Molecular Recognition of the Imidazole Residue by a Dicopper(II) Complex with a Bisdien Macrocycle bearing Two Pendant Arms

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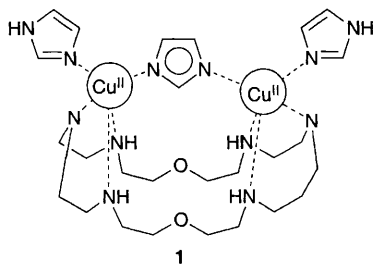
The dicopper(II) macrocyclic complex **4** tightly binds the imidazolate ion in aqueous solution at pH 9 and recognises molecules containing an imidazole fragment, *e.g.* L-histidine, in the presence of any other amino acid.

Imidazole has a definite tendency to bridge two Cu^{II} ions with the simultaneous extrusion of a proton. The imidazolate dimetallic complex which forms is stabilised by an extended electron delocalisation over the $Cu^{II}NCNCu^{II}$ framework and its solution stability can be further enhanced by prepositioning the two metal centres at the right distance through the coordination by either a polyamine ring[1–8] or a cage.[9,10]

For instance, in the system **1**, two Cu^{II} ions, encircled by a bisdien macrocycle, tightly bind a bridged imidazolate fragment and, as each metal centre possesses a further coordination site, they also bind two further imidazole molecules.[11] We considered that a specific receptor for imidazole (and for any molecule bearing an imidazole residue) could be designed by taking advantage of this coordination of the imidazolate ion to a pair of Cu^{II} ions. We chose to position the two metal centres by using a bisdien ring containing *p*-xylyl spacers, which has a shape and size similar to that of **1**. Moreover, in order to avoid the coordination of two more imidazole molecules, we appended a 2-picolyl arm to the middle nitrogen atom of each triamine moiety. Each pendant arm is expected to block the fifth coordinative position of each Cu^{II} centre, preventing the coordination of further imidazole fragments. The synthetic pathway to the bisdien macrocycle bearing two pendant arms **3** is illustrated in Scheme 1.†

The coordinating behaviour of the octadentate ligand **3** in aqueous solution was investigated through pH titration experiments. In particular, least-squares treatment of titration data[13] showed that in an aqueous solution containing 1 equiv. of **3** and 2 equiv. of Cu^{II}, the dimetallic species begins to form at pH 6.5. At pH 9, 100% of the copper(II) is present as a dinuclear complex of **2**.‡ Thus, an aqueous solution containing 1 equiv. of **3** and 2 equiv. of Cu^{II} was adjusted to pH 9 with morpholine–HNO_3 buffer and was titrated with a standard solution of imidazole. On titration, the original pale blue solution took on a progressively more intense blue colour, whereas the absorption band of the $Cu^{II}N_4$ chromophore, centred at *ca.* 640 nm, shifted at 690 and increased its intensity (ε = 320 mol^{-1} dm^3 cm^{-1}). An absorption band at around 700 nm and of similar intensity is typically observed on formation of Cu^{II}–imidazolate–Cu^{II} bridges.[15]

The profile of the spectrophotometric titration (Fig. 1) corresponds to the formation of a 1:1 receptor–imidazolate adduct (**5** in Scheme 1). Addition of even a large excess of the titrating solution does not cause any increase of the absorbance or alteration of the spectrum, indicating that further imidazole molecules are not able to remove the 2-picolyl pendant arms from their coordination sites and to modify the 1:1 stoichiometry. On least-squares treatment of the titration data,[13] a binding constant of 4.7 ± 0.1 log units was calculated for the dimetallic complex–imidazolate adduct. Analogous titration experiments were carried out with ambidentate anions displaying a special affinity towards a pair of prepositioned Cu^{II} ions (N_3^-, NCO^-, NCS^-, HCO_3^-), but the corresponding binding constants were distinctly lower than that observed for imidazolate (2.1 ± 0.1, 3.2 ± 0.1, 2.9 ± 0.1 and 2.9 ± 0.1, respectively). Interestingly, the selective affinity of the dimetallic receptor **4** is not restricted to the plain heterocycle, but can be extended to



