Nickel(II) Complexes of Novel Tetraaza Macrocyclic Ligands bearing Pendant Donor Groups

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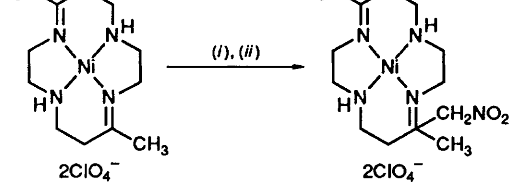
The addition of nitromethanide to two less hindered C=N double bonds of polyalkyl-1,4,8,11-tetraazacyclotetradeca-1,4,8,11-tetraenenickel(II) diperchlorate complexes, **1**, gave nickel(II) complexes, **2**, of novel macrocyclic ligands containing two co-ordinated, pendant *aci*-nitromethyl groups. Reduction of the nitro groups leads to 2,9-bis(aminomethyl) substituted nickel(II) complexes **5**. High-spin complexes **2** and **5** (pendant groups co-ordinated) and their corresponding low-spin protonated derivatives **3** and **6** (pendant groups unco-ordinated) have been prepared and characterised.

The synthesis and properties of polyaza macrocycles bearing pendant arms have attracted considerable attention in recent years.[1,2] Compounds of this class combine the properties of a rigid macrocyclic unit with those of a flexible side-chain to which the functional group is bound. The introduction of additional co-ordinating groups into a macrocycle modifies its properties, so that more stable complexes are formed or the specificity of metal-ion binding can be increased.[3] The properties of a co-ordinated metal ion (for example the redox potential) can be changed by the co-ordination of an additional ligand in the axial position.[4,5] Attachment of long lipophilic side-chains makes the macrocyclic ligand and its metal complexes soluble in organic solvents.[6,7] Another application of pendant-arm macrocycles could be to bring a metal ion and a weakly binding group close together so that an interaction between them can take place.[8] Also placing an organic substrate group in the vicinity of co-ordinated metal ion allows a metal catalysed reaction to be followed on a molecular basis and information obtained about the mechanisms of such processes.[9] Macrocyclic ligands bearing pendant aminoalkyl groups can be linked to a monoclonal antibody, allowing the specific labelling of macrocycle-conjugated antibodies with radioisotopes[10,11] and their consequent use as targeting agents in the diagnosis and therapy of cancer or other diseases.

The complexes of N-functionalised tetraaza macrocycles have been studied more extensively than their C-functionalised analogues probably due to the relative simplicity of their synthesis. However, tertiary amino groups, for steric reasons, are poorer donors than secondary amino groups in the parent macrocycle. This disadvantage can be avoided by the synthesis of C-functionalised macrocycles. Recently a facile synthesis of C-functionalised 1,4,8,11-tetraazacyclotetradecane (cyclam) derivatives has been developed which involves the nucleophilic addition of deprotonated nitromethane to one of the C=N double bonds of nickel(II) co-ordinated tetraazadiimines (Scheme 1).[12,13] Here I describe the synthesis and properties of nickel(II) complexes of C-functionalised cyclam derivatives bearing two pendant chains, by the nucleophilic addition of nitromethanide anions to two C=N bonds of 1,4,8,11-tetraazacyclotetradeca-1,4,8,11-tetraenes. To my knowledge this is the first application of cyclam tetraenes as a substrate for the synthesis of pendant arm ligands.



Scheme 1 Solvent CH_3NO_2, (*i*) NEt_3; (*ii*) $HClO_4$

Experimental

Measurements.—IR spectra (paraffin oil-mulls) were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Electronic spectra in water or 0.1 mol dm^{-3} $HClO_4$ solution were recorded in the range 200–1300 nm on a Shimadzu UV 3100 spectrometer, and in nitromethane solution in the range 350–650 nm on a Sonopan ASP-87 array spectrometer. The NMR spectra were obtained on a Bruker AM 500 spectrometer with tetramethylsilane as internal standard. Elemental analyses for compounds **2**–**7** are given in Table 1.

Materials.—The preparation of substrates **1a**, **1b**, **1d**[14] and **1c**[15] has been described elsewhere. Nitromethane, triethylamine, zinc powder, hydrochloric acid, perchloric acid and solvents were commercial materials and used without further purification.

*Synthesis.—Polyalkyl-*2,9*-bis*(aci*-nitromethyl*)-1,4,8,11*-tetraazacyclotetradeca-*4,11*-dienenickel*(II) **2**. Triethylamine (2 equiv.) was added to a saturated solution of an appropriate 1,4,8,11-tetraazacyclotetradeca-1,4,8,11-tetraenenickel(II) diperchlorate (**1a**–**1c**) in nitromethane at room temperature. After 2 h the mixture was placed in a refrigerator to complete the crystallisation and the product (**2a**–**2c**) was filtered off, washed with a small quantity of nitromethane and dried *in vacuo*. Samples for analysis were obtained upon dissolving the crude products in ethanol and crystallising them by slow addition of diethyl ether. Yields: **2a**, 30; **2b**, 75; **2c**, 70%.

*Polyalkyl-*2,9*-bis*(*nitromethyl*)-1,4,8,11*-tetraazacyclotetradeca-*4,11*-dienenickel*(II) *diperchlorates* **3a**–**3c**. Neutral complexes **2** were dissolved in ethanol and acidified with 72% perchloric acid. An immediate colour change from purple to orange occurred and the precipitated product was filtered off, washed with ethanol and dried *in vacuo*. Yield *ca.* 90%. Isomerisation and substantial decomposition was observed during recrystallisation from nitromethane.

