Regiospecific Introduction of Four Substituents to Porphyrin Systems at Antipodal Pyrrolenic Positions

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Electrophilic bromination occurs regiospecifically at the antipodal pyrrolenic ring of free-base porphyrins bearing substituents that fix the aromatic delocalization pathway; this new feature of porphyrin chemistry is not observed in the reactions of the corresponding metalloporphyrins as the pre-requisite bond fixation is only possible in free-base compounds.

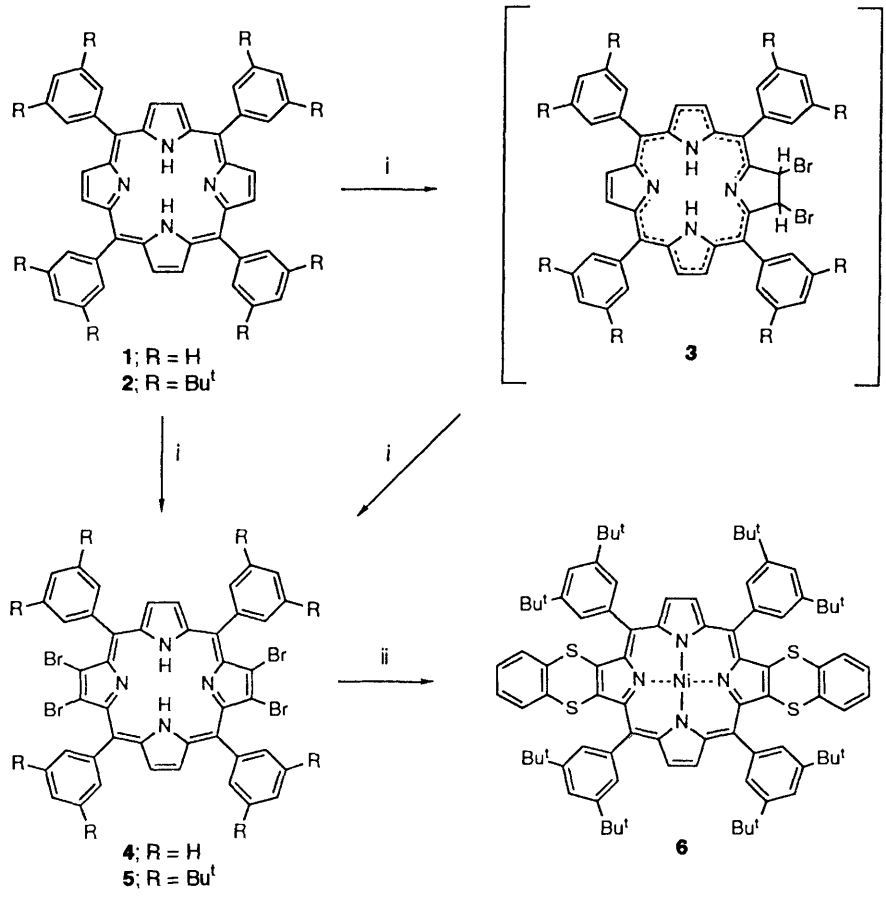
We report a hitherto unrecognized feature of porphyrin chemistry. 5,10,15,20-Tetraarylporphyrin systems in which the electrons of a β,β′ carbon pair of atoms are held from participation in the macrocyclic aromatic delocalization pathway have full double-bond character imposed on the antipodal (trans-annular) β-β′ site making it more susceptible to electrophilic reaction than the rest of the molecule. It is thereby possible to regiospecifically functionalize antipodal pyrrolenic rings on the porphyrin periphery.

Treatment of 5,10,15,20-tetraphenylporphyrin **1** with 4.3 equiv. of *N*-bromosuccinimide (NBS) in boiling ethanol-free chloroform afforded 7,8,17,18-tetrabromo-5,10,15,20-tetraphenylporphyrin†‡ **4** in 80% yield (Scheme 1). The D_{2h} symmetry of the product was confirmed by the ^{1}H NMR spectrum (δ 8.71, d, ^4J 1.4 Hz, H-2, H-3, H-12, H-13; on irradiation of the N-*H* at δ −2.83, this doublet collapsed to a singlet) and by the subsequent transformations. Similar treatment of 5,10,15,20-tetra(3,5-di-*tert*-butylphenyl)porphyrin **2** with NBS gave the corresponding 7,8,17,18-tetrabromoporphyrin **5** (δ 8.82 d, ^4J 1.4 Hz, H-2, H-3, H-12, H-13; on irradiation of the N-*H* at δ −2.90, this doublet collapsed to a singlet) in 70% yield. The nickel(II) chelate of **5** was reacted with the dianion of *o*-benzenedithiol in dry *N*,*N*-dimethylformamide (DMF) to give the antipodally ring-extended 2,3,12,13-bis[*b*]1,4-dithia-1,4-dihydronaphthalylporphyrin **6** by nucleophilic substitution of the bromo groups; the overall yield from **5** was 48%.

