A New Route to the Synthesis of Tetra-azamacrocyclic Ligands with a Single Pendant-arm, including a Quinquedentate Penta-azamacrocycle with a Pendant Co-ordinating Pyridyl Group

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A new route is described for the synthesis of tetra-azamacrocycles functionalised with a pendant-arm which can co-ordinate to a centrally placed metal ion; the first example of a macrocycle with a pendant pyridyl group is reported.

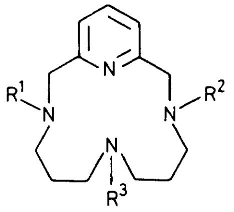
Kaden has reviewed the methods available for the synthesis of azamacrocyclic ligands containing pendant-arms with additional ligating groups,[1] and recently we have described the synthesis of tetra-azamacrocyclic ligands containing a single co-ordinating pendant-arm, based on the well known routes of Richman and Atkins, and on template methods.[2—5]

We report here a reasonably high yielding route to the synthesis of azamacrocycles of structure (**1**) (R^1 = R^2 = benzyl, R^3 = co-ordinating pendant-arm), including, we believe, the first example of a macrocycle with a pendant co-ordinating pyridyl group (R^3 = 2-pyridylmethyl). These ligands are especially interesting because of their steric

Table 1. ^1H-decoupled ^{13}C n.m.r. chemical shifts at 298 K (δ; figures in parentheses indicate numbers of carbon atoms).

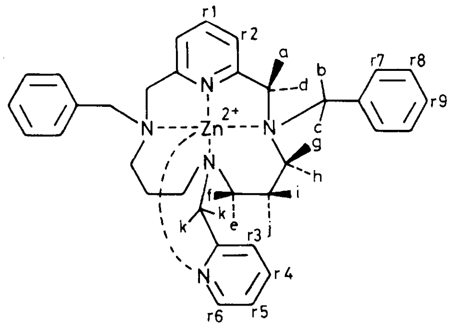
Compound	Aromatic carbons	N–CH_2–C carbons	C–CH_2–C carbons
(**1a**)	159.37(2), 136.36(1), 120.44(2)	54.47(2), 47.77(2), 46.73(2)	29.31(2)
(**1c**)	158.10(2),[a] 138.41(2), 136.87(1),[a] 128.94(4), 128.45(4), 127.36(2), 122.04(2)[a]	58.49(2), 57.99(2), 50.60(2), 49.22(2)	22.85(2)
[Zn(**1f**)]$(ClO_4)_2$	156.63(1),[a] 156.03(2),[a] 151.00(1),[a] 144.95(1),[a] 144.00(1),[a] 132.89(4 + 1), 131.51(1),[a] 130.23(4), 129.93(2), 127.50(2), 127.04(2)	61.91(2), 60.07(1), 58.36(2), 57.07(2), 54.97(2)	23.38(2)

[a] Pyridine carbons.



(**1a–f**)

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^2 = H$; $R^3 = Me$
c; $R^1 = R^2 = CH_2Ph$; $R^3 = H$
d; $R^1 = R^3 = CH_2Ph$; $R^2 = H$
e; $R^1 = R^2 = R^3 = CH_2Ph$
f; $R^1 = R^2 = CH_2Ph$; $R^3 = CH_2C_5H_4N$



(**1g**)

(**1g**): the co-ordinated pyridyl group is drawn as shown for clarity.

requirements which can force metal ions into unusual geometries, and because of their potential use in the activation of centrally placed metal ions such as Co^{2+} or Fe^{2+} towards molecular dioxygen. In the well known O_2-active complexes of Co^{2+}, a heterocyclic base such as pyridine or imidazole is often found in an axial *trans*-position to the co-ordinated O_2, and for this reason we have sought to synthesise a tetra-azamacrocycle with a pendant co-ordinating pyridyl group.

The parent macrocycle (**1a**) was synthesised from pyridine-2,6-dialdehyde and 1,5,9-triazanonane in a template reaction with nickel(II) as described recently for the related macrocycle (**1b**).[6] The purity of (**1a**) was confirmed by ^{13}C n.m.r. (Table 1). When (**1a**) (0.65 g) was stirred overnight at room temperature and under nitrogen with *ca.* 4.5 molar equivalents of benzyl chloride (1.58 g), in a two phase mixture of water (50 cm^3) and chloroform (50 cm^3) containing NaOH (0.50 g), the dibenzyl derivative (**1c**) was recovered as the major product. The chloroform layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 150 cm^3). The combined organic layers were dried with $MgSO_4$, and evaporated under vacuum with a rotary evaporator to leave a viscous oil. When this oil was triturated with petroleum ether (40—60 °C) a white solid (0.61 g; 53%) was obtained which may be recrystallised from a mixture of CH_2Cl_2 and Et_2O. The product was identified as a pure sample of the symmetrically substituted dibenzyl derivative (**1c**) by its ^{13}C n.m.r. (Table 1) and electron impact mass spectrum (*m/z* 414 as expected for $C_{27}H_{34}N_4$). The ^{13}C n.m.r. spectrum showed the absence of the unsymmetrically substituted dibenzyl derivative (**1d**), and to obtain the tribenzyl derivative (**1e**) it is necessary to use a ten-fold excess of benzyl chloride at a higher temperature (55 °C) for a longer time (*ca.* 4 days).