5,7,7,12,14,14*-Hexamethyl-*2,9*-bis*(*nitromethyl*)-1,4,8,11*-tetraazacyclotetradeca-*4,11*-dienenickel*(II) *diperchlorate* **3d**. Triethylamine (6 cm^3, 0.07 mol) was added to a solution of diperchlorate complex **1d** (15 g, 0.028 mol) in nitromethane (50 cm^3). After 14 min the mixture was diluted with ethanol (250

Table 1 Elemental analyses[a] for nickel(II) complexes **2**–**7**

		Analysis (%)		
Compound		C	H	N
2a	$C_{16}H_{28}N_6NiO_4{\cdot}2H_2O$	41.4 (41.50)	7.1 (6.95)	18.4 (18.15)
2b	$C_{20}H_{36}N_6NiO_4{\cdot}2H_2O$	46.6 (46.25)	7.8 (7.75)	16.3 (16.20)
2c	$C_{16}H_{28}N_6NiO_4$	44.7 (44.95)	6.6 (6.60)	19.7 (19.25)
2c[b]	$C_{28}H_{60}Cl_2N_8NiO_{12}$	44.4 (40.50)	7.5 (7.30)	13.6 (13.50)
β-**3a**	$C_{16}H_{30}Cl_2N_6NiO_{12}$	30.7 (30.60)	5.1 (4.80)	13.3 (13.40)
3b	$C_{20}H_{38}Cl_2N_6NiO_{12}$	35.0 (35.10)	6.0 (5.60)	11.9 (12.30)
α-**3c**	$C_{16}H_{30}Cl_2N_6NiO_{12}$	30.7 (30.60)	4.8 (4.80)	13.1 (13.40)
β-**3c**	$C_{16}H_{30}Cl_2N_6NiO_{12}$	30.3 (30.60)	4.8 (4.80)	13.5 (13.40)
β-**3d**	$C_{18}H_{34}Cl_2N_6NiO_{12}$	32.9 (32.95)	5.4 (5.20)	12.9 (12.80)
4d	$C_{17}H_{31}Cl_2N_5NiO_{10}$	34.4 (34.30)	5.3 (5.25)	11.8 (11.75)
5b	$C_{20}H_{42}Cl_2N_6NiO_8{\cdot}2H_2O$	36.6 (36.40)	7.1 (7.00)	12.6 (12.75)
5d	$C_{18}H_{38}Cl_2N_6NiO_8$	36.2 (36.25)	6.6 (6.45)	14.2 (14.10)
6b	$C_{20}H_{44}Cl_4N_6NiO_{16}$	29.6 (29.10)	5.3 (5.35)	10.3 (10.20)
6d	$C_{18}H_{39}Cl_3N_6NiO_{12}$	31.2 (31.10)	6.0 (5.65)	12.2 (12.05)
7d	$C_{32}H_{46}Cl_2N_6NiO_{10}$	47.7 (47.80)	5.7 (5.75)	10.6 (10.45)

[a] Required values given in parentheses. [b] **2c**·2($NHEt_3ClO_4$).

cm^3), acidified with perchloric acid (72%, 10 cm^3) and placed in a refrigerator to complete the crystallisation. An orange product **3d** (12 g, 65%) was filtered off and dried *in vacuo*. A sample for analysis was obtained by recrystallisation from nitromethane.

5,7,7,12,14,14-*Hexamethyl*-2-*nitromethyl*-1,4,8,11-*tetraazacyclotetradeca*-4,8,11-*trienenickel*(II) *diperchlorate* **4d**. Complex **3d** (10 g) was dissolved in boiling acetonitrile (100 cm^3), precipitated upon addition of ethanol (300 cm^3) and filtered off. The filtrate was allowed to evaporate slowly at room temperature. After *ca.* two weeks an orange crystalline decomposition product **4d** (0.3 g) was filtered off, washed with ethanol and dried *in vacuo*.

2,9-*Bis*(*aminomethyl*)-5,7,7,12,14,14-*hexamethyl*-1,4,8,11-*tetraazacyclotetradeca*-4,11-*dienenickel*(II) *diperchlorate* **5d** *and* 2-(*aminomethyl*)-9-(*ammoniomethyl*)-5,7,7,12,14,14-*hexamethyl*-1,4,8,11-*tetraazacyclotetradeca*-4,11-*dienenickel*(II) *triperchlorate* **6d**. Concentrated hydrochloric acid (11 cm^3) was added dropwise to a vigorously stirred mixture of zinc powder (3.5 g, 0.054 mol) and complex **3d** (3.5 g, 0.0054 mol) in acetonitrile at room temperature. After *ca.* 2 h, when all the zinc had dissolved, the mixture was diluted with water (300 cm^3) and adsorbed on a Dowex 50WX2 cation-exchange column (H$^+$ form). The column was washed with 1 mol dm^{-3} HCl (500 cm^3) and eluted with 3 mol dm^{-3} HCl. The orange eluate was evaporated to dryness, dissolved in water and absorbed on an SP Sephadex C-25 column. The column was washed with water and eluted with 0.1 mol dm^{-3} trisodium citrate. A violet band was collected, adsorbed on a Dowex 50WX2 column and after washing with 1 mol dm^{-3} HCl was eluted with 3 mol dm^{-3} HCl. The orange solution was evaporated to dryness, dissolved in 1 mol dm^{-3} $HClO_4$ and neutralised with NaOH (50%). After cooling the mixture, violet crystals of **5d** were filtered off, washed with water and recrystallised from water. Yield 1.4 g (44%).

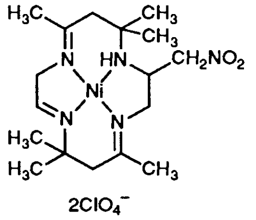
Complex **5d** (0.60 g, 0.0001 mol) was dissolved in ethanol–methanol (1:1) (50 cm^3) and acidified with perchloric acid (72%, 0.2 cm^3). After slow evaporation of the solvent orange crystals of the triperchlorate **6d** were collected. Yield 0.67 g (96%).

