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Preparation and characterisation of some new asymmetric tetraaza macrocyclic complexes of nickel(II)

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Abstract

The synthesis of a new neutral, asymmetrically substituted nickel(II) tetraaza macrocyclic complex has been performed via the template condensation of an asymmetric, acyclic precursor with 1,3-propanediamine. The peripheral aromatic nitro group of this asymmetric macrocycle undergoes catalytic reduction with hydrogen to produce the corresponding aromatic primary amine complex. The asymmetric nature of these materials is clearly demonstrated with the aid of ^{1}H and ^{13}C NMR spectroscopy. The synthesis of a new 15-membered macrocycle is also described. Deacylation of this macrocycle gives either the neutral macrocycle or the related asymmetric, monoprotonated macrocyclic salt, depending upon the reaction conditions.

Introduction

There has been considerable recent interest in the synthesis of new macrocyclic ligand systems [1]. Interest in these species stems largely from the enhanced kinetic and thermodynamic stability of their complexes relative to those of related open chain ligands. Generally macrocyclic complexes are also of interest because of the synthetic flexibility involved in their preparation which allows for systematic variation in parameters such as ring size, the nature of the donor atoms, and the steric and electronic effects associated with groups located on the periphery of the macrocyclic ring – the 'ligand superstructure' [2]. Recently a large number of reports has appeared concerning the chemistry of specifically functionalised macrocycles where the complex contains reactive groups which are not directly coordinated to the metal ion but are available for further reaction [3]. Systems of this type have been proposed for a variety of uses, for example, in the 'tagging' of tumours, using technetium-containing macrocycles covalently bound to an antibody which is specific for the tumour cells [4] or in the production of novel synthetic membrane materials, where the reactive function is used to covalently bind the complex to the backbone of a synthetic polymer [5]. The topic of functionalised macrocycles has recently been reviewed as has the complementary area of 'macromolecular complexes' [6, 7].

We have been interested in preparing asymmetrically substituted ligand systems where a single site exists for linking the resulting complex to a polymer [8]. Recently we have reported on the functionalisation of a known macrocyclic complex to introduce suitable reactive sites into the molecule and we have successfully demonstrated the inclusion of some of these macrocycles into the structure of various polymers [9].

In this paper we wish to report the direct synthesis of some new macrocyclic systems with this structural feature, utilising the template condensation mechanism for macrocyclic formation. This is a well established route to macrocyclic systems [2]. For example, Jäger has described the synthesis of a family of tetraaza macrocyclic complexes of nickel(II), prepared by the template condensation of α,ω-diamines with square planar N_2O_2 acyclic complexes [10]. These neutral macrocyclic complexes have attracted a great deal of interest in recent years and a series of studies have been published, including investigation of the mechanism of the ring closure step [11]. By far the greatest amount of work, however, has been reported by Busch and co-workers, who have used some examples of Jäger's macrocycles as parent molecules for their elegant family of 'lacunar cyclidene' complexes [12].

We also wish to report upon the synthesis and reactivity of a new, symmetrical substituted macrocyclic

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complex, also prepared by the ring closure procedure of Jager. This material can be modified to produce an asymmetrically substituted macrocyclic species.

Experimental

All materials were reagent grade. Solvents were purified by standard methods. NMR spectra were recorded on a Bruker WP200 spectrometer, operating at 200.133 (^{1}H) or 50.323 (^{13}C) MHz. Chemical shifts are reported with respect to an external tetramethylsilane reference (positive shifts to low field). IR spectra were recorded as Nujol mulls using a Perkin-Elmer 580 spectrophotometer, and mass spectra using a VG updated MS9 spectrometer.

