A New Cyclam with an Appended Imidazole. The First Biomimetic Ligation of Imidazole for Axial π-Interaction with Metal Ions

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A new cyclam functionalised with a pendant imidazole (**4**) is reported; the *X*-ray crystal structure of its Ni^{II} complex (**6**) shows the most appropriate orientation of the imidazole for axial π-interaction with metal ions.

Cyclam (tetra-1,4,8,11-azacyclotetradecane) is the most familiar macrocyclic N_4 ligand in co-ordination chemistry, biomimetic chemistry, or catalysis. To date, few structural modifications have been made with the aim of attaching more selective or multiple functions to the ligand.

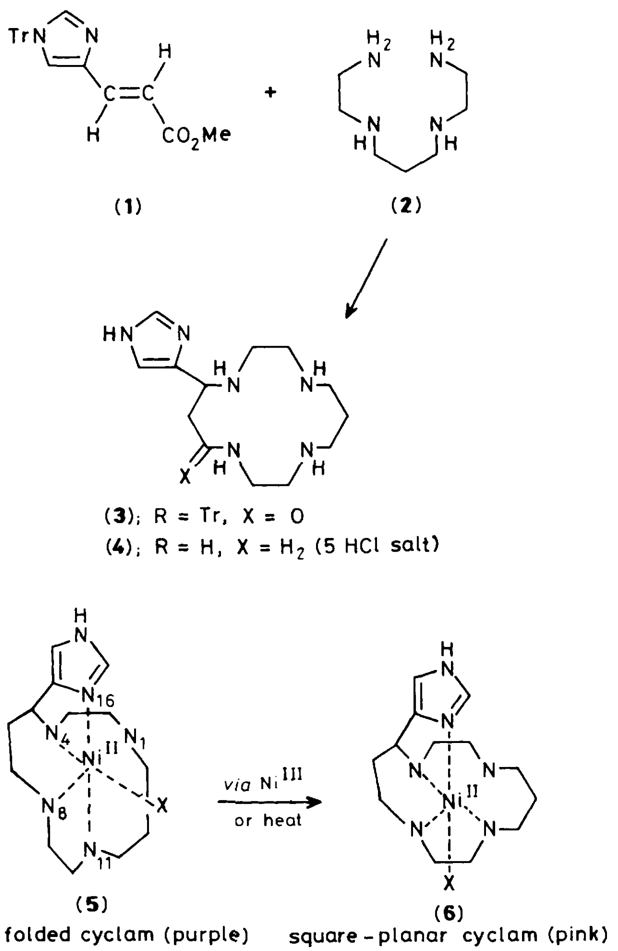
We now have succeeded in synthesizing the first cyclam (**4**) bearing an appended imidazole that acts as an ideal axial donor for effective imidazole → metal π-interaction. The synthetic procedure is also suitable for the preparation of pyridyl-[1] and phenol-appended cyclams.[2,3]

The acrylate (**1**) (2.5 mmol) and 1,9-diamino-3,7-diazanonane (**2**) (2.5 mmol) were refluxed in MeOH-tetrahydrofuran (thf) (10:1, 55 ml) for 3 weeks to give the cyclic amide (**3**) in 8% yield.† Reduction of the amide with B_2H_6 in thf, followed by treatment with HCl yielded the crystalline product (**4**) as the pentahydrochloride salt in 75% yield (Scheme 1).† The proximity of the imidazole N to the macrocycle in (**4**) is illustrated by its extremely low pK_a value of 5.6 (normally 7.1)[4] as a result of the strong influence of the two protons lying in the N_4 ring.‡

Purple and pink crystals were precipitated when equimolar $NiSO_4$ and (**4**) were heated at 50 °C for 10 minutes as an aqueous solution (pH 8) in the presence of $NaClO_4$. Initially the two products were separated by hand-picking. Later, it was found that the purple crystals (the kinetic product) could be converted quantitatively into the pink (thermodynamic) product by heating the aqueous solution at 70 °C for longer periods. The purple (**5**) and pink (**6**) crystals were subjected to *X*-ray structure analysis.