2,9-*Bis*(*aminomethyl*)-7,14-*diisopropyl*-5,12-*dimethyl*-1,4,8,11-*tetraazacyclotetradeca*-4,11-*dienenickel*(II) *diperchlorate* **5b** *and* 2,9-*bis*(*ammoniomethyl*)-7,14-*diisopropyl*-5,12-*dimethyl*-1,4,8,11-*tetraazacyclotetradeca*-4,11-*dienenickel*(II) *tetraperchlorate* **6b**. Complexes **5b** and **6b** were obtained from **3b** and **5b** respectively following the same procedures as above. Yields *ca.* 25 and 95% respectively.

2,9-*Bis*[(*benzoylamino*)*methyl*]-5,7,7,12,14,14-*hexamethyl*-1,4,8,11-*tetraazacyclotetradeca*-4,11-*dienenickel*(II) *diperchlorate* **7d**. An excess of benzoyl chloride (0.28 g, 0.002 mol) was added to a solution of the diperchlorate **5d** (0.30 g, 0.0005 mol) and triethylamine (0.20 g, 0.002 mol) in acetonitrile (10 cm^3). The mixture was stirred for 30 min, diluted with ethanol (20 cm^3) and left in a refrigerator to crystallise. Orange crystals of **7d** were filtered off and recrystallised from acetonitrile. Yield 0.20 g (50%).

Results and Discussion

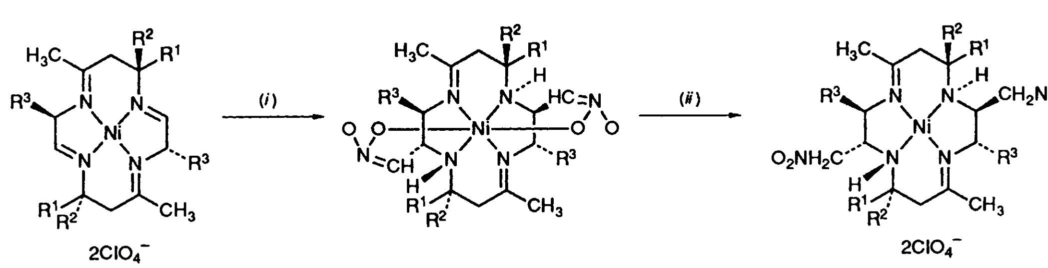
Synthesis.—In nitromethane solution in the presence of base *meso*-polyalkyl-1,4,8,11-tetraazacyclotetradeca-1,4,8,11-tetraenenickel(II) diperchlorates **1a**–**1c** add two nitromethanide anions to the two less hindered C=N groups to give the sparingly soluble, neutral bis(*aci*-nitromethyl) derivatives **2a**–**2c** (Scheme 2). The neutral complexes **2** are soluble in water and alcohols, and slowly decompose in solution. The raw product **2c** was contaminated with triethylammonium perchlorate and after crystallisation from an aqueous methanol solution crystals of **2c**·2($NHEt_3ClO_4$) suitable for X-ray analysis were obtained.[16] Upon protonation with perchloric acid the paramagnetic complexes **2** form the orange, diamagnetic, square-planar diperchlorates **3**. The 5,7,7,12,14,14-hexamethyl tetraene **1d** reacts with nitromethamide to form a nitromethane-soluble product which was not isolated, but which after the addition of perchloric acid was transformed into the diperchlorate **3d**. Only single isomers of **2** were isolated from the reaction mixtures. However, isomerisation of the secondary amino groups of the macrocycle in perchlorates **3a**, **3c** and **3d** occurred during crystallisation from nitromethane solutions to give the β and γ isomers. Slow elimination of nitromethane with formation of monosubstituted macrocycles was observed during NMR experiments [**3b** in $(CD_3)_2SO$ and **3d** in CD_3CN]. The monosubstituted decomposition product **4d** was isolated from the acetonitrile–ethanol filtrate after crystallisation of **3d**.



$2ClO_4^-$

4d

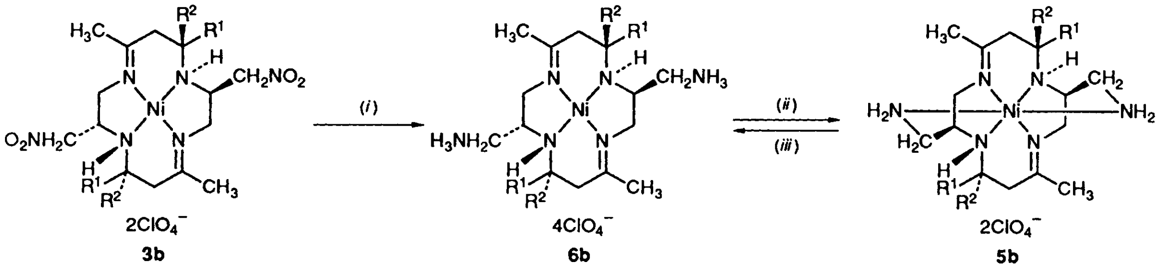
Reduction of the nitro groups in complexes **3** with zinc powder and hydrochloric acid produced the 2,9-bis(amino-



$2ClO_4^-$ $2ClO_4^-$

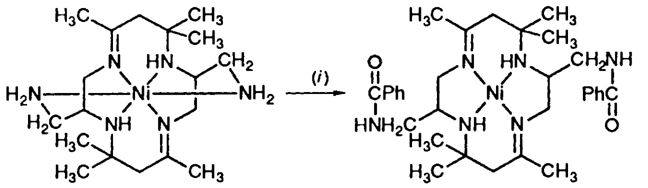
1a $R^1 = CH_3, R^2 = R^3 = H$ **2a** α-**3a**
1b $R^1 = CH(CH_3)_2, R^2 = R^3 = H$ **2b** **3b**
1c $R^1 = R^2 = H, R^3 = CH_3$ **2c** α-**3c**
1d $R^1 = R^2 = CH_3, R^3 = H$ α-**3d**

