A General Synthetic Route to Fully *N*-Alkylated Azamacrocycles, and an Uncommon Geometry for a Six-coordinate Nickel(II) Complex of 1,4,8,11-Tetrapropyl-1,4,8,11-tetraazacyclotetradecane (L^1). Crystal Structure of *trans*-(*R,S,R,S*)-[Ni(L^1)(NCS)$_2$]

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A two-step route to a range of fully *N*-alkylated azamacrocycles has been developed; the crystal structure of *trans*-[Ni(L^1)(NCS)$_2$] (L^1 = 1,4,8,11-tetrapropyl-1,4,8,11-tetraazacyclotetradecane) shows the nickel(II) to be six-coordinate, but with the uncommon (*R,S,R,S*)-or *trans*-(I)-set of N-configurations.

Although a few tetra-*N*-alkyl derivatives of 1,4,8,11-tetraazacyclotetradecane (cyclam) such as L^2–L^4 have been known for some time,[1–4] a convenient synthetic route to a wider range of simple *N*-alkylated azamacrocycles (*e.g.* cyclam with R = ethyl, propyl, butyl · · ·) has not been reported. Such ligands are of interest because of the effect of *N*-alkylation upon the conformations of the macrocycles in the complexes they form, and consequentially upon the coordination number and geometry of the metal ion.[1,5–7] For example, $[Ni(tmc)]^{2+}$ (tmc = L^2) can be isolated in several forms, the two most common of which are those with the (*R,S,R,S*)-[*trans*-(I)] and (*R,R,S,S*)-[*trans*-(III)] set of N-configurations.[8] These two conformations usually result in complexes which are five- and six-coordinate respectively,[1,5,6] as shown in Fig. 1 (**A**) and (**B**) (X = unidentate ligand).

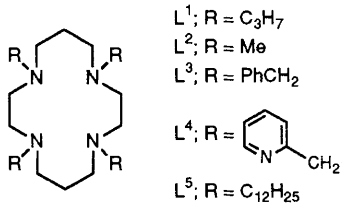
We report here the synthesis of a range of azamacrocycles with bulkier *N*–R groups, including some with very lipophilic R groups such as L^5. We also report the crystal structure of *trans*-[Ni(L^1)(NCS)$_2$] in which the metal ion is six-coordinate, but the macrocycle has adopted the *trans*-(I) geometry rather than the more usual geometry for six coordination, the *trans*-(III) form [Fig. 1(**B**)].

Direct alkylation of the secondary amino groups of azamacrocycles like cyclam with simple aliphatic alkyl halides, such as ethyl or propyl bromide, usually leads to quaternization of the N atoms, producing species with no metal ligating properties. To overcome this problem, we developed the two-step synthesis shown in Scheme 1 (R_2NH represents a secondary amine, or a secondary amino group of an azamacrocycle; thf = tetrahydrofuran). For example, cyclam was converted to L^1 in

$$R_2NH + R'COCl + Et_3N \rightleftharpoons R_2NCOR' + [Et_3NH]^+Cl^-$$

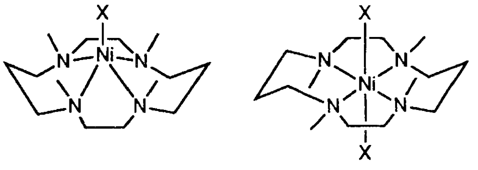
$$R_2NCOR' \xrightarrow{BH_3\cdot thf} R_2NCH_2R'$$

Scheme 1



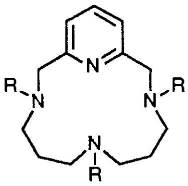
71% yield.† The generality of the method is shown by the ready preparation of the much more lipophilic macrocycle L^5, in an overall yield of 50% using dodecanoyl chloride ($R' = C_{11}H_{23}$). We have also converted 3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (L^6; R = H) to the *N*-tripropyl derivative (L^6; $R = C_3H_7$) in 60% yield by the same method. The new macrocycles L^1, L^5 and L^6 ($R = C_3H_7$) have been characterised by their ^1H and ^{13}C NMR spectra, and by their mass spectra.