3,10-Diacetyl-14-nitro-2,11-dioxo-5,8-diazacyclo[4.^{6,7}0]hexadeca-3,6,9,13,15-pentaene (1)

To a solution of 4-nitro-1,2-diaminobenzene (3.83 g, 2.5 mmol) in dimethyl sulfoxide (100 cm^3) was added 3-ethoxyvinylidene-2,4-pentanedione (20.0 g, 0.128 mol). The mixture was heated at reflux for 15 min, the solvent reduced to a small volume *in vacuo* and methanol was added to precipitate the product. The solid was collected by filtration and washed with copious amounts of methanol. Yield 5.0 g (54%). *Anal.* Found: C 57.9; H, 5.2; N, 11.1. Calc. for $C_{18}H_{19}N_3O_6$: C, 57.9; H, 5.1; N, 11.2%.

(3,10-Diacetyl-14-nitro-5,8-diazacyclo[4.^{6,7}0]hexadeca-3,6,9,13,15-pentaene-2,11-dionato)nickel(II) (2)

To a rapidly stirred suspension of **1** (2.8 g, 7.5 mmol) in methanol was added potassium t-butoxide (1.8 g, 16.0 mmol) followed by nickel(II) acetate tetrahydrate (1.86 g, 7.5 mmol). The reaction mixture was heated to just below reflux, during which time an orange solid appeared which was collected by filtration of the hot solution. The product was washed well with warm methanol and dried. Yield 2.4 g (90%). *Anal.* Found: C, 48.1; H, 3.8; N, 9.3. Calc. for $C_{18}H_{17}N_3NiO_6 \cdot H_2O$: C, 48.3; H, 4.2; N, 9.4%.

(3,10-Diacetyl-2,11-dimethyl-17-nitro-1,5,8,12-tetraazabicyclo[13.4.0]nonadeca-1,3,6,8,10,16,18-heptaenato)nickel(II) (3)

To a suspension of **2** (1.0 g, 2.33 mmol) in dry DMF was added 1,3-diaminopropane (0.37 cm^3, 4.7 mmol). The reaction mixture was heated at reflux for 30 min then the solvent volume was reduced *in vacuo*. Addition of water resulted in formation of a dark coloured precipitate which was collected by filtration and washed with copious amounts of water followed by diethyl ether. The crude solid was dissolved in methyl ethyl ketone (MEK) and passed down an alumina column, with MEK as eluant. The mobile orange coloured band was collected and the solvent removed to yield the product as an orange solid. Yield 10%. M^+, *m/z* 467 (^{58}Ni), 469 (^{60}Ni).

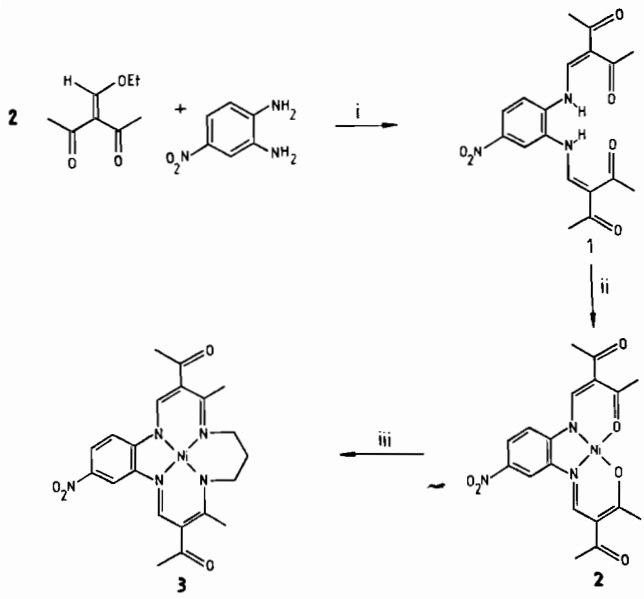
(3,10-Diacetyl-17-amino-2,11-dimethyl-1,5,8,12-tetraazabicyclo[13.4.0]nonadeca-1,3,6,8,10,16,18-heptaenato)nickel(II) (4)

To a suspension of **3** (0.2 g, 0.43 mmol) in ethyl acetate was added 5% Pd/C (0.2 g) and the apparatus was placed under an atmosphere of hydrogen gas. After stirring for 2.5 h at room temperature, uptake of hydrogen had ceased. The reaction mixture was filtered and the orange filtrate was evaporated to dryness to yield the product as a dark red–brown solid. Yield 0.1 g (54%). *Anal.* Found: C, 54.7; H, 5.9; N, 11.5. Calc. for $C_{21}H_{25}N_5NiO_2 \cdot 1.75\ C_4H_8O_2 \cdot H_2O$: C, 55.1; H, 6.7, N, 11.5%.

