Iron(II) 'Hanging Imidazole' Porphyrin: Synthesis and Proximal Ligand Effect on CO and O_2 Binding

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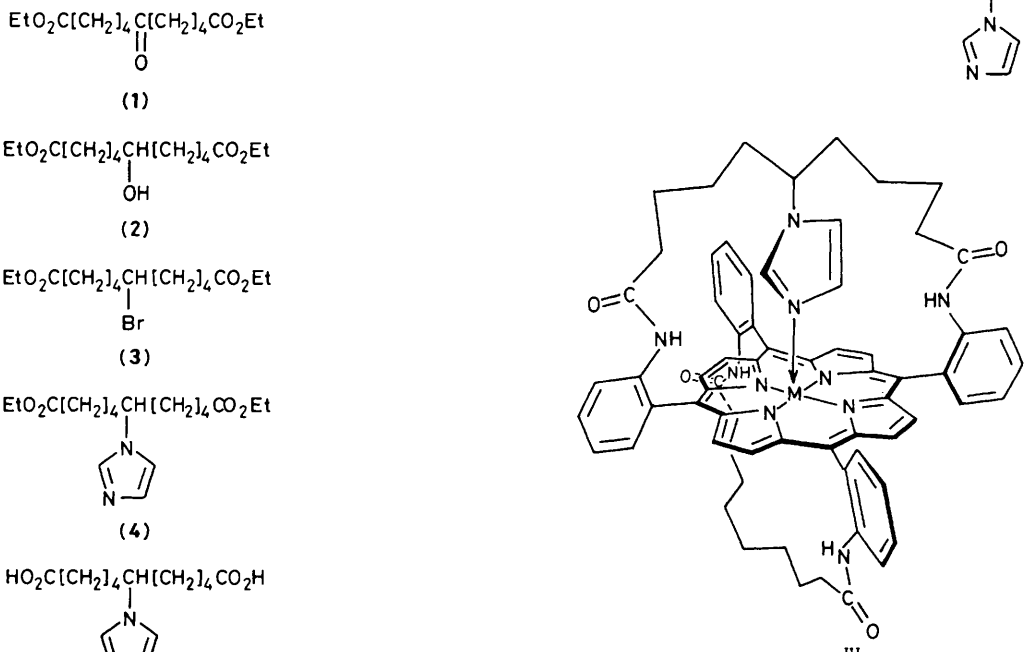
The preparation of the title compound, a model for the active site of oxygen carrier hemoproteins, is described and the kinetic parameters of the CO and O_2 adducts show the importance of the co-ordinated imidazole in stabilization.

The interest in the design of 'hanging base' porphyrins is due to the stepwise changes in the chemical environment on the distal or proximal side of the heme which can be achieved and to their effect on the kinetic rate parameters for binding gaseous ligands. We previously reported the dioxygen stabilization in 'hanging pyridine' porphyrins on replacing the ether linkage by an amino group in the proximal and distal handles.[1] We now describe the synthesis of the new compound (**9**), which incorporates an imidazole in the proximal handle. Preliminary kinetic results indicate that the proximal base affects O_2 and CO binding.

Ethyl 5-oxo-nonane-1,9-dicarboxylate (**1**)[2] was reduced to the corresponding alcohol (**2**) in almost quantitative yield with sodium borohydride in EtOH. Subsequent bromination with PBr_3 gave (**3**). Treatment of (**3**) with lithium imidazolate, prepared from n-butyl-lithium and imidazole in refluxing toluene, gave the diester substituted imidazole (**4**) in 21.5% yield after purification by column chromatography (silica gel, $CHCl_3$–acetone 1 : 1 v/v). Acid hydrolysis of (**4**) gave 5-(*N*-imidazoyl)nonane-1,9-dicarboxylic acid (**5**). The imidazole derivative (**5**) was treated with 1 equiv. of the porphyrin (**6**)[1] (which has one face protected) in dimethylformamide under high dilution conditions at room temperature and in the presence of thionyl chloride. The resulting porphyrin (**7**) was purified by preparative t.l.c. on silica gel (20% MeOH–CH_2Cl_2) and isolated in 16% yield. ^{1}H N.m.r. spectral data ($CDCl_3$) were in complete agreement with the indicated structure (Figure 1). Iron insertion into the 'hanging imidazole' porphyrin (**7**) was accomplished using iron(II) chloride under reflux in dimethylformamide.

