Synthetic Studies Related to Myoglobin: Syntheses of Bridged Porphyrin Systems

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Summary Routes are developed for synthesis of porphyrins carrying functionalised bridges over the macrocycle; the Fe^{II} complexes of these products are of interest in relation to myoglobin and haemoglobin.

There has been considerable effort recently on the synthesis of model systems related to the oxygen-binding haem proteins.[1] These elegant studies have shown that an important function of the haem pocket in haemoglobin and myoglobin is to prevent dimeric interactions between haems; these interactions are known to result in irreversible oxidation of the Fe^{II} by the co-ordinated oxygen.[2] A possible way to prevent such reactions is to allow the oxygen to shelter under a single bridge constructed across the porphyrin macrocycle as shown schematically in the Figure at (a) and for a specific case at (b).

Such a model with the bridge joining the carboxy-residues of a 3,13-(2′-carboxyethyl)porphin, leaving the carbons at 5, 10, 15, and 20 unencumbered, has several attractions. It should have electronic and geometric properties close to the natural haems, and the size of the cavity can readily be adjusted to that of myoglobin.[3] Clearly the bridge can be chosen to be bulky, polar, apolar, or chiral or combine several of these features. We now report the synthesis by different methods of a number of bridged porphyrins.

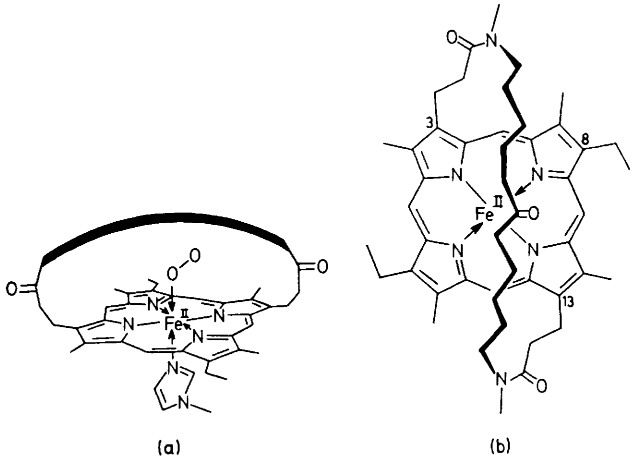
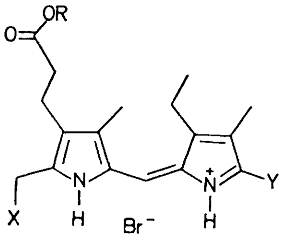


FIGURE. Bridged porphyrin systems.

Mesoporphyrin-II dimethyl ester (**4**) was chosen for elaboration since it has a centre of symmetry and was thus available in quantity (25% overall from monopyrroles) by Fischer's method[4] from the pyrromethene (**1**). The porphyrin acid chloride (**6**) reacted with hex-5-yn-1-ol[5] to yield the diester† [(**7**), 80% from (**4**)] into which Fe^{III} was inserted[6] forming (**8**). The bridge was closed by oxidative coupling at high dilution with copper(II) acetate in pyridine–ether[7] to give (**9**). When the metal-free diester (**7**) was similarly oxidised, the copper complex (**11**) was obtained in 60% yield which was hydrogenated to the saturated bridge system (**12**) and demetallated[6] yielding the crystalline porphyrin (**13**). This was identical with the product obtained by hydrogenation of the Fe^{III} complex (**9**) to form (**10**) followed by demetallation.[6]

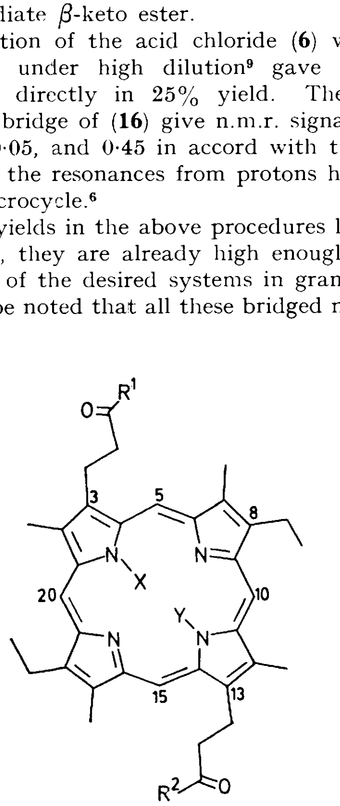


	R	X	Y
(**1**)	Me	H	CO_2H
(**2**)	Et	Br	Br
(**3**)	H	H	CO_2H

An alternative bridge-forming method used the Diekmann reaction with the bis-amide (**14**) prepared from (**6**) and methyl 6-methylaminohexanoate, the latter being available from *N*-methylcaprolactam.[8] Treatment of (**14**) under high dilution conditions in boiling toluene with $KOBu^t$ gave the ketone (**15**, 30%) after hydrolysis and decarboxylation of the intermediate β-keto ester.