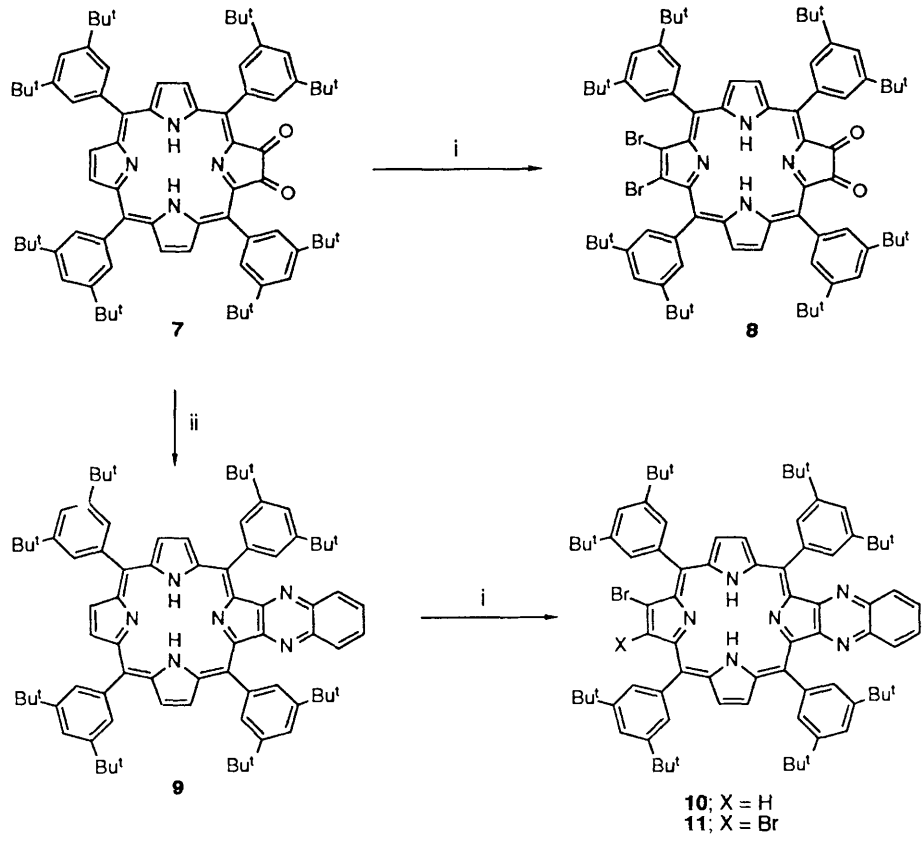
We attribute the regiospecificity observed in the tetrabromination reaction to the intermediacy of a bond-fixed chlorin, either **3** or a similar radical species, having an 18 π-electron 18-atom 'inner–outer–inner–outer' aromatic delocalization pathway which consequently imposes double-bond character on the $\Delta^{17,18}$ double bond in the antipodal (trans-annular) pyrrolenic ring;[1–3] subsequent electrophilic- or radical-bromination is then directed to this relatively electron-rich bond. We have shown previously that incorporation of a bromo substituent into a free-base porphyrin strongly influence the position of tautomeric equilibria in such systems towards the tautomer in which the bromo substituent resides on a carbon with double bond rather than aromatic character.[1] Thus, it should be a straightforward matter of oxidation of chlorin or bacteriochlorin intermediates, further bromine additions, and a final oxidation to the porphyrin level to arrive at the 7,8,17,18-tetrabromoporphyrin **4** or **5**. In reactions of **1** involving the use of less than four equivalents of NBS, we have

† Named in this way because none of the alternate tautomer, 2,3,12,13-tetrabromo-5,10,15,20-tetraphenylporphyrin, resulting from hydrogen movement on the inner periphery of the molecule was detected by ^{1}H NMR studies; evidently the inner hydrogens are fixed on N-21 and N-23 with the consequence that the macrocycle itself is bond fixed into an 18 atom 18π-electron aromatic delocalized pathway and two double bonds, $\Delta^{7,8}$ and $\Delta^{17,18}$. On metallation of the porphyrin the numbering reverts to 2,3,12,13-tetrasubstituted porphyrin as, unlike the free-base compounds, metalloporphyrins do not consist of a mixture of tautomeric forms.

‡ The structure of this compound has been previously misassigned as 2,7,12,17-tetrabromo-5,10,15,20-tetraphenylporphyrin (H. J. Callot, *Bull. Soc. Chim. Fr.*, 1974, 1492) in which one bromo group is in each pyrrolic/pyrrolenic ring; the structures of each of the dibromo-, dicyano-, the tribromo-, the tricyano-, and the tetracyano-5,10,15,20-tetraphenylporphyrins reported therein have also been erroneously assigned.