The iron(II) compound (**9**) was obtained by reduction of the hemin (**8**) using either zinc amalgam in dry toluene, or aqueous sodium dithionite.[3] In both cases, the pentaco-ordination of (**9**) was confirmed by ^{1}H n.m.r. spectroscopy. In dry toluene (34 °C) downfield-shifted resonances were observed in the δ 30—67 range where the pyrrole and imidazole protons' lines are expected, shifted in a high spin ($S = 2$) state.[4–6] At the concentration used (3.1×10^{-3} M) no dimerization was



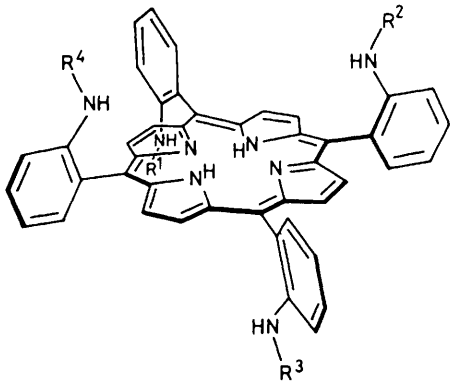
(**1**)

(**2**)

(**3**)

(**4**)

(**5**)



(**6**) $R^1, R^3 = OC[CH_2]_{10}CO$; $R^2 = R^4 = H$

(**7**) $R^1, R^3 = OC[CH_2]_{10}CO$; R^2, $R^4 = OC[CH_2]_4CH[CH_2]_4CO$

(**8**) M = $Fe^{III}OH$

(**9**) M = Fe^{II}

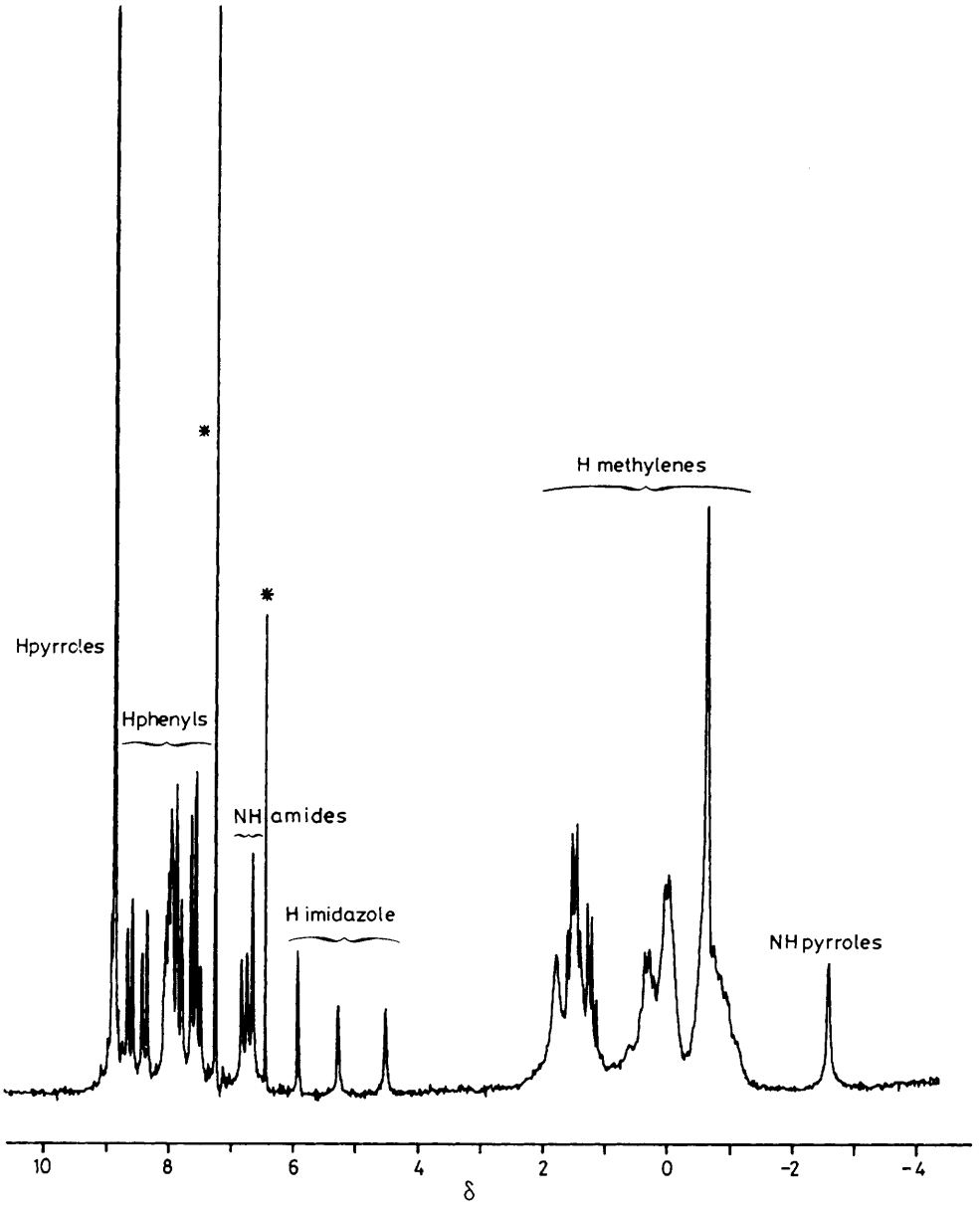


Figure 1. 100 MHz ^{1}H N.m.r. spectrum of (7) in $CDCl_3$ at 34 °C.