Scheme 2 (*i*) CH_3NO_2, NEt_3; (*ii*) $HClO_4$



$2ClO_4^-$ $4ClO_4^-$ $2ClO_4^-$
3b **6b** **5b**
3d **6d*** **5d**

Scheme 3 (*i*) Zn–HCl; (*ii*) NaOH; (*iii*) $HClO_4$ 2-NH_2CH_2 instead of 2-NH_3CH_2 and $3ClO_4^-$



$2ClO_4^-$ $2ClO_4^-$
5d **7d**

Scheme 4 (*i*) C_6H_5COCl, NEt_3

methyl)-substituted purple complexes **5**, which are readily protonated with perchloric acid to give the orange, square-planar, diamagnetic species **6** (Scheme 3).

The ability to use the co-ordinating, primary pendant amino groups for further derivatisation was checked by treating **5d** with benzoyl chloride. The expected orange diamide **7d** was formed in acetonitrile solution, in the presence of triethylamine at room temperature (Scheme 4).

Infrared Spectra.—The characteristic IR absorption bands for all the compounds isolated are given in Table 2. For **2**–**7** the N–H stretching absorption bands of the co-ordinated secondary amino groups were observed in the region 3131–3287 cm^{-1}. Two additional absorption bands at *ca.* 3310 and 3360 cm^{-1} in the spectra of complexes **5** were assigned to co-ordinated primary amino groups since they disappeared upon protonation as shown in the spectra of compounds **6**. A single absorption band due to the secondary amino group stretching vibration (3213 cm^{-1}) and a single band arising from amide N–H stretching (3419 cm^{-1}) were observed for the diamide **7d**. Intense C=N stretching aborption bands appeared near 1680 and 1650 cm^{-1} for the octahedral (**2** and **5**) and square-planar (**3**, **4**, **6** and **7d**) complexes, respectively. A broad, medium intensity band at *ca.* 1550 cm^{-1} assigned the C=N stretching vibration of the *aci*-nitromethyl groups in the neutral complexes **2** disappeared upon protonation and a strong NO_2-stretching absorption band at *ca.* 1560 cm^{-1} appeared in the spectra of complexes **3** and **4**. Very strong, broad bands occurring at *ca.* 1100 and *ca.* 625 cm^{-1} were characteristic of a non-co-ordinated perchlorate anion.

Table 2 Characteristic infrared absorption bands (cm^{-1}) of complexes **2**–**7** in Nujol

Compound	ν_{N-H}	ν_{NO_2}	$\nu_{C=N}$	$\nu_{C=NO_2^-}$	$\nu_{ClO_2^-}$	$\delta_{ClO_4^-}$
2a	3211	—	1678	1558	—	—
2b	3211	—	1674	1547	—	—
2c	3210	—	1670	1549	—	—
2c[a]	3287	—	1667	1564	1091	625
β-**3a**	3195	1559	1655	—	1093	624
3b	3131	1560	1650	—	1093	624
α-**3c**[b]	3216	1558	1640	—	1088	625
β-**3c**[c]	3220	1566	1646	—	1083	625
β-**3d**	3202	1561	1651	—	1108	626
4d[d]	3206	1568	1650	—	1099	624
5b	3358, 3307, 3255	—	1679	—	1098	624
5d	3368, 3308, 3277	—	1671	—	1094	623
6b	3189	—	1644	—	1106	627
6d	3188, 3108(sh)	—	1664	—	1093	625
7d[e]	3419, 3213	—	1645	—	1118	625

[a] **2c**·2($NHEt_3ClO_4$); ν_{N^+-H} broad absorption band at 2300–2600 cm^{-1}. [b] Three characteristic weak bands in the region 1200–1300 cm^{-1} at 1291, 1251 and 1224 cm^{-1}. [c] Five characteristic weak bands in the region 1200–1300 cm^{-1} at 1280, 1264, 1244, 1235 and 1222 cm^{-1}. [d] $\nu_{C=N}$ of five-membered ring at 1670 cm^{-1}. [e] $\nu_{C=O}$ at 1665 cm^{-1}.

Ultraviolet and Visible Spectra.—The change in spin multiplicity resulting from pH-induced ligand rearrangement due to the acid–base equilibrium involving the pendant functional groups was reflected in the electronic spectra of complexes **2**, **3**, **5** and **6** (Table 3). At neutral pH several weak absorption bands were observed in the visible region of the spectra of complexes **2** and **5**. These indicate that the Ni^{II} ion is in a tetragonally distorted octahedral environment[17] with the

Table 3 Electronic spectral data for the nickel(II) complexes **2**–**7** [λ/nm (ε/dm^3 mol^{-1} cm^{-1})]

Compound	Charge transfer	d–d
2a[a]	232 (13 700)	326(sh) (269), 650(sh) (4.0), 961(br) (2.9), 1160 (1.5)
2b[a]	231 (12 360)	326(sh) (156), 640(sh) (6.7), 960(br) (4.4), 1153 (3.7)
2c[a]	232 (12 950)	326(sh) (288), 647(sh) (5.6), 922(br) (3.8), 1151 (2.4)
β-**3a**[b]		451 (87)
3b[b]		448 (80)
α-**3c**[b]		441 (69)
β-**3c**[b]		432 (73)
β-**3d**[b]		432 (78)
4d[b]		439 (91)
5b[a]	239(sh) (2025)	325(sh) (135), 476 (21), 780(br) (12), 1153 (10)
5d[a]	242(sh) (1380)	330(sh) (114), 485 (8.6), 784(br) (12), 1154 (2.5)
6b[c]	219 (13 050), 276 (4040)	446 (113)
6d[c]	219 (11 630), 271 (3210)	435 (92)
7d[a]	230 (31 640), 273 (6040)	439 (114), 441 (99)[b]

sh = shoulder, br = very broad. [a] In water. [b] In MeNO$_2$. [c] In 0.1 mol dm^{-3} HClO$_4$.

