Novel Synthesis and Complex Properties of Macrocyclic Tetra-amines appended with Phenol as an Axial Donor

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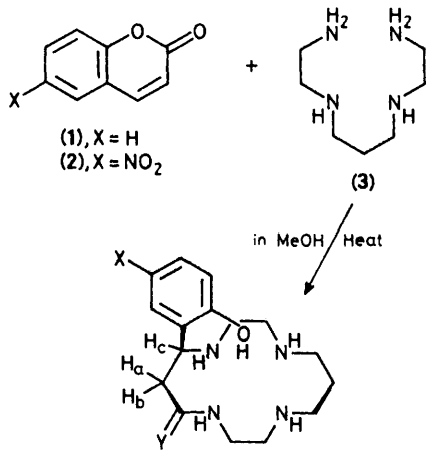
A novel annelation method is reported for the synthesis of the axial phenolate co-ordinating cyclam (**5**) from coumarin and linear tetra-amine (**3**); the product is similar in structure to macrocyclic polyamine alkaloids and is a good ligand for $Fe^{II,III}$ in aqueous solution.

The inclusion of metal ions within saturated macrocyclic tetra-amine cavities has been well documented. However, limited efforts[1] have been made to attach axial donors that might dramatically affect the properties of the tetra-amine complex. The critical roles of the axial donors are most obvious in heme–iron systems of normal[2] or abnormal[3] hemoglobin and redox enzymes such as cytochrome P-450[4] and catalase.[5] Herein, we report a new one-step annelation method for obtaining the new phenol-appended tetra-amine macrocycles (**4**), (**5**), and (**6**) and describe some of their unique complexing properties.

The novel feature of our synthetic method is the use of the coumarins (**1**) and (**2**) as the source of the phenol appendant and at the same time providing reactive sites for the addition of tetra-amine rings in a reaction that successively involves Michael addition followed by lactam formation.

Refluxing coumarin (**1**) and 1,9-diamino-3,7-diazanonane (**3**) in MeOH for two weeks afforded the 14-membered oxotetra-amine (**4**) as its trihydrochloride (decomp. 185 °C) in 20% yield, after purification by silica gel column chromatography (eluant CH_2Cl_2–MeOH–28% aq. NH_3, 100 : 5 : 1) and recrystallization from EtOH–HCl. Reduction of (**4**) with B_2H_6 in tetrahydrofuran (THF) yielded the cyclam derivative (**5**) (m.p. 142—143 °C, from MeCN) in 50% yield. The 6-nitro substituent in (**2**) greatly shortened the reaction time for the cyclization to ~3 days to give (**6**) (19% yield).

This annelation principle can be extended to the preparation of the analogue (**7**) (m.p. 154—155 °C, from MeCN) from methyl cinnamate (30% yield), which has a structural resemblance to the macrocyclic spermine alkaloid verbascenine (**9**).[6] Thus, our annelations open a new synthetic route not only to metal chelating agents but also to various macrocyclic polyamine alkaloids and suggest a biosynthetic pathway to the polyamine alkaloids.



(**1**), X = H
(**2**), X = NO_2
(**3**)
(**4**), X = H, Y = O
(**5**), X = H, Y = H_2
(**6**), X = NO_2, Y = O

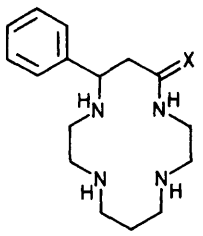
A significant effect of the directly bonded aromatic ring in (**4**) and (**5**) is that the motion of the phenolic group is frozen with the OH group held inside the macrocyclic hole. The ^1H n.m.r. spectrum ($CDCl_3$; 35 °C) of (**5**) shows an unusually high chemical shift for OH (br. s, δ 0—1.5, H–D exchangeable) and a well resolved doublet of doublets for the benzylic H_c signal (δ 3.7—4.0) owing to couplings with H_a and H_b, supporting the conclusion that there is internal hydrogen bonding between the phenolic hydrogen and the encircling tetra-amine bases and that the resulting macrocyclic conformation is fixed. In aqueous solution the overhead phenolate can well shield two protons in the macrocycle, as concluded from their higher (mixed) deprotonation constants pK_a. The deprotonation constants were determined pH-metrically at 25 °C and I = 0.10 M ($NaClO_4$) to be 10.84 and >12 for (**5**) and 10.06 and 10.70 for (**8**). The pK_a value of the phenol group in (**5**) is 8.86 (confirmed spectrophotometrically).