In six-co-ordinate (**5**) ($X = OClO_3^-$),§ the cyclam moiety is in a folded conformation with the imidazole nitrogen N(16) and a perchlorate oxygen O(1) occupying the remaining two *cis*-sites. The metal–macrocyclic nitrogen bond Ni–N(1), Ni–N(4), Ni–N(8), and Ni–N(11) lengths are 2.090(4), 2.087(5), 2.108(4), and 2.091(5) Å, respectively, and are in the normal range of 2.05—2.10 Å for high-spin Ni^{II}–N bonds. The Ni–N(imidazole) bond is extremely short, 2.067(5) Å. The Ni–O(perchlorate) bond length is 2.219(5) Å.

Pink crystals (**6**) (X = MeCN) suitable for *X*-ray analysis were grown from MeCN–H_2O. The structure (Figure 1)§ reveals high-spin Ni^{II} in planar cyclam (chair form) with imidazole N(16) and acetonitrile N(20) in axial positions. The bond lengths for Ni–cyclam N(1) 2.060(11), –N(4) 2.058(12), –N(8) 2.121(12), and –N(11) 2.046(12) Å of the 'metal-in'



(**1**) (**2**)

(**3**); R = Tr, X = O

(**4**); R = H, X = H_2 (5 HCl salt)

(**5**) folded cyclam (purple)

(**6**) square-planar cyclam (pink)

Scheme 1. Tr = CPh_3.

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† (**3**); m.p. 172.5—173.5 °C (from MeCN); i.r. (KBr) $\nu_{C=O}$ 1670 cm^{-1}. (**4**); m.p. 228 °C (decomp.); M^+, *m/z* 266 (free base); ^{1}H n.m.r. (90 MHz, D_2O) δ 2.1—2.6 (m, 4H), 2.8—3.2 (m, 2H), 3.2—3.8 (m, 12H), 4.3—4.4 (m, 1H), 7.50 (s, 1H), 8.65 (s, 1H).

‡ The amine pK_a values for (**4**) are 11.5, 10.2, 5.6 (imidazole), <2, and <2 at I = 0.1 M ($NaClO_4$) and 25 °C.

§ *Crystal data* for (**5**): $C_{13}H_{26}N_6Ni{\cdot}2ClO_4$, M = 523.99, monoclinic, space group $P2_1/c$, a = 8.780(4), b = 14.309(7), c = 17.759(9) Å, U = 524.8 Å^3, Z = 4, D_c = 1.658 g cm^{-3}. The structure was solved by the heavy-atom method and refined using 2841 unique data $I > 2\sigma(I)$ measured on a Philips PW1100 diffractometer with Cu-K_α radiation, μ = 42.1 cm^{-1}. The final R value is 0.062.

Crystal data for (**6**) $C_{13}H_{26}N_6Ni{\cdot}2ClO_4{\cdot}CH_3CN$, M = 565.04, monoclinic, space group $P2_1/n$, a = 17.242(10), b = 12.515(7), c = 11.576(7) Å, U = 2387 Å^3, Z = 4, D_c = 1.578 g cm^{-3}. The structure was solved by the heavy-atom method and refined using 1903 unique data $I > 2\sigma(I)$ measured on a Philips PW1100 diffractometer with Cu-K_α radiation, μ = 37.7 cm^{-1}. The final R value is 0.095.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

