

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

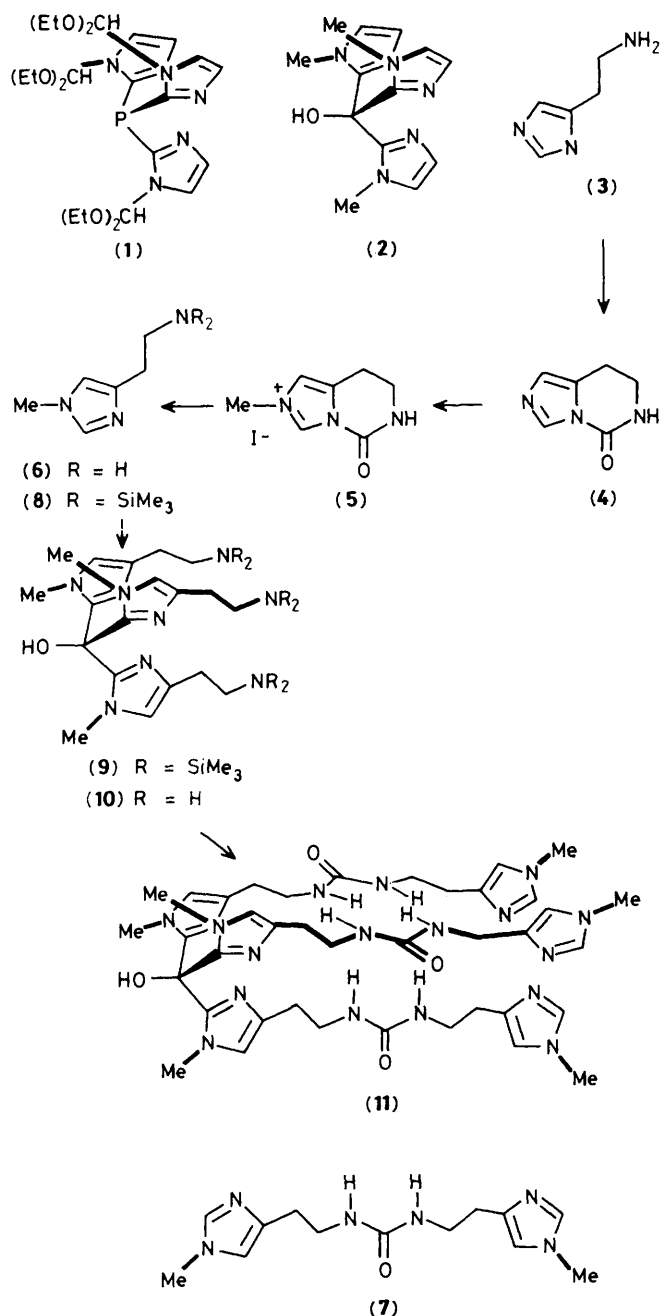
Pierre G. Potvin* and Man Hung Wong

Department of Chemistry, York University, Downsview, Ontario, Canada M3J 1P3

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 oxidase¹) are hetero-dimetallic. Approaches to the construction of heterodimetallic complexes include the assembly of two pre-formed complexes² 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^T -protected imidazole tripodes for tripod-tripode coupling³ 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-lithio⁶ 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+} [$\text{p}K_M$ values up to 11.9 for Cu^{2+} and (2) in aqueous medium⁵]. Unfortunately, tris-lithiation at C-5 of tripod (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 $N^T(1)$ -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–Et₂O) 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^T -methylhistamine[‡] (6) with no trace of the urea (7). This preparation of (6) has fewer steps and is more convenient than the literature method⁹ 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 $(\text{EtO})_2\text{C}=\text{O}$ (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-GF₂₅₄ 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 $(\text{Et}_4\text{N})_2\text{Fe}_2\text{OCl}_6$ and PhCO_2Na ,¹¹ on which we shall report in detail elsewhere.

We thank Research Corporation for a Cottrell Research Grant and the Natural Sciences and Engineering Research Council of Canada for generous financial support.

Received, 10th November 1986; Com. 1606

References

- 1 A. L. Lehninger, in 'The Mitochondrion,' Benjamin, New York, 1973.
- 2 Such as was used in the recent preparation of a cytochrome c oxidase model: R. J. Saxton and L. J. Wilson, *J. Chem. Soc., Chem. Commun.*, 1984, 359.
- 3 B. Dietrich, M. W. Hosseini, and J.-M. Lehn, *Helv. Chim. Acta*, 1985, **68**, 289.
- 4 R. S. Brown and J. Huguet, *Can. J. Chem.*, 1980, **58**, 889.
- 5 N. J. Curtis and R. S. Brown, *J. Org. Chem.*, 1980, **45**, 4038.
- 6 C. C. Tang, D. Davalian, P. Huang, and R. Breslow, *J. Am. Chem. Soc.*, 1978, **100**, 3918; R. Breslow, J. T. Hunt, R. Smiley, and T. L. Tarnowski, *ibid.*, 1983, **105**, 5337.
- 7 S. S. Moore and G. M. Whitesides, *J. Org. Chem.*, 1982, **47**, 1489.
- 8 R. Mechoulam and A. Hirschfeld, *Tetrahedron*, 1967, **23**, 239.
- 9 G. J. Durant, J. C. Emmett, R. Ganellin, A. M. Roe, and R. A. Slater, *J. Med. Chem.*, 1976, **19**, 923.
- 10 R. E. Stenkamp, L. C. Sieker, L. H. Jensen, and J. Sanders-Loehr, *Nature (London)*, 1981, **291**, 263; R. E. Stenkamp, L. C. Sieker, and L. H. Jensen, *J. Am. Chem. Soc.*, 1984, **106**, 618.
- 11 W. H. Armstrong, A. Spool, G. C. Papaefthymiou, R. B. Frankel, and S. J. Lippard, *J. Am. Chem. Soc.*, 1984, **106**, 3653.
- 12 K. Wieghardt, K. Pohl, and W. Gebert, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 727.