A Heteroditopic Hexa-imidazole 'Encapsulating' Podand and a Facially Differentiated Hexadentate Ligand

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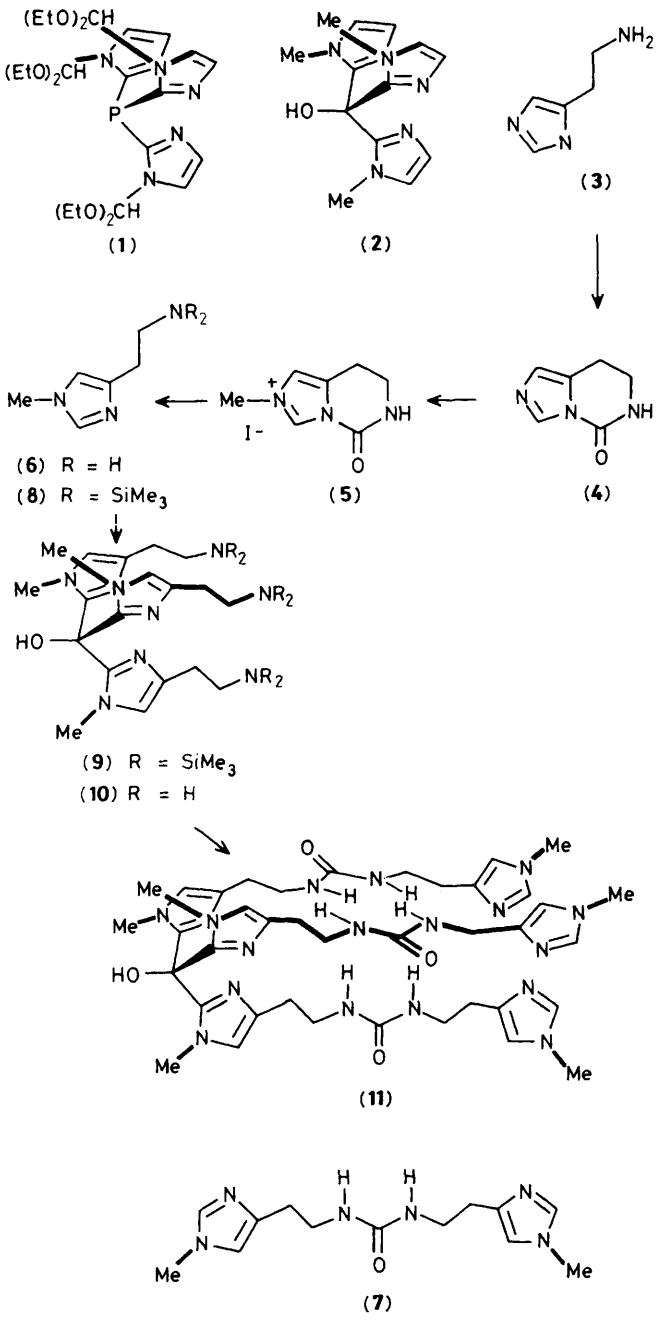
Syntheses of the facially differentiated tris-imidazole triamine (**10**) and of the novel 'hetero'-ditopic hexa-imidazole ligand (**11**), from histamine (**3**), are described.

Many metalloproteins are polyhomonuclear complexes and some (such as the Cu^{2+}–Fe^{2+} combination in cytochrome c oxidase[1]) are hetero-dimetallic. Approaches to the construction of heterodimetallic complexes include the assembly of two pre-formed complexes[2] and the use of heteroditopic ligands, but the least efficient approach is the successive metallation of each site of a homoditopic ligand. Heteroditopicity usually implies two sites that differ substantially in nature and/or geometry for binding quite different metals. In this communication, we describe the synthesis of a hybrid ligand



where heteroditopicity results from the combination of a rigid, strongly binding site with a similar but weaker site only loosely held in the same geometry. We are particularly interested in three-dimensional 'encapsulating' architectures containing imidazole binding groups for the modelling of histidine-containing metalloprotein active sites (such as in carbonic anhydrase, hemocyanin, hemerythrin, and others). Synthesis required either 2-linked 4-substituted or 4-linked 2-substituted N^{τ}-protected imidazole tripodes for tripode–tripode coupling[3] or capping. Many 2- or 4-linked poly-imidazoles such as (**1**)[4] and (**2**)[5] have been prepared by reactions of suitably protected 2-[4—7] or 4-lithio[6] derivatives with electrophiles, or reaction of 2-trimethylsilyl derivatives with phosphorus electrophiles.[7] These poly-imidazoles strongly bind Zn^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+} [pK_M values up to 11.9 for Cu^{2+} and (**2**) in aqueous medium[5]]. Unfortunately, tris-lithiation at C-5 of tripode (**1**) failed in our hands. Since 2-substituted imidazoles with α-hydrogens are incompatible with lithiation at C-4(5), we investigated the use of 4-functionalized imidazoles.