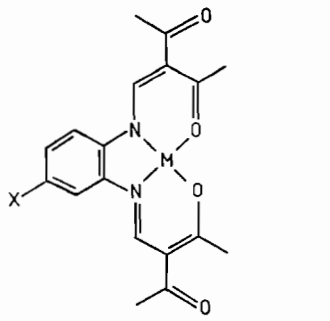
Results and discussion

The aim of this work was the production of macrocyclic complexes containing a single reactive functional site. Such complexes could then be bound into the structure of a synthetic polymer. Earlier work had demonstrated that use of a difunctional macrocycle in such reactions resulted in the production of polymers that were highly cross-linked and hence insoluble [13]. Since Jäger's work had identified facile, high yielding routes to macrocyclic complexes utilising the coordination template effect, it seemed sensible to follow this kind of synthetic procedure. It was proposed that the desired asymmetry could be introduced into the product at the first step of the synthesis by making use of the commercially available 4-nitro-1,2-diaminobenzene. The synthetic pathway shown in Scheme 1 was adopted.

Most diamines react readily, at room temperature or below, with two equivalents of the versatile reagent, 3-ethoxyvinylidene-2,4-pentanedione, via a Michael addition followed by elimination, to give the 1:2 substitution product. Under mild conditions, however, 4-nitro-1,2-diaminobenzene formed merely the 1:1 species, indicating the lower reactivity of the nitro substituted aromatic amine. By using dimethyl sulfoxide (DMSO) as solvent, a large excess of the ethoxyvinylidene compound, and heating the reaction mixture at reflux for *c.* 15 min it proved possible to prepare the desired product, **1**, in reasonable yield (54%). This was characterised by a combination of microanalysis and spectroscopy. The ^{13}C NMR spectrum was assigned with the aid of a DEPT experiment (distortionless enhancement by polarisation transfer). While the ^{1}H NMR spectrum in $CDCl_3$ solution gave little indication of the asymmetry of the molecule, the ^{13}C NMR spectrum was much more revealing (Table 1). With the exception



Scheme 1.
i: DMSO, △
ii: KO^{t}Bu (2.1 equiv), $Ni(OAc)_2 \cdot 4H_2O$, MeOH
iii: DMF, 1,3-diaminopropane, △



1, X = NO_2, M = 2H
2, X = NO_2, M = Ni

of the four acetyl groups at the termini of the molecule, which gave rise to two sets of signals, unique resonances were observed for all other carbon atoms. In $(CD_3)_2SO$ solution, the asymmetric nature of **1** was even more clearly seen. In this solvent, the ^{13}C NMR spectrum showed discrete signals for every carbon atom in the molecule. The IR spectrum of **1** had two bands above 1600 cm^{-1} assigned to ν(C=O) and two bands, at 1525 and 1340 cm^{-1} ascribed to $\nu(NO_2)$ (Table 2).

In common with all of the nitro derivatives reported in this work, **1** has a markedly reduced solubility relative to its unsubstituted analogue, presumably arising from the extended planar π-network which results in enhanced stacking of the molecules in the solid state.

