was the only *meso*-proton which did not experience n.O.e. from any of the ring methylene groups, and which did show n.O.e. from two ring methyl groups. Each of the other *meso*-proton resonances, δ 10.01 (H-15), 10.02(5) (H-5), 10.03 (H-10), was found to integrate to 1.0(0) hydrogens showing that the reaction is regiospecific within the limits of detection (±3%).

† All new porphyrins have been adequately characterized by analytical and/or spectroscopic data.



(7) M = 2H
(8) M = Zn

(9) $R^1 = H$, $R^2 = NO_2$
(10) $R^1 = [^2H]$, $R^2 = NO_2$
(11) $R^1 = H$, $R^2 = [^2H]$

Scheme 1. i, $AgNO_2–I_2$ in $MeCN–CH_2Cl_2$, HCl, neutralization, h.p.l.c.; ii, $^2H_2O–^2H_2SO_4$(cat.); iii, LiO^2H-[*N*,*N*,*S*-$^2H_3$]2-aminobenzenethiol in DMF, protic work-up, CH_2N_2.

The mechanism of the reductive denitration reaction is under investigation. Preliminary studies suggest that it involves electron transfer from thiolate to generate a porphyrin anion radical, followed by loss of nitrite ion to give a porphyrin radical which abstracts a hydrogen (or deuterium) atom, the process being analogous to the methoxide ion promoted reductive dehalogenation of 3-iodopyridine and 4-bromoisoquinoline.[9]

The method outlined in this communication provides an efficient, regiospecific method for deuteriation of the porphyrin nucleus and is a further illustration of the synthetic versatility of nitroporphyrins.[7,10]

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