In the co-ordination of (**5**) with metal ions, an unusual characteristic of the axial phenolate donor is the ability to take into solution an equimolar amount of a precipitate of $Fe(OH)_3$ and form a red 1 : 1 complex [*e.g.* (**10**)] (measured by atomic absorption spectroscopy) at neutral pH in aqueous solution. No other saturated macrocyclic polyamines [*e.g.* cyclam or (**8**)] have succeeded in taking up solid Fe^{III} into aqueous solutions. From the pH-metric titration of (**5**) in the presence of 1 equiv. of Fe^{II} under Ar [25 °C, I = 0.10 M ($NaClO_4$)], we determined that $K(Fe^{II}H_{-1}L)$ (=$[Fe^{II}H_{-1}L]\,[H^+]/[Fe^{II}]\,[L]$), where $H_{-1}L$ denotes the phenolate form of (**5**), has a value of 1.2×10^3 and that the conditional constant $K'(Fe^{II}H_{-1}L)$ (= $[Fe^{II}H_{-1}L]/[Fe^{II}]$ [total uncomplexed L]) has a value of 2.5×10^4 dm^3 mol^{-1} at pH 7.0. The yellow Fe^{II}–(**5**) complex in aqueous solution ($\lambda_{max.}$ 455 nm, ε 200 at pH 7.4) is high-spin, $\mu_{eff.}$ = 5.19 μ_B at 35 °C by Evans method,† and is oxidized immediately in air to give the red (turning purple on acidifying) Fe^{III}–(**5**) complex [$\lambda_{max.}$ 480 (555) nm, ε = 2200 (2300) at pH 7.4 (4.3)].‡ An identical Fe^{III} complex was obtained by mixing Fe^{III} with (**5**) or by electrochemical oxidation of the Fe^{II}–(**5**) complex in aqueous solution. The red Fe^{III}–(**5**) complex can be reduced again to the $Fe^{II}H_{-1}L$ with $Na_2S_2O_4$ or by electrochemical reduction. The Fe^{II}–(**5**) complex shows a quasi-reversible (one electron) cyclic voltammogram§ which enabled us to determine the redox potentials for $Fe^{III/II}$ as −0.16 V *vs.* saturated calomel electrode (S.C.E.) (non-buffered at 7 < pH < 9). On the basis of the reversible $Fe^{III/II}$ redox behaviour, we calculated the conditional constant

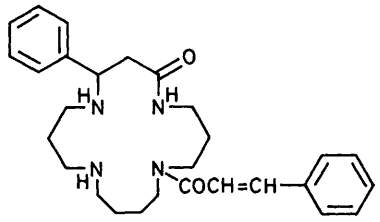
† The phenol-less tetra-amine, cyclam, yields a six-co-ordinate, *low-spin* Fe^{II} complex in nonaqueous solutions, which is very rapidly oxidized to Fe^{III} oxide precipitates in water (see ref. 7).

‡ These two absorptions have isosbestic points at 343, 394, and 510 nm on varying the solution pH. We tentatively assign the red species to the phenolate-capped, encapsulated complex $Fe^{III}H_{-1}L$ and the purple species to a protonated complex.

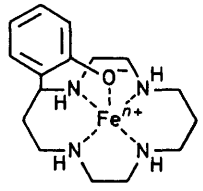
§ The separations of anodic and cathodic peaks are less than 90 mV and the peak height ratios are unity. With other criteria also satisfied, the midpoints between the two peaks are determined.



(7), X = O
(8), X = H_2



(9)



(10)

$K'(Fe^{III}H_{-1}L)$ (= $[Fe^{III}H_{-1}L]/[Fe^{III}]$ [total uncomplexed L]) at pH 7.0 to be 1.2×10^{16} dm^3 mol^{-1}, indicating strong Fe^{III} affinity, although it is smaller than 5.0×10^{21} dm^3 mol^{-1} of Fe^{III}–ethylenediaminetetra-acetic acid (EDTA).[8] Owing to the kinetic inertness of macrocyclic ligand dissociation, the ligand exchange reaction of Fe^{III} from (5) to EDTA practically does not occur.

Evidently, the phenolate group should contribute to stabilization of the Fe^{III} state with respect to the Fe^{II} state. This is understood by comparing its redox potential with those for phenolate-free Fe complexes: *e.g.* the 16-membered saturated penta-amine macrocyclic complex (−0.04 V)[9] or hemoglobin (−0.07 V at pH 7).[10] However, the value of −0.16 V is higher than those for Fe^{III}-carriers such as a mugineic acid (−0.34 V),[11] microbial hydroxamates (−0.59 to −0.69 V),[11] and enterobactin (−0.99 V).[12]

In conclusion, the present phenolate appended ligands may provide new types of macrocyclic $Fe^{II,III}$-sequestering agents and simplified models for the study of phenolate co-ordinating effects in tyrosine co-ordinating Fe^{III} nonheme oxygenases (having similar visible absorptions)[13] or axial phenolate co-ordinating hemes (having low $Fe^{III,II}$ redox potentials).[5] Furthermore, the simplicity and versatility of the annelation method will be useful in the synthesis of a variety of spermine and spermidine alkaloid analogues.

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