Nickel(II) complexes of L^1 and L^5 were obtained by the reaction of equimolar amounts of $[Ni(dmso)_6][BF_4]_2$ or $[Ni(dmso)_6][ClO_4]_2$ (dmso = dimethyl sulphoxide) with each ligand in dry ethanol or butan-1-ol solution. Reaction of L^1 with $[Ni(dmso)_6][BF_4]_2$ in ethanol solution gave a purple precipitate, and this was filtered off, and pumped *in vacuo* for several hours to remove traces of dmso. Recrystallisation from a mixture of dry nitromethane and diethyl ether (1 : 2) gave dark purple crystals of the low-spin, diamagnetic, square-planar $[Ni(L^1)][BF_4]_2\cdot0.25Et_2O$ (89% yield). This was converted to the high-spin, paramagnetic ($\mu_{eff} = 2.5\ \mu_B$) dithiocyanate complex by stirring a solution of $[Ni(L^1)][BF_4]_2$ (0.32 mmol) with a slurry of NaSCN (86 mmol) in ethanol for 12 h. The resulting blue solid was collected by filtration and recrystallised from methanol–dmso (1 : 1) to give $[Ni(L^1)(NCS)_2]$ (83% yield). With L^5 (0.21 g, 0.24 mmol), the reaction with $[Ni(dmso)_6][ClO_4]_2$ (0.17 g, 0.24 mmol) in hot butan-1-ol (20 cm^3) was found to be slow, and the reaction was left for 12 h to ensure completion. (**CARE!** Perchlorate salts are potentially explosive.) Steric hindrance by the long alkyl chains is evident in the slow complex formation (the analogous reactions of Ni^{2+} with tmc and L^1 are rapid). On cooling, dark purple crystals were obtained which analysed‡ as $[Ni(L^5)(dmso)][ClO_4]_2$ (m.p. 101–104 °C; 0.17 g, 61%).



(**A**) *trans*-(I) (**B**) *trans*-(III)

Fig. 1



L^6

A comparison of $[Ni(tmc)(NCS)_2]$ with $[Ni(L^1)(NCS)_2]$ shows some interesting differences. Based on IR and UV-VIS spectra, $[Ni(tmc)(NCS)_2]$ has been assigned a six-coordinate *cis*-geometry, presumably with a folded (*R,R,R,R*)-tmc conformation.[1] In nitromethane solution $[Ni(tmc)(NCS)_2]$ remains six-coordinate, and is non-conducting.[1] The IR spectrum of $[Ni(L^1)(NCS)_2]$ shows two bands at 2080 and 2060 cm^{-1} indicating the presence of two coordinated thiocyanate ions. In contrast to $[Ni(tmc)(NCS)_2]$, conductivity measurements show $[Ni(L^1)(NCS)_2]$ to be a 1 : 1 electrolyte in nitromethane solution, and its visible spectrum in this solvent is as expected for a five-coordinate complex. We conclude that $[Ni(L^1)(NCS)_2]$ readily dissociates in solution to give $[Ni(L^1)NCS]^+$ and NCS^- ions, which is consistent with one relatively weak Ni–thiocyanate bond.

We undertook a single crystal X-ray structure determination to confirm this conclusion, and to establish the conformation of the macrocycle.§ The molecular geometry of *trans*-$[Ni(L^1)(NCS)_2]$ is shown in Fig. 2, together with the atomic numbering scheme and selected bond lengths and angles. The Ni is six-coordinate, with Ni–NCS bond lengths of 2.137(5) and 2.017(4) Å, confirming the presence of one strong and one weak Ni–NCS bond. The macrocycle has the *trans*-(I) conformation, with all four propyl groups on the same side of