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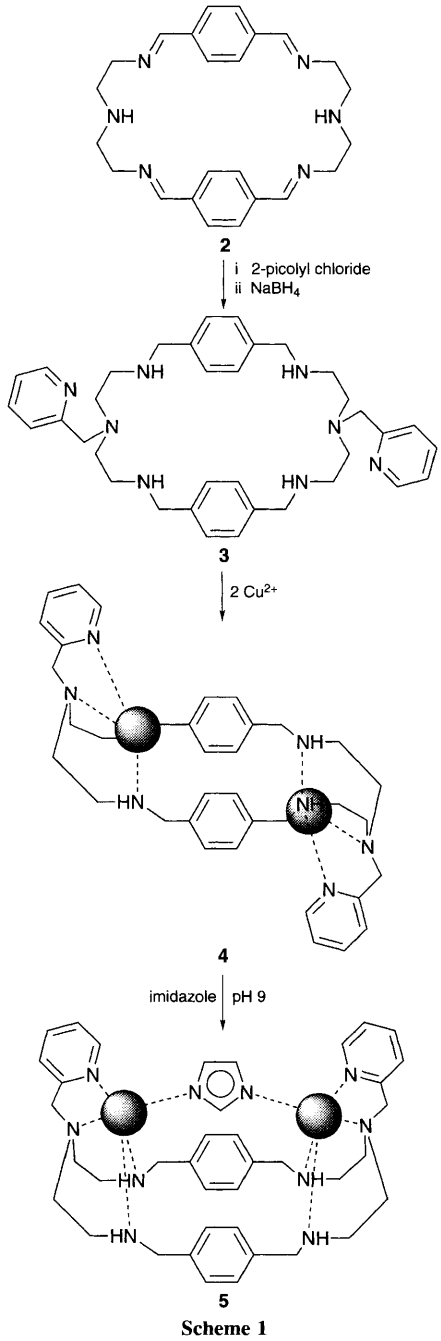


Scheme 1

any molecule containing an imidazole residue. In particular, the development of the band at 690 nm and similar titration profiles were obtained in the same conditions with histamine (log K = 4.3 ± 0.1) and with L-histidine (log K = 5.5 ± 0.1). Binding of histidine appeared especially relevant for its specific recognition among other amino acids, as shown by competition experiments. In particular, addition of 1 equiv. of a representative aminoacid (L-glycine, L-proline, L-cysteine, L-valine, L-arginine, L-serine or L-tryptophan) to a blue solution containing 1 equiv. of **4** and 1 equiv. of L-histidine caused a decrease of the intensity of the band at 690 nm of less than 5%. This behaviour is consistent with the lower binding tendencies towards the dimetallic receptor **4** of the carboxylate group, the available coordinating anion group of aminoacids. In fact, spectrophotometric titration using acetate gave log K = 2.4 ± 0.1. A binding constant of a similar value cannot ensure a serious competition with the imidazolate residue at pH 9. Thus, the dicopper(II) receptor **4** recognises L-histidine in aqueous solution in presence of any other amino acid. The specificity derives from the unique ability of the imidazole fragment to bridge a prepositioned pair of Cu^{II} cations, with the simultaneous release of a proton. Histidine binding can be visually perceived even at a 10^{-4} mol dm^{-3} level through the appearance of the blue colour and can be quantitatively determined through a simple spectrophotometric titration experiment.

It should be finally noted that the dicopper(II) complexes with the bistren cage **6** display an even stronger affinity than **4** towards imidazole. However, the incorporation of the imidazolate fragment within the cage is remarkably slow, probably due to steric effects, an undesirable feature for sensing purposes. For instance, equilibration of a 1 equiv. of the dicopper(II) cage receptor with 1 equiv. of imidazole at pH 8 takes several hours. On the other hand receptor **4**, in view of its open and flexible nature, guarantees instantaneous binding of the imidazole residue.

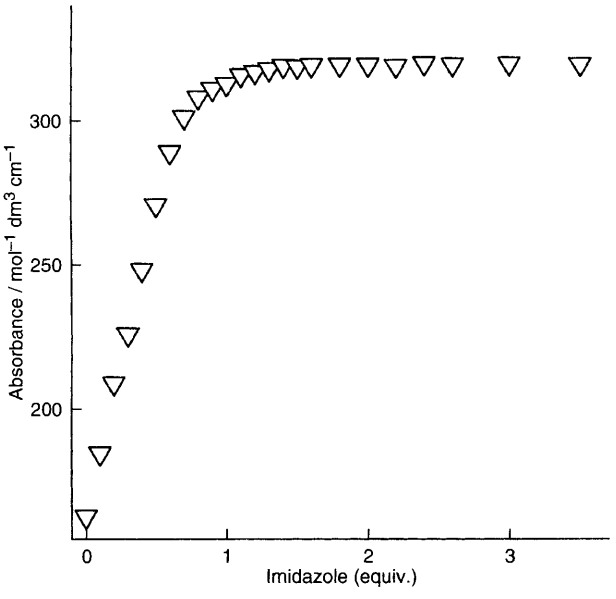
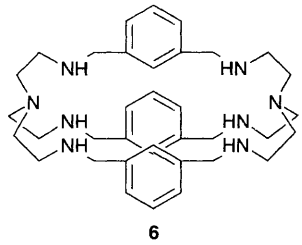


Fig. 1 Variation of the intensity of the band centred at 690 nm, corresponding to the dicopper(II) imidazolate system **5**, during the titration of **4** with imidazole, in an aqueous solution adjusted to pH 9



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This work has been supported by the European Union, within the HCM program (Network Contract n. ERBCHRXCT940492).