Scheme 1 *Reagents*: i, NBS; $Ni(OAc)_2$ in DMF then *o*-benzenedithiol–LiOH in DMF



Scheme 2 *Reagents*: i, NBS; ii, *o*-phenylenediamine

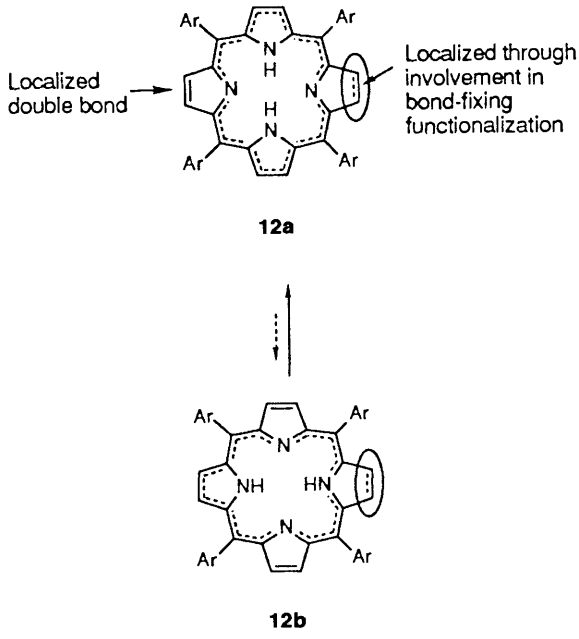


Fig. 1 The position of tautomeric equilibrium in a free-base porphyrin with bond-fixing functionalization at one of the β-β′ positions strongly favours the tautomer **12a** and is the basis of regioselective reactions

isolated the corresponding 7,8-, 7,17-, and 7,18-dibromoporphyrins and the 7,8,17-tribromoporphyrins. These findings will be reported in full elsewhere.

Similar regiospecific bromination in the antipodal pyrrolenic ring at the $\Delta^{17,18}$ double bond, can be achieved in other *free-base* 7,8-disubstituted porphyrins in which the 7,8-substituents cause substantial bond fixation in the macrocyclic system.

Treatment of the free-base porphyrin-7,8-dione **7**,[4] having $\Delta^{17,18}$ double bond character, with NBS (3.35 equiv.) gave only the 17,18-dibromoporphyrin **8**, in 73% yield. No regiospecificity was seen in electrophilic reactions on a metallated analogue; nitration of the palladium chelate of compound **7** with nitrogen dioxide gave the three possible mononitroporphyrins (as yet unassigned but in a 9 : 1 : 11 ratio).[5] Also in accordance with the above observations, bromination of the free-base porphyrinoquinoxaline **9** (prepared in 98% yield by treatment of **7** with *o*-phenylenediamine) using NBS (1.10 equiv.) gave only the 17-bromo- and the 17,18-dibromoderivatives, **10** and **11**, in 80 and 12% yield, respectively; when 2.8 equiv. of NBS were used, the dibromoporphyrin **11** was obtained in 88% yield. Evidently, the electrons in the $\Delta^{7,8}$ bond of the porphyrin **9** are shared with the quinoxaline system thereby imposing essentially full double-bond character between C-17 and C-18 and directing bromination to this site of the molecule. That the outcome is due to electronic and not steric factors is readily demonstrated. Bromination of the copper(II) chelate of porphyrin **9** under the same conditions gave a complex mixture consisting of all three possible bromoporphyrins together with a number of dibromoporphyrins. After demetallation of the mixture, ^{1}H NMR and preparative chromatography studies on the resultant free-base compounds revealed that the 17-bromoporphyrin **10** made up only 30% of the monobrominated compounds. Similarly, nitration of the copper(II) chelate of porphyrin **9** with nitrogen dioxide[6] also gave a mixture of the three possible mononitroporphyrins (7-, 8-, 12-nitro derivatives in 46, 16 and 38%, respectively). The lack of regiospecificity in the reactions on the metalloporphyrin, as distinct from the free-base analogue, is a consequence of the fact that there is no localized double-bond character in a metalloporphyrin[3] and the bond orders of each of the β-β′ pyrrolic units of the macrocycle are essentially identical.[7]

In summary, the conditions for achieving regiospecific functionalization of antipodal pyrrolenic positions of porphyrins have been determined and a new feature of porphyrin reactivity has been revealed. This is summarized in Fig. 1 and is a result of the aromatic delocalization pathway in free-base porphyrins which have the electrons of a β-β′ position localized in bond-fixing functionality being essentially fixed as in **12a**; the tautomeric form **12b** which has a 17-atom 18-π-electron 'inner–inner–inner–outer' aromatic delocalization pathway, it being the 18-electron analogue of pyrrole is of much higher energy, and indeed has not been detected in low-temperature ^{1}H NMR studies of **7** and related compounds.[3]

The use in the synthesis of linearly extended porphyrin systems of the regiospecific reactions developed in this work is reported in the following two communications.

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