$[RhDCl(ttp)(CO)]PF_6$, 58463-93-7; $[RhHBr(ttp)(CO)]PF_6$, 58485-80-6; $[RhDBr(ttp)(CO)]PF_6$, 58463-95-9; $[Rh(CH_3)Cl(ttp)(CO)]FSO_3$, 58463-97-1; $[Rh(CH_3)Cl(ttp)(MeCN)]FSO_3$, 58463-99-3; $[Rh(NO)Cl(ttp)]PF_6$, 50981-73-2.

References and Notes

(1) Lubrizol Fellow, 1972–1973.
(2) W. Mowat, A. J. Shortland, N. J. Hill, and G. Wilkinson, *J. Chem. Soc., Dalton Trans.*, 770 (1973); S. Moorhouse and G. Wilkinson, *ibid.*, 2187 (1974).
(3) G. W. A. Fowles, D. A. Rice, and J. D. Wilkins, *J. Chem. Soc., Dalton Trans.*, 961, 2313 (1973).
(4) R. E. Harmon, S. K. Gupta, and D. J. Brown, *Chem. Rev.*, **73**, 21 (1973).
(5) G. Yagupsky, C. K. Brown, and G. Wilkinson, *J. Chem. Soc. A*, 1392 (1970); C. K. Brown and G. Wilkinson, *ibid.*, 2753 (1970).
(6) H. C. Clark, C. R. Jablonski, and C. S. Wong, *Inorg. Chem.*, **14**, 1332 (1975).
(7) A. Wojcicki, *Adv. Organomet. Chem.*, **11**, 87 (1973); **14**, 31–81 (1974).
(8) J. Chatt, *Adv. Organomet. Chem.*, **14**, 1–20 (1974).
(9) B. R. James, "Homogeneous Hydrogenation", Wiley, New York, N.Y., 1973.
(10) E. L. Muetterties, Ed., "Transition Metal Hydrides", Marcel Dekker, New York, N.Y., 1971.
(11) T. E. Nappier, Jr., Ph.D. Dissertation, The Ohio State University, 1972.
(12) T. E. Nappier, Jr., D. W. Meek, R. M. Kirchner, and J. A. Ibers, *J. Am. Chem. Soc.*, **95**, 4194 (1973).
(13) J. L. Peterson, T. E. Nappier, Jr., and D. W. Meek, *J. Am. Chem. Soc.*, **95**, 8195 (1973).
(14) H. C. Clark and L. E. Manzer, *Inorg. Chem.*, **11**, 2749 (1972).
(15) J. F. Nixon and A. Pidcock, *Annu. Rev. NMR Spectrosc.*, 2, 345–442 (1969).
(16) E. G. Finer and R. K. Harris, *Prog. Nucl. Magn. Reson. Spectrosc.*, **6**, 61 (1971).
(17) J. G. Verkade, *Coord. Chem. Rev.*, **9**, 1–106 (1972).
(18) L. Vaska, *J. Am. Chem. Soc.*, **88**, 4100 (1966).
(19) A. P. Gaughan, Jr., B. L. Haymore, J. A. Ibers, W. H. Myers, T. E. Nappier, Jr., and D. W. Meek, *J. Am. Chem. Soc.*, **95**, 6859 (1973).

Contribution from the W. A. Noyes Laboratory,
School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Synthesis of Macrocyclic Tetramines by Metal Ion Assisted Cyclization Reactions

E. KENT BAREFIELD,* F. WAGNER, and KEITH D. HODGES

Received November 13, 1975 AIC50827W

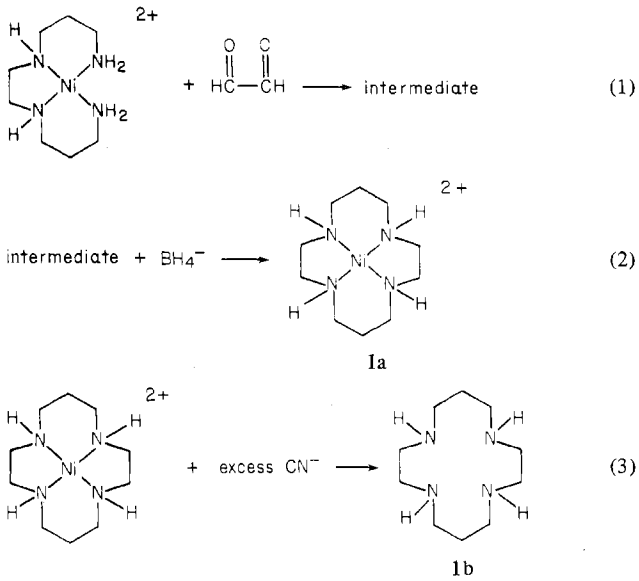
Eleven substituted 1,4,8,11-tetraazacyclotetradecanenickel(II) complexes were prepared by the nickel ion assisted cyclization of 1,5,8,12-tetraazadodecanes with glyoxal and reduction of the unsaturated complex obtained in the cyclization reaction. Sodium borohydride or hydrogen and Raney nickel catalyst were used for the reduction. With two exceptions, yields of the saturated complexes were in the range 50–75%. Macrocyclic tetramines were obtained by decomposition of the nickel complexes with cyanide ion. 1,5,9,15-Tetraazacyclopentadecane was prepared in 45% yield from 1,5,9,13-tetraazatridecane by this method.