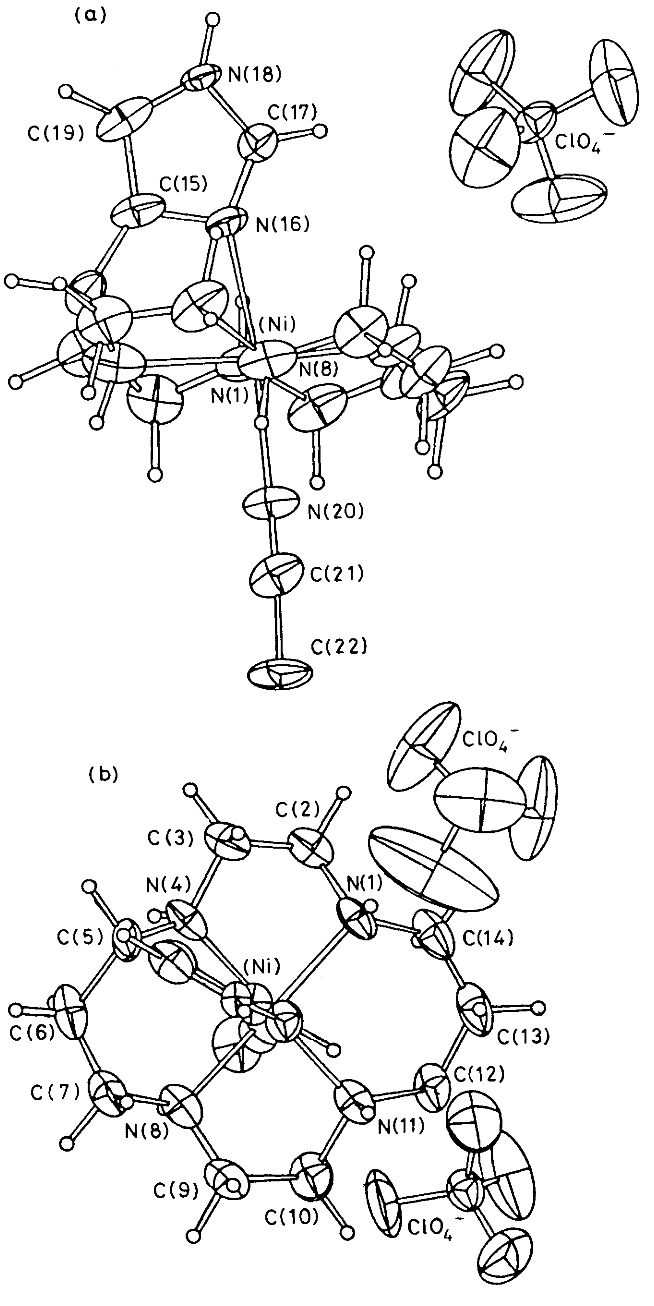
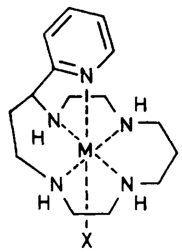
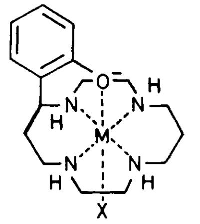


Figure 1. ORTEP drawing of complex (**6**; X = MeCN); (a) side-on view (one perchlorate anion is omitted for clarity) and (b) top view. Atoms are drawn with 30% probability ellipsoids. Important bond lengths (Å) and bond angles (°) are as follows: Ni–N(1) 2.060(11), Ni–N(4) 2.058(12), Ni–N(8) 2.121(12), Ni–N(11) 2.046(12), Ni–N(16) 2.098(9), Ni–N(20) 2.132(10); N(1)–Ni–N(4) 85.0(4), N(1)–Ni–N(16) 94.0(4), N(1)–Ni–N(20) 92.1(4), N(4)–Ni–N(8) 94.2(4), N(4)–Ni–N(16) 80.6(4), N(8)–Ni–N(16) 88.1(4), N(11)–Ni–N(16) 96.9(4), N(4)–Ni–N(20) 92.6(4), Ni–N(16)–C(15) 109.2(8).

complex (**6**) are shorter than the corresponding ones of the 'metal-out' complex (**5**). The imidazole ring stands vertically to the cyclam N_4 plane to become an axial donor. Moreover, the imidazole plane lies at an angle of 20° to the line described by the N(4)–Ni–N(11) bonds. This, in addition to the short Ni–N(16) (imidazole) distance of 2.098(9) Å, may facilitate the imidazole → metal π-donation. Similar bond lengths (2.06—2.1 Å)[5] and orientations of the imidazole ring of the proximal histidine with respect to the porphyrin plane (20—22.5°)[5] are found in haems or their models, and are recognised as serving the Im-Fe^{II} π-interaction for the *trans*-O_2 binding.[6] Our new cyclam (**4**) is thus found to be equipped with an imidazole ligand suitable for axial co-ordination.