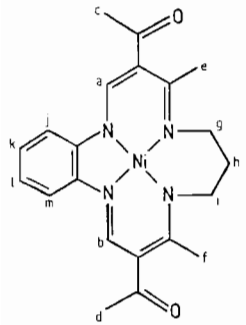
A suspension of **1** in methanol at reflux, in the presence of potassium t-butoxide, reacted with nickel(II) acetate tetrahydrate to generate the corresponding orange coloured complex **2** in high yield (90%). The ^1H NMR spectrum of **2** gave clear evidence for the asymmetric nature of the compound, with the methine protons, H_a and H_b, and all three aromatic protons giving rise to separate signals. In the latter case the resolved spin–spin coupling of the signals, allied to their chemical shift, allowed them to be assigned to specific protons of the aromatic ring. The IR spectrum of **2** was, as expected, very similar to that of **1**, the major changes being loss of the band above 3000 cm^{-1} ascribed to ν(N–H) and a shift in the position of one of the ν(C=O) bands from 1630 to 1656 cm^{-1}, resulting from coordination of the oxygen atom to the nickel(II) ion.

In Jäger's work, quadridentate acyclic complexes were ring closed via a double condensation reaction under very forcing conditions involving the use of neat diamines at reflux [10]. However, attempted ring closure of **2** under these conditions, using 1,3-diaminopropane, merely resulted in the isolation of a range of decomposition products. Under the more gentle conditions of heating a suspension of **2** in dimethyl formamide (DMF) at reflux, in the presence of two equivalents of 1,3-diaminopropane, the required macrocyclic complex was formed, albeit in modest yield (10%). Characterisation of the orange macrocyclic product, **3**, was hampered by its very low solubility which prevented measurement of its ^{13}C NMR spectrum. The ^1H NMR spectrum, in $(CD_3)_2SO$ solution, was very poorly resolved giving only very broad peaks. This broadening was believed to arise from intermolecular association of the macrocycles in solution which adversely affects the rate of tumbling of the molecules in solution, thereby decreasing the relaxation rate of the protons. The success of the macrocyclisation reaction was indicated by the mass spectrum of **3** which had peaks at *m/z* 467 (^{58}Ni) and 469 (^{60}Ni) in the correct isotopic ratio. The IR spectrum had only one peak assigned to ν(C=O) at 1632 cm^{-1}.

Catalytic reduction of a suspension of **3** in ethyl acetate solution by hydrogen readily produced the corresponding primary amine substituted macrocycle, **4**. This complex proved to be much more soluble than the parent compound. Data from microanalysis suggested that the analysed sample was an ethyl acetate/water solvate. The proposed structure of **4** was confirmed by NMR spectroscopy. In the ^1H NMR spectrum, resonances at δ 3.70 and 1.80 were assigned to the trimethylene unit of the macrocycle. Signals assigned to all three protons of the aromatic ring were observed, with chemical shifts consistent with the presence of the strongly shielding amine group. Again the presence of well resolved coupling allowed assignment of the signals to specific protons of the aromatic ring. A signal