Table 4 Carbon-13 NMR data (δ) for complexes **3**, **4d**, **6** and **7d** (125.7 MHz, SiMe$_4$)

		CH$_3$			CH$_2$N	Ring C atoms				
Compound	Solvent	5,12	R		2,9	2,9	3,10	5,12	6,13	7,14
β-**3a**	CD$_3$CN	25.2	16.1		72.7	45.4	56.4	182.8	44.5	54.0
3b[a,b]	(CD$_3$)$_2$SO	25.9	14.7	20.2	74.3	56.5	57.1	191.1	40.2	57.3
α-**3c**[a]	CD$_3$NO$_2$	22.3	17.6		75.5	61.3	62.5	185.7	37.9	40.9
β-**3c**[a]	(CD$_3$)$_2$SO	22.5	21.2		76.1	66.2	67.4	187.6	39.9	47.9
γ-**3c**[c]	CD$_3$NO$_2$	21.0	17.6		75.2	61.1	62.3	185.7	37.9	40.7
		23.6	20.5		75.4	63.4	65.2	182.5	38.2	45.8
β-**3d**[a]	(CD$_3$)$_2$SO	22.1	25.3[d]	27.3[e]	75.7	51.9	60.1	183.0	52.6	55.7
4d	(CD$_3$)$_2$SO	22.7	25.3	25.0	75.9	50.5	59.2	184.5	52.6	55.7
		24.5	25.7	26.3		173.5	64.1	185.0	52.0	52.7
6b[f]	(CD$_3$)$_2$SO	25.3	14.4	19.7	35.2	53.4	54.4	188.0	38.5	54.3
6d[a]	(CD$_3$)$_2$SO	23.7	28.0[d]	27.4[e]	42.7	53.7	60.3	184.6	53.3	57.8
7d[g]	(CD$_3$)$_2$SO	22.7	26.0	26.9	41.3	52.0	60.2	181.6	55.3	55.4

[a] Assignments confirmed by two-dimensional ^{1}H–^{13}C chemical shift correlation NMR spectra. [b] CH of isopropyl groups at δ 28.0. [c] Not isolated, obtained upon dissolution of isomer β-**3c** in (CD$_3$)$_2$SO. [d] Equatorial. [e] Axial. [f] CH of isopropyl groups at δ 25.7. [g] Broad, amide C=O groups at δ 167.3; aromatic C atoms at δ 127.3, 128.4, 133.7 and 133.7.

macrocycle occupying four 'equatorial' co-ordination positions, whereas the 'axial' positions are taken up by the pendant functional groups. Under acidic conditions, the pendant amino groups (complexes **6**) or *aci*-nitromethyl groups (complexes **3**) are protonated leaving the Ni^{II} ion in a square-planar configuration. The single absorption band at *ca.* 450 nm is characteristic of such co-ordination patterns as exemplified by the parent polyalkyl-1,4,8,11-tetraazacyclotetradeca-4,11-dienenickel(II) complexes.[15,18,19] The diamido substituted complex **7d** exists in a square-planar configuration with non-co-ordinated pendant arms at neutral pH.

NMR Spectra and Structures.—Inspection of Dreiding models shows that the axial co-ordination of pendant *aci*-nitro or amino groups is possibly only if the five-membered chelate rings adopt an 'envelope' conformation with carbon atoms C^2 and C^9 lying on opposite sides of the NiN$_4$ plane. The expected geometry is as shown in Fig. 1 and is supported by a preliminary X-ray structural analysis[16] for the complex **2c**·2(NHEt$_3$ClO$_4$).

Under acidic conditions the co-ordinated *aci*-nitromethyl groups are protonated and transformed into nitromethyl groups having very poor donor properties. Therefore, on protonation with perchloric acid, complexes **2** give orange, diamagnetic complexes **3**. An important stereochemical feature of square-planar 1,4,8,11-tetraazacyclotetradeca-4,11-dienenickel(II) complexes is the chirality of the nitrogen atoms of the co-ordinated secondary amino groups (N^1 and N^8), which renders N-*meso* and N-*racemic* modifications possible.[19] The configuration of the secondary nitrogen atoms in nickel(II) complexes of 1,4,8,11-tetraazacyclotetradeca-4,11-diene derivatives at room temperature, in the presence of perchloric acid usually remains unchanged.[15,19] Therefore, the configuration of

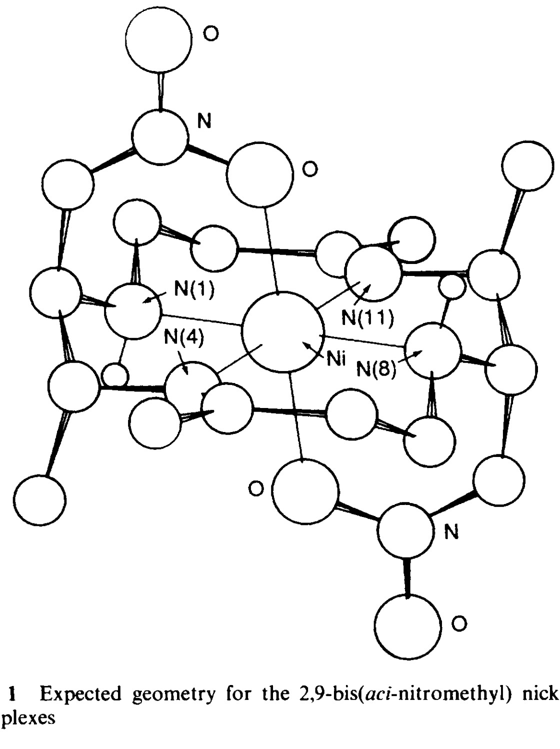


Fig. 1 Expected geometry for the 2,9-bis(*aci*-nitromethyl) nickel(II) complexes

Table 5 Proton NMR data for nickel(II) complexes **3**, **4d**, **6** and **7d** (500.14 MHz, $\mathrm{SiMe_4}$, J in Hz)