(**7**)



(**8**)

The pyridyl-pendant cyclam complex (**7**) (X = H_2O) has an analogous crystal structure.[1] The axial bond distance is found to be significantly shorter in the imidazole-bearing cyclam than that in the pyridine case, 2.124(3) Å,[1] despite the fact that steric considerations alone (using a Dreiding model) suggest that the opposite would be more likely. Closer comparison of these crystal structures discloses a greater displacement of Ni from the mean N_4 plane (of cyclam) towards the apical base in (**6**) (0.05 Å) than in (**7**) (0.02 Å). The preferred co-ordination of acetonitrile over water for the sixth ligand (despite repeated recrystallization from H_2O, this acetonitrile is not displaced) may reflect the *trans*-imidazole π-basicity serving to favour back-bonding between Ni^{II} and the π* orbital of the MeCN.¶

The unique axial imidazole co-ordination in (**6**) affects the $Ni^{III/II}$ redox potential. Cyclic voltammetry (c.v.) shows a quasi-reversible peak at $E_{1/2}$ +0.54 V *vs.* saturated calomel electrode (s.c.e.) (0.5 M Na_2SO_4, pH 7.0, 25 °C). This lies between the value of +0.61 V for the pyridyl co-ordinated homologue (**7**) and +0.35 V for the phenol co-ordinated species (**8**), but is near to that of cyclam (without pendant) complex (+0.50 V). The cyclic voltammograms provided evidence for the conversion of (**5**) into (**6**). The folded cyclam of (**5**) is seen to rearrange rapidly to the planar cyclam of (**6**). An irreversible anodic peak at +0.69 V in the first scan of (**5**) gradually diminishes and is replaced by a new growing quasi-reversible wave at +0.54 V in the subsequent scans. The results suggest that the electrochemically generated Ni^{III} of (**5**) occupies the cyclam cavity rapidly, with conversion of the macrocyclic configuration from *cis* to *trans*.

Another effect of the destined axial co-ordination of the imidazole is seen in the O_2 binding of the Co^{II} complex at room temperature in aqueous solution. The brown solid 1 : 1 Co^{II}–O_2 complex was precipitated as the diperchlorate salt. The e.s.r. parameters in a frozen aqueous solution at 77 K are $g_{\perp}$ 2.01, $g_{\parallel}$ 2.08, $A_{\perp}{}^{Co}$ = 13.3, $A_{\parallel}{}^{Co}$ 20.0 G (G = 10^{-4} T), and are identical to those reported for paramagnetic 1 : 1 Co^{II}–O_2 adducts.[7] Without the pendant imidazole, Co^{II}(cyclam) yields only diamagnetic 2 : 1 O_2 adducts (μ-peroxo complex). In the iron complex of (**4**), $Fe^{III/II}$ has a redox potential (pH 7, *I* 0.1 M, $NaClO_4$, 25 °C) of +0.00 V *vs.* s.c.e., compared with −0.16 V of (**8**) and +0.12 V of (**7**). The Fe^{II}–(**4**) complex also

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¶ I.r. (Nujol) $\nu_{C\equiv N}$ occurs at 2320, 2290 cm^{-1}; for comparison, $\nu_{C\equiv N}$ 2300, 2270 cm^{-1} for (**7**) (X = MeCN) and 2270 cm^{-1} for (**8**) (X = MeCN).

forms an O_2 adduct, with appearance of an $O_2 \rightarrow$ Fe charge-transfer band at 344 nm, which is currently under investigation.

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References

1 E. Kimura, T. Koike, H. Nada, and Y. Iitaka, *J. Chem. Soc., Chem. Commun.*, 1986, 1322.

2 E. Kimura, T. Koike, and M. Takahashi, *J. Chem. Soc., Chem. Commun.*, 1985, 385.

3 Y. Iitaka, T. Koike, and E. Kimura, *Inorg. Chem.*, 1986, **25**, 402.

4 R. J. Sundberg and R. B. Martin, *Chem. Rev.*, 1974, **74**, 471.

5 G. B. Jameson, F. S. Molinaro, J. A. Ibers, J. P. Collman, J. I. Brauman, E. Rose, and K. S. Suslick, *J. Am. Chem. Soc.*, 1980, **102**, 3224.

6 B. R. James, 'The porphyrins. Vol. V. Physical Chemistry, Part C,' ed. D. Dolphin, Academic Press, New York, 1978, 238.

7 E. Kimura, M. Kodama, R. Machida, and K. Ishizu, *Inorg. Chem.*, 1982, **21**, 595, and references cited therein; Y. Sugiura, *J. Am. Chem. Soc.*, 1980, **102**, 5216, and references cited therein; K. Kumer and J. F. Endicott, *Inorg. Chem.*, 1984, **23**, 2447.