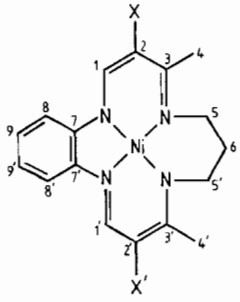
TABLE 1. NMR spectroscopic data

^{1}H NMR data



Compound	H_a, H_b	H_c, H_d, H_e, H_f	H_g, H_i	H_h	H_j, H_m	H_k, H_l	Others
1[a]	8.20 (s, 2H)	2.58, 2.43 (2×s, 12H)			7.47 8.20 (d, 1H) (m, 1H) J=9.6 Hz	8.20 (m, 1H)	13.14 (NH) (t, 2H)
2[a]	8.29, 8.30 (s, 1H) (s, 1H)	2.62, 2.50, 2.52 (s, 6H) 12×s, 6H)			7.63 8.40 (d, 1H) (d, 1H) J=9.2 Hz J=2.2 Hz	8.06 (dd, 1H)	
4[c]	7.95, 7.89 (s, 1H) (s, 1H)	2.36–2.32 (4×s, 12H)	3.70 (dt, 4H)	1.80 (qn, 2H)	7.27 6.69 (d, 1H) (d, 1H) J=8.7 Hz J=1.9 Hz	6.63 (dd, 1H)	5.01 (NH_2) (s, 2H)
5[a]	8.06 (s, 2H)	2.45, 2.43 (2×s, 12H)	3.88 (t, 4H)	1.80 (qn, 2H)	7.29 (m, 2H)	7.04 (m, 2H)	
6[b]	8.00, 7.05 (s, 1H) (d, 2H)	2.20, 2.10 (2×s, 6H)	3.45, 4.00 (2×t, 4H)	1.80 (qn, 2H)	7.24 6.90 (t, 1H) (t, 1H)	7.35 (t, 2H)	4.13 (CH_2) 5.12 (CH) (s, 2H) (d, 1H)
7[b]	7.26 (d, 2H)	2.09 (s, 6H)	3.75 (t, 4H)	1.72 (qn, 2H)	7.30 (m, 2H)	6.76 (m, 2H)	5.02 (2×CH) (d, 2H)

^{13}C NMR data



Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1′	C-2′	C-3′	C-4′	C-5′	C-7′	C-8′	C-9′	X		X′	
1[a]	152.4	116.6	202.0	31.7			137.3	122.0	118.1	150.2	116.0	[d]	[d]		131.7	115.9	145.0	27.4	194.7	[d]	[d]
4[c]	148.7	114.7	166.2	18.4	45.9	24.3	134.1	115.1	110.7	147.4	114.1	165.7	18.2	46.2	144.5	99.2	146.3	28.3	194.4	28.1	194.0
5[a]	148.5	115.8	166.6	18.5	45.8	24.2	143.9	113.7	123.7	[d]	[d]	[d]	[d]	[d]	[d]	[d]	[d]	27.9	195.2	[d]	[d]
6[b]	141.2	101.5	166.0	21.7	46.7	24.4	149.3	115.1	123.1	163.3	49.2	175.2	[d]	[d]	139.3	[e]	131.8				
7[b]	141.0	99.8	162.6	21.3	46.8	24.6	145.1	113.5	122.0	[d]	[d]	[d]	[d]	[d]	[d]	[d]	[d]				

[a]In $CDCl_3$ solution. [b]In CD_3CN solution. [c]In d^6-DMSO solution. [d]Same chemical shift as symmetry related carbon atom. [e]Obscured by solvent signal.

TABLE 2. IR spectroscopic data (cm^{-1})

Compound	ν(C=O)	ν(C=N, C=C)	$\nu(NO_2)$	Others
1	1671, 1630	1603, 1562	1525, 1340	
2	1671, 1656	1599, 1574	1510, 1333	
3	1632	1599, 1570	1509, 1320	
4	1625	1598, 1568		3440, 3400 3342, 3232
5	1629	1588, 1569		
6		1580		1665[a], 840, 560
7		1590, 1576		

[a]See text.

at δ 5.01 was ascribed to the $-NH_2$ group and the asymmetry of the amino macrocycle was confirmed by the appearance of discrete resonances for both methine protons as well as all for all four methyl groups (Fig. 1). The asymmetry of the system was even more firmly underlined by the ^{13}C NMR spectrum which had a separate signal for each of the 21 carbon atoms of the molecule (Table 1). Assignments were made by reference to literature compounds and from the results of a DEPT experiment. The IR spectrum of **4** contained a series of four bands above 3000 cm^{-1}, ascribed to ν(N–H) of the amino group. Only two bands are expected, for the symmetric and asymmetric stretches, respectively, and it is believed that the extra bands arise as a result of hydrogen bonding effects in the solid state.

Preliminary studies of the reactivity of the amino macrocycle, **4**, imply that the complex behaves, as expected, as a weak nucleophile. Thus complex **4** can be potentially used in binding to synthetic polymers which contain strongly electrophilic side chains. Studies in this area are continuing.