Compound	**α-3a**[a]	**β-3a**[b]	**3b**	**α-3c**[b]	**β-3c**[a]	**γ-3c**[b]	
δ (5,12-$\mathrm{CH_3}$)	2.32 (s)	2.14 (s)	2.34 (s)	2.19 (s)	2.28 (s)	2.02 (s)	2.09 (s)
(A)	5.28 (dd)	4.82 (dd)	5.27 (dd)	5.34 (dd)	4.68 (dd)	5.33 (dd)	4.74 (dd)
δ (2,9-$\mathrm{CH_2}$)							
(B)	5.44 (dd)	4.89 (dd)	5.56 (dd)	5.72 (dd)	4.84 (dd)	5.72 (dd)	4.83 (dd)
J_{AB}	13.9	15.2	13.9	15.0	15.7	15.0	16.8
δ ($\mathrm{H^{2,9}}$)		3.64 (br)	3.71 (br m)	3.19 (m)	3.42 (m)	3.23 (dd)	3.25 (br)
J ($\mathrm{H^2H^{3a}}$)[c]		≈8.0	0	—	—	—	—
J ($\mathrm{H^2H^{3e}}$)[d]		4.0	≈4.0	0	1.1	0	<2.0
J ($\mathrm{H^2H^1}$)		<3.0	≈2.0	3.1	≈1.8	<3.0	<2.0
J ($\mathrm{H^2H^A}$)	2.8	4.0	2.7	4.7	8.1	3.1	4.6
J ($\mathrm{H^2H^B}$)	8.7	3.3	9.0	6.0	3.7	9.1	6.0
δ ($\mathrm{H^{3a,10a}}$)		3.23 (br m)[e]	3.55 (br d)[f]	—	—	—	—
δ (3,10-$\mathrm{CH_3{}^a}$)		—	—	1.27 (d)	1.96 (d)	1.27 (d)	1.83 (d)
J ($\mathrm{H^{3a}H^{3e}}$)		14.8	14.5	6.9	7.0	6.9	6.9
δ ($\mathrm{H^{3e,10e}}$)		3.95 (dd)	3.73 (d)	3.85 (q)	4.08 (dq)	3.88 (q)	3.85 (q)
δ ($\mathrm{N^{1,8}H}$)		5.01 (br)	14.45 (br d)	4.58 (br m)	3.86 (br d)	4.50 (br d)	5.02 (d)
J ($\mathrm{H^1H^{14a}}$)		—	11.0	10.9	12.0	≈8.5	12.0
J ($\mathrm{H^1H^{14e}}$)		<3.0	—	<2.0	<2.0		<2.0
δ ($\mathrm{H^{6a,13a}}$)		2.65 (br d)[e]	2.81 (m)[f]	2.66 (m)	3.01 (m)	≈2.60–2.80 (m)	
J ($\mathrm{H^{6a}H^{6e}}$)		19.0	17.4	18.9	20.0	19.6	
J ($\mathrm{H^{6a}H^{7a}}$)		—	9.5	12.2	10.5		11.7
J ($\mathrm{H^{6a}H^{7e}}$)		≈2.0	—	3.5	5.5	0	
δ ($\mathrm{H^{6e,13e}}$)		2.85(d)	2.98 (d)	2.76 (d)	3.28 (m)	2.97 (dd)	≈2.7 (m)
J ($\mathrm{H^{6e}H^{7e}}$)		0	—	0	≈2.5	0	
J ($\mathrm{H^{6e}H^{7a}}$)		—	0	0	≈3.8	3.3	3.8
δ ($\mathrm{H^{7a,14a}}$)		—	2.89	2.45 (m)	4.35 (m)	≈2.65 (m)	4.13 (m)
δ (7,14-$\mathrm{CH_3}$)		1.71 (d)	—	—	—	—	—
J ($\mathrm{H^{7a}H^{7e}}$)	6.5	6.0	≈3.5	10.6	12.0		11.4
δ ($\mathrm{H^{7e,14e}}$)		3.14 (m)	—	2.06 (m)	3.03 (m)	≈2.5 (m)	≈2.6 (m)
δ (7,14-R)[g]	1.32 (d)	—	0.90 (d, J 6.8, Me) 1.06 (d, J 6.8, Me) 2.23 (m, C*H*$\mathrm{Me_2}$)	—	—	—	—