Histamine (**3**) is a convenient source of N^{τ}(1)-protected 4-functionalized imidazoles. The free base (**3**) (generated from the dihydrochloride by passing through a column of DOWEX IRA-400 OH^- form) was treated with 1.1 equiv. of *N*,*N*′-carbonyldi-imidazole ($CHCl_3$, reflux). The oily *N*-carbamoylated intermediate precipitated immediately, and slowly redissolved over 2 h to afford, after work-up by trituration of the solvent-free residue with EtOH, a 74—82% yield of the imidazopyrimidine (**4**), m.p. 215—220 °C (lit.[8] 221—222 °C). Methylation of (**4**) [1.1 equiv. of MeI, dimethylformamide (DMF), room temp., overnight] produced the methiodide (**5**), m.p. 225 °C (decomp.) (lit.[9] 225—227 °C, decomp.), in 89—90% yield after removal of solvent and simple washing of the residue with cold MeOH. Recrystallization (from MeOH–Et_2O) lowered the yield significantly. Overnight hydrolysis (refluxing 12 M HCl under Ar†) followed by neutralization (NaOH) and trituration of the dried reaction mixture with $CHCl_3$ afforded a quantitative yield of very pure N^{τ}-methylhistamine‡ (**6**) with no trace of the urea (**7**). This preparation of (**6**) has fewer steps and is more convenient than the literature method[9] and proceeds in comparable overall yield (66—74%) from (**3**) [lit. 72% for the dihydrochloride of (**6**)]. In principle, (**6**) can be lithiated at C-2 but reaction with Bu^nLi forms an anion that is insoluble in tetrahydrofuran (THF). Diprotection of the amino function was difficult, but achieved by silylation (excess of Me_3SiCl, Et_3N, CH_2Cl_2, room temp.), giving (**8**)‡ in 37% yield. The balance of the material could be recovered as (**6**) after hydrolysis with H_2O. Without purification, (**8**) was lithiated (1.05 equiv. of Bu^nLi, THF, −42 °C, under Ar, 1 h), then treated with $(EtO)_2C{=}O$ (0.33 equiv., −78 °C to room temp., overnight).§ After quenching with H_2O, isolation by extraction into hexane afforded a 93% yield of pure (**9**).‡ Other electrophiles (PCl_3,[5] PBr_3, BCl_3) failed to give hetero-analogues of (**8**) and methylation of the intermediate alkoxide of (**9**) did not occur, probably owing to the sensitivity of the N–Si bonds towards these electrophiles even at the low temperatures used. Deprotection (1% aqueous HOAc) proceeded in quantitative yield, giving the trisimidazolyl alcohol (**10**).‡ Overnight reaction with salt (**5**) and Et_3N (3 equiv. each, DMF or H_2O, room temp.) followed by neutralization (DOWEX IRA-400 OH^- form) and centrifugal chromatography¶ afforded 11—24% yields of the ligand (**11**).‡

The triamine (**10**) may be useful as a facially differentiated octahedral ligand. We intend to transform it into novel

† The urea (**7**) is produced as a contaminant when weaker acid is used (*cf.* ref. 9), and as the main product in the basic hydrolysis of the salt (**5**). We have explicitly prepared (**7**), by reaction of (**5**) with (**6**), in quantitative yield by the same procedure as was used for (**11**), to use as a homoditopic analogue of (**11**). If unprotected from the air, I_2 (from oxidation of liberated HI) accumulates along the reflux path and colours the product.

‡ All new compounds were fully characterized by n.m.r. and mass spectra and, stability permitting, microanalyses.

§ The conditions of this reaction appear to be critical. Although lithiation seemed rapid even at −78 °C, as judged by quenching experiments with D_2O, no significant yield of (**9**) was obtained if either the lithiation or the coupling was carried out at the lower temperature, or for shorter times.

¶ On a Harrison Labs. Chromatotron Model 5924T using rotors coated with 4 mm Merck-GF_{254} Al_2O_3 and 5—20 vol.% MeOH in CH_2Cl_2 as eluant.

imidazole-containing cryptands for the modelling of carbonic anhydrase. We are currently engaged in the determination of the binding constants of the individual sites of (**11**) with various divalent metal ions, and shall use differences in affinities in preparing hetero-dimetallic complexes by successive metallation steps. We also consider ligand (**11**) suitable for modelling the active site of the oxygen transport protein hemerythrin. This is composed of a μ-oxo-bis-μ-(carboxylato)-di-iron(II) core bound by five histidines and, presumably, H_2O,[10] which can reversibly exchange with O_2 as the iron centres are reversibly oxidized. Static models of this core have been prepared.[11,12] The terminal imidazole units of (**11**), being more weakly bound than the others, may undergo that exchange in a dynamic model. We have prepared complexes of ligand (**11**) and the monotopic analogue (**2**)[5] with $(Et_4N)_2Fe_2OCl_6$ and $PhCO_2Na$,[11] on which we shall report in detail elsewhere.

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