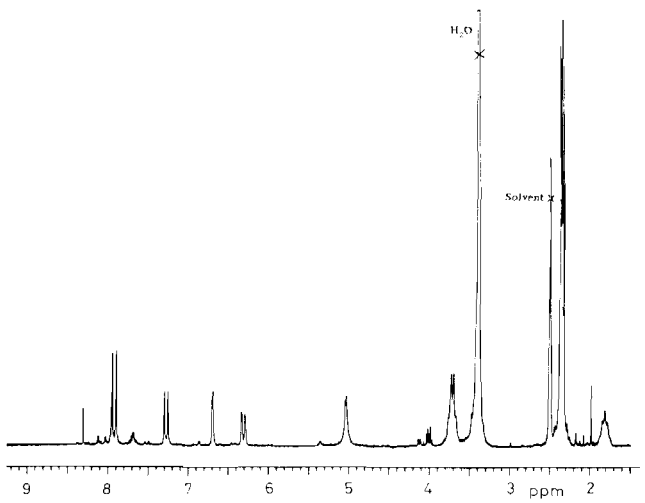
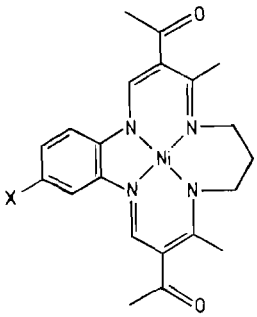


Fig. 1. ^1H NMR spectrum of **4**, in d^6-DMSO solution.



3, X=NO_2
4, X=NH_2
5, X=H

Concurrent with studies of these asymmetrically substituted macrocycles, the new macrocycle, **5**, was prepared via direct application of Jäger's procedure, using 1,3-diaminopropane to ring close the system. This species represents a relatively trivial extension of Jäger's work, the corresponding macrocycles which were ring closed with either ethylenediamine, or 1,2-diaminobenzene, having been reported previously [14]. This new macrocyclic complex was characterised by a combination of microanalysis and spectroscopy and the mirror symmetry of the species was clearly shown by the NMR spectra (^1H NMR spectrum, Fig. 2). The relevance of this macrocycle to the work described in this paper stems from the subsequent reactivity of complex **5**.

It is well known from the extensive studies of Busch and co-workers that bis keto macrocycles of a type similar to **5** may be deacylated by reaction of the complexes with a strong acid in a nucleophilic solvent [15]. This reaction was attempted with complex **5** in methanol solution, using toluenc-4-sulfonic acid. By analogy with other macrocycles, under these conditions the diprotonated, bis deacylated derivative was expected to precipitate, once ammonium hexafluorophosphate had been added to the reaction mixture. With complex **5**, however, it was found that the product depended upon the amount of toluene-4-sulfonic acid used in the reaction. If a large excess (>3 equivalents) were used, then the product which precipitated was found to be

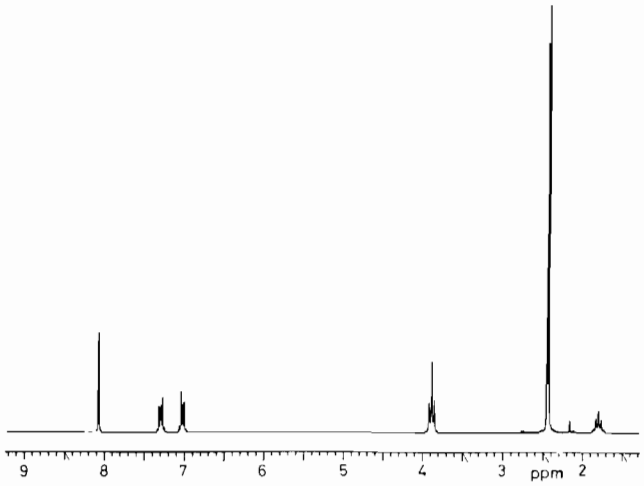
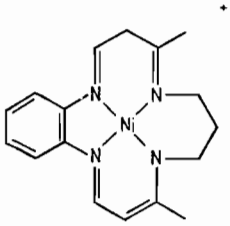


