A New General Route to the Synthesis of Polyazamacrocyclic Ligands with Pendant Biomimetic Imidazole Groups

Massimo Di Vaira, Fabrizio Mani, and Piero Stoppioni

Dipartimento di Chimica, Università di Firenze, Via Maragliano 77, 50144 Firenze, Italy

Reaction of the secondary amine groups of 1,4,7-triazacyclononane and 1,4,7,10-tetra-azacyclododecane with 1-methyl-2-chloromethylimidazole in the presence of base in non aqueous solvent gives in high yield two new ligands having three (L^1) and four (L^2) pendant arms on the macrocyclic frame; complexes of the general formula $[ML]Y_2$ (M = Fe to Cu; L = L^1, L^2; Y = ClO_4, BPh_4) have been obtained, and the structure of $[NiL^1][ClO_4]_2$ has been established by *X*-ray crystallography.

To date several macrocyclic ligands containing pendant groups have been reported.[1] The N-functionalisation of macrocycles has been achieved either with sterically hindering groups[2] or with side arms capable of further co-ordination.[3] The latter ligands may yield homo- and hetero-dinuclear complexes in which metal ions are held in proximity so that they may behave independently or co-operatively.[4] The functionalised macrocyclic systems not only may exhibit the characteristics of polytopic ligands but also may afford an entry into the study of higher forms of molecular behaviour.[5] Only two of the functionalised macrocycles reported up to now contain pendant arms which are valuable as biomimetic donors, namely a monoimidazole cyclam[6] and a bisadenine 4,13-diaza-18-crown-6.[5] The former has been obtained through a particular synthetic strategy and the latter has been isolated in low yield from a reaction under drastic conditions. The high reactivity of the different ring positions[7] and the easy side reactions undergone by substituents on the imidazole ring, both in the free molecule and in condensed bases,[5] have prevented the development of general synthetic routes affording biologically relevant polyimidazole ligands.

We have devised a general, high yielding, route which permits imidazole groups to be introduced in preformed macrocyclic ligands bearing secondary amine groups. We report here the functionalisation of 1,4,7-triazacyclononane (**3**)[8] and 1,4,7,10-tetra-azacyclododecane (**4**)[9] with three (L^1) and four (L^2) 1-methylimidazole groups connected to the macrocycle through methylene chains. The crystal structure of the complex $[NiL^1][ClO_4]_2$ is also reported.

1-Methyl-2-chloromethylimidazole hydrochloride (**1**) (45 mmol)[10] was suspended in dry acetonitrile (50 ml) and treated at 0 °C with the stoicheiometric amount of triethylamine in acetonitrile (10 ml). Et_3NHCl was filtered off and the solution