Finally, reaction of the acid chloride (**6**) with 1,12-diaminododecane under high dilution[9] gave the bridged porphyrin (**16**) directly in 25% yield. The methylene protons of the bridge of (**16**) give n.m.r. signals in groups at δ −0·4, −0·05, and 0·45 in accord with the expected upfield shift of the resonances from protons held over the conjugated macrocycle.[6]

Though the yields in the above procedures have not yet been optimised, they are already high enough to provide a wide variety of the desired systems in gram quantities. It should also be noted that all these bridged molecules are chiral.



	X	Y	R¹	R²
(**4**)	H	H	OMe	OMe
(**5**)	H	H	OEt	OH
(**6**)	H	H	Cl	Cl
(**7**)	H	H	$-O[CH_2]_4C{\equiv}CH$	$-O[CH_2]_4C{\equiv}CH$
(**8**)	$-Fe^{III}(Cl)-$		$-O[CH_2]_4C{\equiv}CH$	$-O[CH_2]_4C{\equiv}CH$
(**9**)	$-Fe^{III}(Cl)-$		$-O[CH_2]_4C{\equiv}C{-}C{\equiv}C[CH_2]_4O-$	
(**10**)	$-Fe^{III}(Cl)-$		$-O[CH_2]_{12}O-$	
(**11**)	$-Cu^{II}-$		$-O[CH_2]_4C{\equiv}C{-}C{\equiv}C[CH_2]_4O-$	
(**12**)	$-Cu^{II}-$		$-O[CH_2]_{12}O-$	
(**13**)	H	H	$-O[CH_2]_{12}O-$	
(**14**)	H	H	$-NMe[CH_2]_5CO_2Me$	$-NMe[CH_2]_5CO_2Me$
(**15**)	H	H	$-NMe[CH_2]_5CO[CH_2]_5NMe-$	
(**16**)	H	H	$-NH[CH_2]_{12}NH-$	
(**17**)	$-Fe^{II}-$		$-O[CH_2]_4C{\equiv}C{-}C{\equiv}C[CH_2]O-$	
(**18**)	$-Fe^{II}-$		$-O[CH_2]_{12}O-$	
(**19**)	H	H	$-NH[CH_2]_3$–imidazole	OEt
(**20**)	$-Fe^{II}-$		$-NH[CH_2]_{12}NH-$ with Et at C-8 replaced by $-[CH_2]_2CONH[CH_2]_3$–imidazole	

We have studied the effect of oxygen on the Fe^{II} complexes (**17**) and (**18**) prepared by reduction (*e.g.*, with dithionite) of the corresponding Fe^{III} systems (**9**) and (**10**); the visible spectra of the Fe^{II} model systems duplicate those of the natural haems. The experiments with oxygen were run at *ca.* 20° C in solutions (*e.g.*, tetrahydrofuran or aqueous acetone) containing *N*-methylimidazole and the characteristic visible spectra[6] showed that rapid irreversible oxidation occurred to the Fe^{III} state. Both Fe^{II} systems (**17**) and (**18**) bind carbon monoxide and the visible spectra of the complexes match those of Chang and Traylor.[10] It appears that the bridge in the present system is sufficiently flexible for the axial base to co-ordinate above the plane

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† Confirmatory analytical and spectroscopic data were obtained for each new substance.

of the porphyrin ring alongside the bridge. This allows oxygen to attach itself to the opposite open face and, consequently, irreversible oxidation occurs.

An example of the type of molecule designed to overcome this effect is structure (**20**) and its synthesis requires a porphyrin having three propionate side-chains, one being differentiated from the others. The feasibility of this approach was established by synthesis of the porphyrin (**5**) by the biladiene-ac method[6] from pyrromethenes (**2**) and (**3**) in 30% yield. The corresponding acid chloride–ester reacted with 1-(3-aminopropyl)-imidazole[11] to yield (**19**) carrying a 'tail' analogous to Traylor's derivatives[10] of protoporphyrin-IX. The way is thus open for construction of the bridged porphyrin (**20**) and its relatives.

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