Received, 26th July 1995; Com. 5/04947D

Footnotes

† Compound **3** was prepared by treatment of the tetraimino macrocycle **2**[12] with 2 equivalents of 2-picolyl chloride in toluene (90 °C) in the presence of $CsCO_3$ followed by reduction of the crude product with $NaBH_4$ in methanol, and was purified as its hexaammonium salt (Found: C, 36.12, H, 4.58, N, 9.40%; $C_{36}H_{48}N_8 \cdot 6HClO_4$ requires C, 36.17, H, 4.55, N, 9.37%). ^{1}H NMR (400 MHz, $CDCl_3$, **3** as free amine) δ 7.18 (8 H, s, phenyl H), 7.10 (8 H, m, pyridine H), 3.75 (8 H, s, $HNCH_2$-phenyl), 3.58 (4 H, s, NCH_2-pyridine), 2.7 (16 H, m, NCH_2CH_2NH); IR ν_{max}/cm^{-1} 3301 (N–H), 3023, 3030 (C–H of phenyl and pyridine rings), 1608 (C=C of phenyl rings), 1592, 1580 (C=C and C=N of pyridine rings).

‡ At pH 9 the following species are present at the equilibrium: $[Cu^{II}_2L]^{4+}$, 15%; $[Cu^{II}_2L(OH)]^{3+}$, 65%; $[Cu^{II}_2L(OH)_2]^{2+}$, 20%. Coordinated H_2O and OH^- have been omitted in formula **4**. Structural formulae **4** and **5** in Scheme 1 have been sketched by taking inspiration from those obtained by molecular modelling (using the AMBER program, within the HYPERCHEM package). Interestingly, a conformational arrangement similar to that of formula **4** has been structurally characterized in the dicopper(II) complex of an octaaza macrocycle containing two ethereal pendant arms.[14]

References

1 P. K. Coughlin, S. J. Lippard, A. E. Martin and J. E. Bulkowski, *J. Am. Chem. Soc.*, 1980, **102**, 7616.
2 P. K. Coughlin and S. J. Lippard, *Inorg. Chem.*, 1984, **23**, 1446.
3 M. G. B. Drew, C. Cairns, A. Lavery and S. M. Nelson, *J. Chem. Soc., Chem. Commun.*, 1980, 1122.
4 M. G. B. Drew, M. MacCann and S. M. Nelson, *J. Chem. Soc., Dalton Trans.*, 1981, 1868.
5 C. A. Salata, M. T. Youinou and C. J. Burrows, *Inorg. Chem.*, 1991, **30**, 3454.
6 C. A. Salata, M. T. Youinou and C. J. Burrows, *J. Am. Chem. Soc.*, 1989, **111**, 9278.
7 M. G. B. Drew, S. M. Nelson and J. Reedijk, *Inorg. Chim. Acta*, 1982, **64**, L189.
8 J. O. Cabral, M. F. Cabral, M. MacCann and S. M. Nelson, *Inorg. Chim. Acta*, 1984, **86**, L15.
9 M. G. B. Drew, J. Hunter, D. J. Marrs, J. Nelson and C. Harding, *J. Chem. Soc., Dalton Trans.*, 1992, 3235.
10 J.-L. Pierre, P. Chautemps, S. Refaif, C. Beguin, A. E. Marzouki, G. Serratrice, E. Saint-Aman and P. Rey, *J. Am. Chem. Soc.*, 1995, **117**, 1965.
11 P. K. Coughlin, A. E. Martin, J. C. Dewan, W.-I. Watanabe, J. E. Bulkowski, J.-M. Lehn and S. J. Lippard, *Inorg. Chem.*, 1984, **23**, 1004.
12 D. Chen and A. E. Martell, *Tetrahedron*, 1991, **47**, 6895.
13 HYPERQUAD, A. Sabatini, A. Vacca and P. Gans, *Coord. Chem. Rev.*, 1992, **120**, 389.
14 N. A. Bailey, D. E. Fenton, P. C. Hellier, P. D. Hempstead, U. Casellato and P. A. Vigato, *J. Chem. Soc., Dalton Trans.*, 1992, 2809.
15 C. J. Harding, Q. Lu, J. F. Malone, D. J. Marrs, N. Martin, V. Mckee and J. Nelson, *J. Chem. Soc., Dalton Trans.*, 1995, 1739.