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† A solution of cyclam (1 g, 5 mmol) and triethylamine (5 g, 50 mmol) in dry CH_2Cl_2 (50 cm^3) was added slowly, with stirring, to a cooled solution of EtCOCl (4.6 g, 50 mmol) in CH_2Cl_2 (100 cm^3). The solution was left to stir for 12 h, then washed with water (2 × 20 cm^3), dried with anhydrous $MgSO_4$, and the CH_2Cl_2 removed with a rotary evaporator to give a brown solid. Column chromatography on silica with CH_2Cl_2 removed unreacted EtCOCl; the intermediate tetrapropionamide was then eluted with methanol. The solvent was removed by rotary evaporation to give a white solid (1.85 g, 87%): ^1H NMR in $CDCl_3$: δ 1.15 (t, 12H), 1.90 (m, 4H), 2.40 (m, 8H), 3.50 (m, 16H); chemical ionisation (CI) mass spectrum: *m/z* 425 (M + 1). The tetraamide (1.77 g, 2.2 mmol) was dissolved in dry tetrahydrofuran (200 cm^3), a solution of $BH_3\cdot thf$ (40 cm^3, 42 mmol) added, and the mixture refluxed overnight under dry N_2. After cooling, the excess of $BH_3\cdot thf$ was destroyed by slow addition of methanol, and the solution evaporated with a rotary evaporator to leave a white solid. This was dissolved in butan-1-ol (30 cm^3), water (30 cm^3) and conc. HCl (80 cm^3), and refluxed for 12 h. After cooling, sodium hydroxide was added until pH ≥ 12, and the product extacted with CH_2Cl_2 (6 × 50 cm^3). The combined CH_2Cl_2 extracts were dried with anhydrous $MgSO_4$, and evaporated to give a yellow oil. This was passed through an alumina column using $CHCl_3$–MeOH (95 : 5) as eluent, and after evaporation of the solvent left pure L^1 (1.26 g, 82%) as a pale yellow oil. Using $C_{11}H_{23}COCl$ as the alkylating agent gave L^5 (1.98 g, 50% yield, from 1 g of cyclam). L^5 was isolated in the same way as L^1.

‡ C,H,N combustion analyses are consistent with the formulae quoted for the complexes.

§ *Crystal data*: $[Ni(L^1)(NCS)_2]$; $C_{24}H_{48}N_6NiS_2$; $M_r = 555.5$; a pale blue, diamond-shaped crystal of dimensions 0.66 × 0.38 × 0.23 mm was selected; monoclinic, space group $P2_1/c$, $a = 15.743(7)$, $b = 9.605(5)$, $c = 19.898(8)$ Å, $\beta = 102.03(4)°$, $U = 2942(2)$ Å^3, $Z = 4$, $D_c = 1.25$ g cm^{-3}, Mo-Kα radiation ($\lambda = 0.71969$ Å), μ(Mo-Kα) = 8.2 cm^{-1}, $T = 293$ K, $R = 0.0668$ ($R_w = 0.0862$) for 5408 unique reflections with $I/\sigma(I) \geq 2.0$.

Data were collected at 293 K with a Nicolet R3 four-circle diffractometer in the ω–2θ mode. Anisotropic thermal parameters were used for all non-H atoms. Hydrogen atoms were given fixed isotropic thermal parameters, $U = 0.07$ Å^2. Those defined by the molecular geometry were inserted at calculated positions and not refined; methyl groups were treated as CH_3 units, with their initial orientation taken from the strongest H-atom peaks in a difference Fourier synthesis. Final refinement was on F by least-squares methods, refining 298 parameters. A weighting scheme was used of the form $w = 1/[\sigma^2(F) + gF^2]$, with $g = 0.0102$, and found to be satisfactory by a weight analysis.

Atomic coordinates, bond lengths and angles, and thermal parameters have been desposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