	α-3d[b]	**β-3d**[b]	**4d**[b]		**6b**[b,h]	**6d**[a,h]	**7d**[b,i]
δ (5,12-$\mathrm{CH_3}$)	2.03 (br s)	2.04 (s)	2.11 (s)	2.23 (s)	2.27 (s)	2.22 (s)	2.04 (br s)
(A)	4.85 (br d)	4.68 (dd)	—	4.74 (dd)	3.28 (m)	3.52 (m)	
δ (2,9-$\mathrm{CH_2}$)							
(B)	5.45 (br d)	4.78 (dd)	—	5.02 (dd)	3.73 (m)	3.90 (m)	3.72 (br m)
J_{AB}	15.0	16.2	—	15.9	12.7		
δ ($\mathrm{H^{2,9}}$)		3.79 (br m)	7.93 (s)	3.8 (br m)	2.93 (d)	3.51 (m)	3.13 (br m)
J ($\mathrm{H^2H^{3a}}$)[c]		0	0	5.0	<1.0	9.5	
J ($\mathrm{H^2H^{3e}}$)[d]		0	—	0	<1.0	5.2	
J ($\mathrm{H^2H^1}$)		<2.0	—	<2.0	<1.0	8.3	
J ($\mathrm{H^2H^A}$)		8.0	—	4.0	<1.0		
J ($\mathrm{H^2H^B}$)		3.2	—	7.1	11.7		
δ ($\mathrm{H^{3a,10a}}$)		3.811 (br d)[j]	4.58 (d)	4.07 (br dd)[k]	3.18 (br d)	3.70 (br m)[l,m]	3.4 (br)
δ (3,10-$\mathrm{CH_3{}^a}$)		—	—	—	—	—	—
J ($\mathrm{H^{3a}H^{3e}}$)		14.2	11.9	13.8	14.7	14.2	
δ ($\mathrm{H^{3e,10e}}$)		3.53 (d)	4.44 (d)	3.63 (d)	3.55 (br d)	4.13 (dd)	≈3.4b
δ ($\mathrm{N^{1,8}H}$)		5.23 (s)	—	5.23 (s)	5.10 (br d)	4.25 (d)	5.07 (br d)
J ($\mathrm{H^1H^{14a}}$)		—	—	—	7.5	—	—
J ($\mathrm{H^1H^{14e}}$)		—	—	—	—	—	—
δ ($\mathrm{H^{6a,13a}}$)		2.69 (dd)[j]	2.85 (d)	2.90 (br d)[k]	2.46 (br dd)	3.01 (dd)[l]	2.27 (br d)
J ($\mathrm{H^{6a}H^{6e}}$)		19.7	20.2	16.5	16.9	20.6	≈20.0
J ($\mathrm{H^{6a}H^{7a}}$)		—	—	—	9.7	—	—
J ($\mathrm{H^{6a}H^{7e}}$)		—	—	—	—	—	—
δ ($\mathrm{H^{6e,13e}}$)		3.00 (d)	3.08 (d)	2.81 (d)	2.72 (d)	3.14 (dd)[m]	2.97 (br d)
J ($\mathrm{H^{6e}H^{7e}}$)		—	—	—	—	—	—
J ($\mathrm{H^{6e}H^{7a}}$)	—	—	—	—	0	—	—
δ ($\mathrm{H^{7a,14a}}$)	2.27 (br s)	—	—	—	2.62 (br m)	—	—
δ (7,14-$\mathrm{CH_3}$)		2.61 (s)	2.46 (s)	1.35 (s)	—	2.66 (s)	2.33 (br s)
J ($\mathrm{H^{7a}H^{7e}}$)		—	—	—	—	—	—
δ ($\mathrm{H^{7e,14e}}$)	—	—	—	—	—	—	—
δ (7,14-R)[g]	1.34 (br s)	1.39 (s)	1.22 (s)	1.34 (s)	0.75 (d, J 6.7, Me) 0.97 (d, J 6.7, Me) 2.06 (m, C*H*$\mathrm{Me_2}$)	1.48 (s)	1.40 (br s)

d = Doublet, t = triplet, q = quartet, m = multiplet, br = broad. [a] In $\mathrm{CD_3NO_2}$. [b] In $\mathrm{(CD_3)_2SO}$. [c] a = Axial. [d] e = Equatorial. [e] ^5J = 2.0 Hz. [f] ^5J = 2.0 Hz. [g] R = Me except for complexes **3b** and **6b** where R = $\mathrm{Pr^i}$. [h] $\delta(\mathrm{N^+H_3})$ in **6b** 7.86 (br t). [i] Amide NH, δ 8.65 (t); aromatic protons *o*- 7.85 (m), *m*- 7.51 (m), *p*- 7.58 (m). [j] ^5J = 3.0 Hz. [k] $^5J \approx 1.5$ Hz. [l] ^5J = 3.4 Hz. [m] ^5J = 1.6 Hz.

the asymmetric products α-**3a**, **3b**, α-**3c** and α-**3d** should be the same. Carbon-13 and ^1H NMR data collected in Tables 4 and 5 indicate symmetric structures for all the diamagnetic complexes (**3**, **6** and **7d**) except for the N-isomerised complex γ-**3c** and the monosubstituted decomposition product **4d**. Since all substrates **1** were centrosymmetric, this indicates that the newly created chiral centres on carbon atoms C^3 and C^9 possess an opposite configuration, and therefore, that pendant arms were introduced on opposite sides of the macrocyclic ring.

Three isomers of complex **3c** were characterised by ^1H NMR spectroscopy (Table 5). The absence of a large coupling constant in the ^1H NMR signals of C^2H and C^9H protons of complexes α-**3c**, β-**3c** and γ-**3c** indicates a pseudo-equatorial conformation for these protons, and pseudo-axial conformation for the pendant nitromethyl groups. However, pendant methylene-group protons in the spectrum of isomer α-**3c** (precipitated with perchloric acid from solutions of paramagnetic complexes **2**) are more markedly deshielded in comparison with signals of the same protons in the N-isomerised complex β-**3c**. According to the known deshielding effect[15,19,20] for protons situated above the plane of square-planar nickel(II) complexes, the low-field CH_2 has to be located further away from the NiN_4 plane, and closer to the Ni^{II} ion than the high-field pendant CH_2 group in complex β-**3c**. This proves that complex α-**3c** maintains the N-*meso* configuration established for **2c** with pendant nitromethyl groups in 'co-ordinating positions' *i.e. trans* to the neighbouring secondary amino group protons. Isomer β-**3c** also exists in an N-*meso* configuration with both secondary amino groups inverted, *i.e.* with the pendant arms *cis* to the neighbouring amino group protons. Inversion of the asymmetric nitrogen atoms causes inversion of the six- and five-membered chelate rings. Simultaneously, five-membered chelate rings, avoiding steric interactions between the equatorial substituents on carbon atoms C^2, C^3, C^5 and C^9, C^{10}, C^{12}, adopt twisted conformations moving the neighbouring substituents to pseudo-axial positions with the pendant nitromethyl groups further away from the central Ni^{II} ion than in the α-**3a** isomer. The non-symmetric complex γ-**3c**, obtained by dissolution of isomer β-**3c** in dimethyl sulfoxide adopts an N-*racemic* conformation.