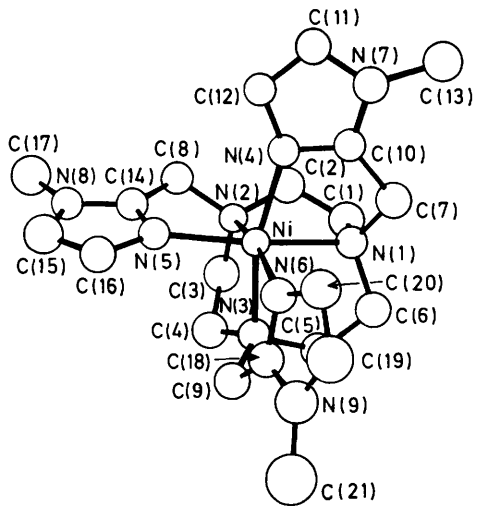
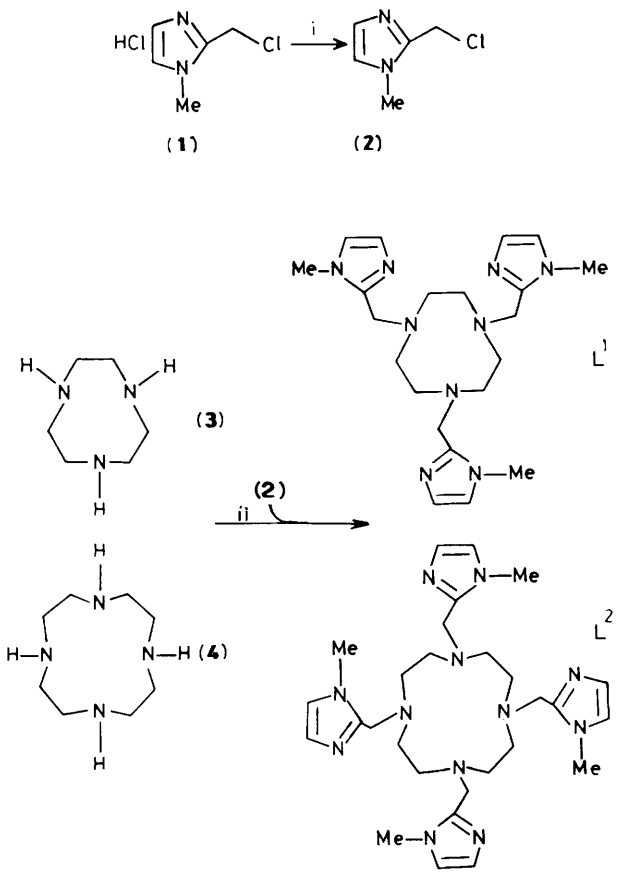


Figure 1. Selected bond lengths (Å) and angles (°) for $[Ni(L^1)][ClO_4]_2$: Ni–N(1) 2.131(5), Ni–N(2) 2.123(5), Ni–N(3) 2.110(5), Ni–N(4) 2.052(5), Ni–N(5) 2.055(5), Ni–N(6) 2.065(5); N(1)–Ni–N(2) 84.1(2), N(1)–Ni–N(3) 83.5(2), N(2)–Ni–N(3) 83.8(2), N(4)–Ni–N(5) 99.9(2), N(4)–Ni–N(6) 97.9(2), N(5)–Ni–N(6) 100.2(2).



Scheme 1. *Reagents*: i, Et_3N; ii, Et_3N, 36 h.

containing the free 1-methyl-2-chloromethylimidazole (**2**) was treated immediately with either (**3**) or (**4**) (Scheme 1). In a typical procedure a solution of (**3**) (15 mmol) and 1-methyl-2-chloromethylimidazole (stoicheiometric amount) in dry acetonitrile (40 ml) was stirred at room temperature in an inert atmosphere for 36 h in the presence of triethylamine (5% excess with respect to the stoicheiometric amount). The resulting slurry was evaporated *in vacuo* to one third of the original volume. Et_3NHCl was filtered off and the filtrate was evaporated to a viscous oil which was finally dried *in vacuo* at room temperature. A portion of the crude product (1 g), which is highly hygroscopic, was dissolved in dichloromethane (10 ml) and passed down a basic alumina column (15 × 2 cm); elution with dichloromethane–methanol (10 : 1, 200 ml) and evaporation gave pure L^1† in 74% yield. L^2† was obtained by a similar procedure in 72% yield.

The complexes $[M(L)][ClO_4]_2$ (M = Co, Ni; L = L^1, L^2) were prepared in ethanol by treating hydrated metal perchlorate and the ligand in the stoicheiometric ratio. Usually crystalline compounds were formed in a short time. The cobalt complexes must be prepared under strictly anaerobic conditions, in order to prevent formation of $[Co(L)][ClO_4]_3$. The complexes $[Fe(L)][BPh_4]_2$ (L = L^1, L^2) were prepared as above under anaerobic conditions using hydrated $FeCl_2$; the addition of a solution of $NaBPh_4$ in acetone gave the required compound. $[Cu(L^1)][BPh_4]_2$ was obtained by allowing an ethanol–acetone solution of copper(I), the ligand, and tetraphenylborate to oxidize slowly in an atmosphere of nitrogen containing traces of oxygen.