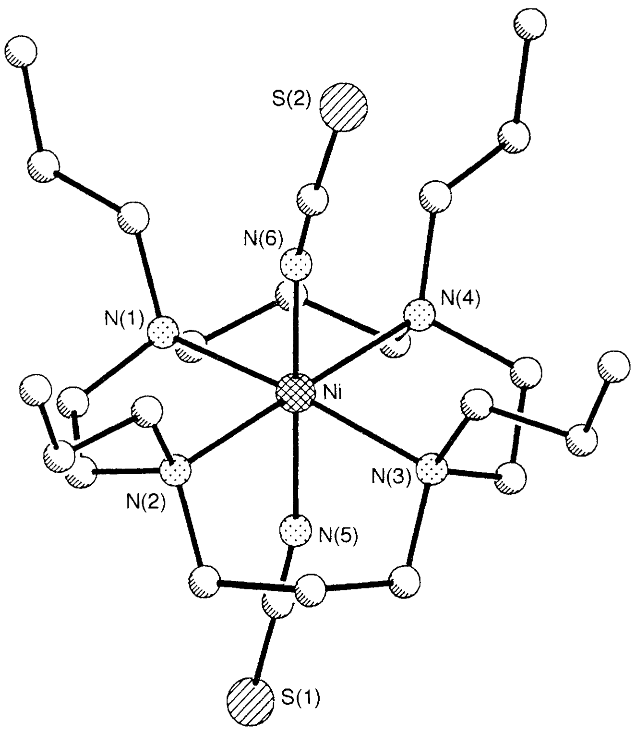

Fig. 2 X-Ray crystal structure of *trans*-(*R,S,R,S*)-[Ni(L^1)($NCS)_2$]: Ni–N(1) 2.183(5), Ni–N(2) 2.170(6), Ni–N(3) 2.170(4), Ni–N(4) 2.210(5), Ni–N(5) 2.137(5), Ni–N(6) 2.017(4) Å; N(5)–Ni–N(6) 178.5(2), N(1)–Ni–N(4) 94.8(2), N(4)–Ni–N(3) 83.2(2), N(3)–Ni–N(2) 96.5(2), N(2)–Ni–N(1) 85.3(2)°. H atoms have been omitted for clarity.

the macrocyclic plane, and with the shorter Ni–NCS bond to the thiocyanate ion flanked by the four propyl groups.

As a result of axial coordination by the second thiocyanate ion, the Ni atom is pulled back towards the centre of the macrocycle, and sits only 0.086 Å above the plane of the four macrocyclic N atoms, in the direction of the four *N*-propyl groups. In the three reported five-coordinate complexes of the type $[Ni(tmc)X]^{n+}$ [X = MeCN, Me_2NCHO(dmf), $n = 2$; X = N_3^-, $n = 1$], in which the tmc adopts the *trans*-(I) conformation, the Ni is found 0.29–0.34 Å above the plane of the four macrocyclic N atoms.[9–12] A six coordinate structure with the *trans*-(I) macrocyclic conformation has not been found previously. In *trans*-[Ni(L^1)($NCS)_2$] the average Ni–N bond distance to the four tertiary amine groups of the macrocycle [2.183(5) Å] is only slightly longer than that found in the five-coordinate Ni^{2+} complexes of tmc (2.104–2.143 Å). In low-spin square-planar complexes of $[Ni(cyclam)]^{2+}$ and $[Ni(tmc)]^{2+}$, the Ni–N distances are 1.93 and 1.99 Å, compared with a strain-free value of 1.91 Å estimated from molecular mechanics calculations.[13] The lengthening of the Ni–N bond in $[Ni(tmc)]^{2+}$ is attributed to the non-bonded repulsions between the H atoms of the *N*-methyl groups.[13] The main consequence of the ligation by the second thiocyanate ion in [Ni(L^1)($NCS)_2$] is the movement of the Ni back towards the macrocyclic plane, and the consequent decrease in the distance between the four propyl groups. For example, in $[Ni(tmc)(dmf)]^{2+}$ the C atoms of the diagonally opposed *N*-methyl groups are 5.79 Å apart, whereas the corresponding C-atoms of the N–CH_2 (propyl) groups in [Ni(L^1)($NCS)_2$] are separated by only 5.69 Å. The result is an increase in the nonbonded interactions between the four *N*-propyl groups, and like (*R,S,R,S*)-$[Ni(tmc)]^{2+}$ we find (*R,S,R,S*)-$[Ni(L^1)]^{2+}$ to be much less stable than (*R,R, S, S*)-$[Ni(cyclam)]^{2+}$ or (*R,R,S,S*)-$[Ni(tmc)]^{2+}$ where the Ni is close to the centre of the macrocyclic plane. For example, $[Ni(L^1)]^{2+}$ is rapidly hydrolysed in acidic solution.

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