The assignment of chemical shifts of methylene protons C^6H_2 and $C^{13}H_2$ was made based on the analysis of vicinal and long-range homoallylic couplings to the protons attached to C^3 and C^{10} respectively. This coupling is most effective when the proton is parallel to an axis of *p* orbitals of a double bond, and nearly zero when the proton lies in the junction plane of the double bond.[21–25] Signals broadened or split by a long range coupling constant were therefore assigned to axial positions. Homoallylic coupling was not observed in the spectra of the isomeric complexes **3c** because the methyl groups on C^3 and C^{10} adopt an axial conformation in all three isomers.

The NMR spectrum of isomer α-**3a** generated by dissolution of the paramagnetic complex **2a** in CD_3NO_2 acidified with $HClO_4$ was contaminated with signals of several decomposition products and could not be interpreted. However, strong signals of the 5,12-methyl groups at δ 2.32, equatorial 7,14-methyl groups at δ 1.32 and pendant 2,9-nitromethyl groups at δ 5.28 and 5.44 indicate a similar conformation of the macrocyclic ring and pendant functional groups to that for α-**3c**. The spectrum of a recrystallised sample of β-**3a** indicates an inverted N-*meso* conformation of the macrocyclic ring with axial 7,14-methyl groups (δ 1.71) and large nitromethyl substituents moved away from the central Ni^{II} ion (δ 4.82 and 4.89). Similarly, two isomers were observed in solutions of complex **3d**. A raw product α-**3d**, precipitated with ethanol from the reaction mixture, gave a very broad NMR spectrum with characteristic signals for the nitromethyl group protons at δ 4.85 and 5.45, indicating a ligand conformation similar to that observed for α-**3c**. The sample recrystallised from nitromethane (β-**3d**) gave a sharp, symmetric NMR spectrum. The multiplets of the pendant-arm methylene groups appeared again at a higher field (δ 4.68 and 4.78) and the signal from the axial 7,14-methyl groups was at very low field (δ 2.61) indicating that during crystallisation, as in the case of complexes **3a** and **3c**, the secondary amino nitrogens N^1 and N^8 had changed their configurations and the macrocyclic ring had adopted an energetically favourable conformation with pseudo-axial nitromethyl groups moved away from central metal ion. Large pseudo-equatorial isopropyl substituents prevented isomerisation of complex **3b** and its NMR spectrum indicates an N-*meso* conformation of the macrocyclic ring with axial pendant arms located close to the Ni^{II} ion.

By taking into account the conformation of the nitromethyl and alkyl substituents as deduced from the NMR spectra, and correlating them with the known relative configuration of the chiral centres of substrates **1**, the relative configuration of all the asymmetric nitrogen and carbon atoms in complexes **3** are assigned as follows:

α-**3a**	1*RS*,2*SR*,7*SR*,8*SR*,9*RS*,14*RS*
β-**3a**	1*SR*,2*SR*,7*SR*,8*RS*,9*RS*,14*RS*
3b	1*SR*,2*SR*,7*RS*,8*RS*,9*RS*,14*SR*
α-**3c**	1*RS*,2*RS*,3*RS*,8*SR*,9*SR*,10*SR*
β-**3c**	1*SR*,2*RS*,3*RS*,8*RS*,9*SR*,10*SR*
γ-**3c**	1*SR*,2*RS*,3*SR*,8*SR*,9*SR*,10*SR*
α-**3d**	1*SR*,2*SR*,8*RS*,9*RS*
β-**3d**	1*RS*,2*SR*,8*SR*,9*RS*

The finding that all the primary products of protonation of the neutral complexes **2** exist in conformations with pendant nitromethyl groups on opposite sides of the macrocycle in the vicinity of central Ni^{II} ion indicates that complexes **2** have structures with the same relative configuration of asymmetric atoms as found in the protonated forms α-**3a**, **3b**, α-**3c** and α-**3d** similar to that established for the complex **2c**·2($NHEt_3ClO_4$) (Fig. 1).[16]

Carbon-13 and ^1H NMR spectra confirm a centrosymmetric structure for complex **6b**, with an equatorial conformation of the 7,14-isopropyl groups and a relative configuration 1*SR*,2*SR*,7*RS*,8*RS*,9*RS*,14*SR*. Small coupling constants of 2,9-protons to 1,8-amino and 3,10-methylene protons indicate an 'envelope' conformation for the five-membered chelate rings and an axial orientation of the pendant arms. Large coupling constants for the 2,9-protons to the 1,8-amino and 3,10-methylene protons in the spectrum of complex **6d** indicate that, due to strong repulsion between the pendant arms and 7,14-methyl groups, the five-membered chelate rings adopt a conformation with eclipsed protons and substituents in positions $C^{2,9}$ and $C^{3,10}$. Since the spectrum of the sample generated in an NMR tube by dissolution of the paramagnetic complex **5d** in CD_3NO_2 acidified with perchloric acid was identical to that of the crystallised sample (Table 5), it is expected that the pendant arms remain in a 'co-ordinating', pseudo-axial conformation (*trans* with respect to the protons of neighbouring secondary amino groups) *i.e.* nitrogen inversion does not occur (1*SR*,2*SR*,8*RS*,9*RS*).

Complex **7d** in solution, at room temperature, due to the strong repulstion between the 2,14- and 7,9-substituents exists as an equilibrium of conformers, which is reflected by the broadening of its NMR signals.

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