Recrystallization from ethanol–acetone led to analytically pure compounds. Crystals of $[Ni(L^1)][ClO_4]_2$ suitable for *X*-ray diffraction were obtained by slow evaporation at room temperature of a water–ethanol solution. The crystal structure of $[Ni(L^1)][ClO_4]_2$ reveals that the metal atom is co-ordinated by the six nitrogen atoms of the L^1 ligand with approximate octahedral geometry (Figure 1).‡ The three nitrogen atoms of the macrocycle span one face of the octahedron and the donor nitrogen atoms of the three methylimidazole groups span the opposite face. Differences between bond lengths and angles involving the nickel atom and the two sets of nitrogen atoms lead to a distortion from the idealized octahedral geometry along one of the threefold axes. The metal atom is tightly bound. Easier access to the metal site may be allowed by the L^2 ligand or by decreasing the number of pendant groups attached to the macrocycles.

The synthetic route reported here provides a general method for N-functionalisation of macrocyclic ligands, overcoming the quaternization reaction easily undergone by the nitrogen atoms of the chloro derivatives of heterocyclic bases.

Received, 25th July 1988; Com. 8/03022G

References

1 K. P. Wainwraight, *J. Chem. Soc., Dalton Trans.*, 1983, 1149; A. Carroy, C. R. Langick, J. M. Lehn, K. E. Matthes, and D. Parker, *Helv. Chim. Acta*, 1986, **69**, 580; M. Studer and T. A. Kaden, *ibid.*, 1986, **69**, 2081, and references therein.
2 N. W. Alcock, K. P. Balakrishnan, P. Moore, and G. A. Pike, *J. Chem. Soc., Chem. Commun.*, 1985, 1731.
3 K. Wieghardt, E. Schöffman, B. Nuber, and J. Weiss, *Inorg. Chem.*, 1986, **25**, 4877.
4 D. Parker, *J. Chem. Soc., Chem. Commun.*, 1985, 1129; B. A. Boyce, A. Carroy, J. M. Lehn, and D. Parker, *ibid.*, 1984, 1546.
5 K. Minsook and G. W. Gokel, *J. Chem. Soc., Chem. Commun.*, 1987, 1686.
6 E. Kimura, M. Shionoya, T. Mita, and Y. Iitaka, *J. Chem. Soc., Chem. Commun.*, 1987, 1712.
7 C. C. Tang, D. Davalian, P. Huang, and R. Breslow, *J. Am. Chem. Soc.*, 1978, **100**, 3918.
8 J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, 1974, **96**, 2268.
9 T. J. Atkins, J. E. Richman, and W. F. Oettle, *Org. Synth.*, 1978, **58**, 86.
10 R. G. Jones, *J. Am. Chem. Soc.*, 1949, **71**, 383.

† ^1H n.m.r. in $CDCl_3$; δ with respect to Me_4Si, coupling constants in Hz. L^1: δ 3.0 (s, 12H, CH_2), 3.8 (s, 9H, CH_3), 4.1 (s, 6H, CH_2), 6.9 (d, 3H, CH, *J* 1.9), 7.0 (d, 3H, CH, *J* 2.0). L^2: δ 3.1 (s, 16H, CH_2), 3.7 (s, 12H, CH_3), 4.0 (s, 8H, CH_2), 6.9 (d, 4H, CH, *J* 2.0), 7.1 (d, 4H, CH, *J* 2.0).

‡ *Crystal data*: $C_{21}H_{33}Cl_2N_9Ni_1O_8$, *M* = 669.17, monoclinic, space group $P2_1/a$ (No. 14), *a* = 13.587(3), *b* = 12.542(2), *c* = 16.749(3) Å, β = 90.75(2)°, *U* = 2854(1) Å^3, *T* = 293 K, *Z* = 4, D_c = 1.557 g cm^{-3}, *F*(000) = 1392, μ(Mo-K_α) = 9.29 cm^{-1}. Final *R* = 0.067 for 3376 unique, observed [$I > 3.0\sigma(I)$], absorption-corrected intensities with $5 < 2\theta < 48°$. 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.