Fig. 2. ^{1}H NMR spectrum of **5**, in $CDCl_3$ solution.

the mono-protonated, mono-hexafluorophosphate salt, **6**, in which one of the apical carbon atoms of the ring is of the sp^3 hybridised, methylene type and the other if of sp^2 hybridised, methine type. A large change was noted in the appearance of the NMR spectra of **6** relative to **5**, consistent with the loss of the mirror symmetry of the parent complex. It is this appearance of induced asymmetry which makes this complex of relevance to the present study. Of particular note in the ^{1}H NMR spectrum of **6**



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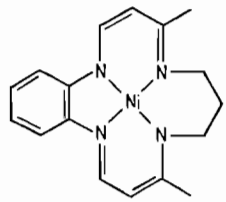
was the appearance of a doublet at δ 7.05 assigned to the proton attached to C-1, which showed coupling to the single proton attached to C-2. The resonance due to this proton appeared at δ 5.12. Interestingly, the two protons bonded to C-2′ (at δ 4.13) did not couple to the proton attached to C-1′ (at δ 8.0). This appears to be due to a rapid (on the NMR timescale) exchange process involving the hydrogen atoms of C-2′ presumably via an intermolecular pathway. Consistent with this proposition, the resonance assigned to these protons showed evidence of broadening. The asymmetric nature of this complex was evidenced by the appearance of two distinct triplets, at δ 3.45 and 4.00, ascribed to the protons of C-5 and C-5′. The ^{13}C NMR spectrum also indicated the asymmetry of the product by displaying separate signals for almost every carbon atom; of particular note was the peak at 49.2 ppm, assigned to the methylene carbon atom, C-2′, as well as a signal at 101.5 ppm, assigned to the methine carbon atom, C-2. The IR spectrum of **6** had, curiously, a peak at 1665 cm^{-1}, the origin of which is uncertain. The NMR results indicate that no acetyl groups were present in **6** and consequently it is believed that this IR band is due to an overtone or combination band of the macrocycle. The presence of the hexafluorophosphate anion was confirmed by the appearance of peaks at 840 and 560 cm^{-1}.

If the quantity of toluene-4-sulfonic acid used in the deacylation step was limited to less than three equivalents, the isolated product was the neutral bis deacylated product, **7**. The NMR spectra of this product were fully consistent with the proposed structure and indicated that it contained the expected plane of symmetry (Table 1). These results indicate that the deacylated macrocycle, **7**,



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which contains an aromatic ring, is a weaker base than the corresponding aliphatic derivatives, which doubly protonate during work up. In the presence of acid, **7** underwent mono-protonation to form **6**. Thus it is possible to form the asymmetric product, **6**, selectively, by controlling the acidity of the reaction mixture.

Conclusions

A new asymmetric quadridentate acyclic ligand has been formed by reaction of 4-nitro-1,2-diaminobenzene with two equivalents of 3-ethoxyvinylidene-2,4-pentanedione. The nickel(II) complex of this ligand undergoes a template controlled ring closure reaction with 1,3-diaminopropane to form the asymmetric nitro substituted macrocyclic complex, **3**. Catalytic reduction of the nitro group of **3** results in formation of the corresponding primary amino substituted macrocycle, **4**. The asymmetric nature of these monofunctionalised macrocycles and their precursors is readily demonstrated by examination of their NMR spectra. An analogous symmetrical macrocycle, **5**, has been prepared using the template method. This material can be readily deacylated and the product of this reaction depends upon the acidity of the reaction medium. At low concentrations of acid, the product is the neutral, symmetric macrocycle, **7**, while under more acidic conditions the asymmetric monoprotonated species, **6**, is formed. The

asymmetric nature of **6** is again most readily demonstrated by the appearance of its NMR spectra.

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