Table 1. CO and O_2 binding rate parameters for heme models in toluene (20 °C) and hemoproteins in water, pH 7 (20 °C).

	k_{on} (CO)/ l mol^{-1} s^{-1}	k_{off} (CO)/ s^{-1}	K_{eq} (CO)/ l mol^{-1}	$P_{\frac{1}{2}}$ (CO)/ Torr	k_{on} (O_2)/ l mol^{-1} s^{-1}	k_{off} (O_2)/ s^{-1}	K_{eq} (O_2)/ l mol^{-1}	$P_{\frac{1}{2}}$ (O_2)/ Torr
(9)	4×10^7	6.7×10^{-3}	6×10^9	1.7×10^{-5}	3.1×10^8	6.2×10^2	5×10^5	0.29
Amide-BHP(C_{12})(C_3PyC_3)[a]	3.5×10^7	3×10^{-2}	1.1×10^9	9×10^{-5}	3.6×10^8	5×10^3	7×10^4	2
Ether-BHP(C_{12})(C_3PyC_3)[a]	6.8×10^7	6.9×10^{-2}	9.9×10^8	1×10^{-4}	3×10^8	4×10^4	7.5×10^3	18
Piv_3(5CIm)P[b]	—	—	(4.5×10^9)[c]	2.2×10^{-5}	—	—	(2.4×10^5)[c]	0.58
Mb[d]	5×10^5	1.7×10^{-2}	2.9×10^7	2.6×10^{-2}	2×10^7	10	2×10^6	0.3
Hb, α chain (R)[d]	6.5×10^6	1×10^{-2}	6.5×10^8	1.1×10^{-3}	5.9×10^7	12	4.9×10^6	0.11
Hb, β chain (R)[d]	6.5×10^6	1×10^{-2}	6.5×10^8	1.1×10^{-3}	5.9×10^7	21	2.8×10^6	0.19

[a] From ref. 1. These compounds, like (9), are derived from 'basket handle porphyrins' (BHP) (ref. 14). The proximal handle includes a pyridine and is connected to the macrocycle by two amide and ether linkages respectively. Amide-BHP(C_{12})(C_3PyC_3) = α-(5,15)-[2,2′-(dodecamethyleneamido)diphenyl] :β-(10,20)-{2,2′-[3,3′-(pyridine-3,5-diyl)dipropioamido]diphenyl}porphyrin. Ether-BHP(C_{12})-(C_3PyC_3) = α-(5,15)-[2,2′-(dodecamethyleneoxy)diphenyl]:β-(10,20)-{2,2′-[3,3′-(pyridine-3,5-diyl)dipropoxy]diphenyl}porphyrin. [b] From ref. 7. Piv_3(5CIm)P = 5,10,15-tri(α,α α-*o*-pivalamidophenyl):20-[β-*o*-5-(*N*-imidazolyl)valeramidophenyl]porphyrin. [c] Calculated from the $P_{\frac{1}{2}}$ value. [d] From ref. 13. Mb = myoglobin, Hb = hemoglobin.

observed, contrary to previous reports for several 'tailed' porphyrins,[7,8] in the temperature range 34 to −10 °C. However, precipitation of the product precludes an examination of the spectrum at lower temperatures.

The CO and O_2 adducts of compound (**9**) displayed the usual u.v.–visible absorption pattern characteristic of carboxy- and oxy-hemochromes. The oxygenated derivative which was quite stable in dry toluene (life-time about one day under 1 atm of O_2), was found to undergo rapid autoxidation when the reduction was performed in the presence of water, as expected from previous reports.[9,10]

The kinetics of CO and O_2 binding were determined from the ligand exchange reaction after laser photolysis of the carboxyhemochrome in the presence of O_2, according to the procedure described previously.[11] In addition, direct titrations were performed with CO in order to measure the carbon monoxide 'off' rates.

Table 1 shows that O_2 and CO combination rates are practically constant in the three 'hanging base' porphyrins. A reduction of the dissociation rates, especially for oxygen, has been achieved in two ways. i, Replacing the ether links by amido groups in the distal handle.[1] This stabilizes the dioxygen molecule, which can be shown to be H-bonded with the NH protons.[12] ii, Replacing pyridine by imidazole. This is a 'proximal' effect, which appears to be consistent with the greater basicity of the imidazole.

Compound (**9**) incorporates the main features present in the 'picket fence' porphyrins.[7] The *affinities* of (**9**) and $Piv_3(5CIm)P$ toward CO or O_2 are quite similar (Table 1). Although kinetic data are not available for 'picket fence' porphyrins, the present results suggest that model compounds tend to react about ten times faster with O_2 than hemoproteins, but that their dissociation rates are still 1—2 orders of magnitude too high.

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