The ease with which the symmetrically substituted dibenzyl derivative (**1c**) is obtained in good yield is especially useful since the remaining secondary amine functionality may be readily derivatised by reactions with a range of reagents such as 2-bromoethanoic acid, *N*-tosylaziridine, acrylonitrile, or 2-picolyl chloride, or converted into linked binucleating macrocycles by reaction with 1,2-dibromoethane and similar reagents.[1,7] For example, when (**1c**) (0.5 g) was heated and stirred under nitrogen at 50 °C for 3 days in H_2O (50 cm^3) and $CHCl_3$ (50 cm^3) containing 3 equivalents of 2-picolyl chloride hydrochloride (0.59 g) and NaOH (0.3 g), work up by the method described for the dibenzyl derivative gave (**1f**) as a thick oil (0.5 g; 80%). The ^1H n.m.r. spectrum of (**1f**) and the ^{13}C n.m.r. spectrum of its zinc(II) complex (Table 1) confirmed it as the desired product, with only traces of impurities. In the room temperature ^1H n.m.r. spectrum of (**1f**), it is evident that even with the three bulky pendant-arms attached to nitrogen, N-inversion is still rapid on the n.m.r. time scale. Also, the bulky pendant-arms do not appear to hinder metal complex formation.

For example, reaction of (**1f**) with an ethanolic solution of either $[Ni(dmso)_6](ClO_4)_2$ or $[Zn(dmso)_4](ClO_4)_2$ (dmso = dimethyl sulphoxide) in a 1 : 1 molar ratio gives immediate precipitates of $[M(L)](ClO_4)_2$ [M = Ni or Zn; L = (**1f**)] as blue or white solids respectively. The blue nickel(II) complex is paramagnetic and five-co-ordinate as shown by its visible spectrum in nitromethane solution. Dissolution of the blue solid in aqueous perchloric acid gives a yellow solution of diamagnetic, square-planar $[Ni(LH)]^{3+}$, showing protonation of the pendant pyridyl group as found previously for pendant dimethylamino groups.[2—4] The ^{13}C n.m.r. spectrum of $[Zn(L)]^{2+}$ (Table 1) shows it to be a single, symmetrically substituted species with the pendant pyridyl group co-ordinated. This was confirmed by two dimensional 400 MHz ^{1}H n.m.r., and by ^{1}H nuclear Overhauser enhancement (n.O.e.) difference spectra. The latter experiments were undertaken to establish that the pendant pyridyl arm is on the same side of the macrocyclic plane as the two benzyl groups, and not on the opposite side of the macrocyclic plane as the ^{13}C n.m.r. spectrum would allow. Referring to structure (**1g**) in which the aliphatic protons are labelled a—k and the aromatic protons numbered r1—r9, the following assignments were made for the zinc(II) complex based on chemical shifts, integrals, spin–spin coupling patterns, and coupling constants: δ 8.93 (r6; d, 1H), 8.36 (r4; t, 1H), 8.27 (r1; t, 1H), 7.97 (r3; d, 1H), 7.82 (r5; t, 1H), 7.64 (r2; d, 2H), 7.44 and 7.43 (r8 + r9; m, 6H), 7.29 (r7; m, 4H), 4.73 (k; s, 2H), 4.38 (a; d, 2H), 4.05 (b; d, 2H), 3.79 (c + d; d + d, 4H), 3.57 (e; m, 2H), 3.23 (f; m, 2H), 2.98 (g; m, 2H), 2.86 (h; m, 2H), 2.47 (i; m, 2H), 2.14 (j; m, 2H). N.O.e. difference spectra were recorded with irradiation at the frequencies of resonances r6, k, b, c + d, e, f, and i. The following proximal protons were revealed by each of these experiments (irradiated resonance first, followed by enhanced resonances in parentheses): r6(b,c,r5); k(b,f,i,r3); b(r6,r7,c,g,i,k); c/d(r6,r7,r2,a,b); e(f,j); f(e,k); i(r7,b,f,k). All of these spectra are consistent with a structure in which the pendant pyridyl group and the benzyl groups are on the same side of the macrocyclic plane. It is noteworthy that irradiation of the resonances from b or c enhanced the resonance from r6, and *vice versa*, showing unequivocally that the pendant-arm is co-ordinated in this way.

Attempts to prepare a potentially sexidentate macrocycle by the reaction of (**1b**) with an excess of 2-picolyl chloride under basic conditions failed owing to quaternisation of the Me–N-group, and it is evident that the benzyl groups play an important part in preventing quaternisation from occurring.

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