Introduction

In earlier reports[1,2] we described the preparation of complex **1a** and the free base **1b** through the reactions described in Scheme I. Yields of **1a** and **1b** in excess of 65% are routine by this route and the entire reaction sequence can be conducted in an open beaker. This synthesis of **1b** is far superior to the earliest versions[3] and provides a more convenient route than the general cyclization procedure recently developed by Atkins and Richman.[4] With respect to metal-assisted cyclization reactions, in general, this example is one of the highest yielding presently known, and it is better than a similar reaction with 2,3-butanedione (biacetyl).[5]

Some of our more recent work on N-alkylation reactions of **1a** resulted in a need for authentic samples of certain partially methylated and benzylated forms of this complex.[6] Because of this we have explored the utility of reactions 1 and 2 as means of synthesizing substituted 14-membered macrocyclic ligand complexes. As this paper reports, this scheme is very useful for the synthesis of such complexes, as well as the free amines, since any substituted ligand can be removed from the metal through a reaction corresponding to (3). As a part of our efforts to define the general utility of cyclization reactions of tetradentate ligands with glyoxal we have also attempted to use tetramines that would produce 15- and 13-membered rings and to use metal ions other than nickel as the template for the reaction. A moderate-yield synthesis for a saturated 15-membered system is reported; however, we were unsuccessful in preparing 13-membered rings.

Scheme I



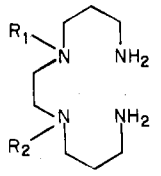
Experimental Section

Ligands. A complete listing of ligands used in this study and references to syntheses of those prepared previously is given in Chart I. Unless otherwise stated, other tetradentate ligands were prepared by cyanoethylation of the appropriate difunctional precursor followed by catalytic reduction of the crude dinitrile. Procedures used were similar to those of Israel et al.[7] and Dehayes and Busch[8] (50 psi of H_2 and Grace Chemical Grade 28 Raney nickel were used in all hydrogenations). The identity of each ligand was established by its NMR spectrum (chloroform solution). Unless otherwise indicated spectra were obtained at 100 MHz.

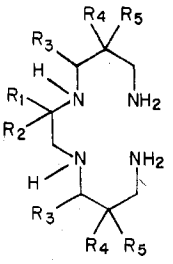
6,6-Dimethyl-1,5,8,12-tetraazadodecane, 3, was prepared from 20 g (0.23 mol) of 1,2-diamino-2-methylpropane (Aldrich) and 25 g (0.45 mol) of acrylonitrile; bp 105 °C (0.05 mm); yield 15 g, 28%. (This preparation was complicated by formation of other products.) NMR: τ 9.0 (s) 6 H; 8.7 (s) 6 H; 8.46 (m) 4 H; 7.2–7.6 (m) 10 H.

4,9-Dimethyl-1,5,8,12-tetraazadodecane, 4, was prepared from 15 g (0.25 mol) of ethylenediamine and 35 g (0.5 mol) of crotonitrile. The dinitrile was formed by heating for 2 days at 70–80 °C; bp 95 °C (0.05 mm); yield 17 g, 35%. NMR: τ 8.97 (d, J = 6 Hz) 6 H; 8.86 (s) 6 H; 8.52 (quartet of doublets) 4 H; 7.32 (m) 10 H.

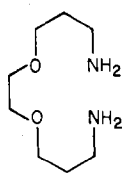
Chart I. Tetradentate Ligands Used in This Work



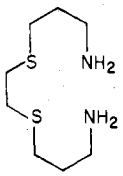
	R_1	R_2
1[a]	H	H
5[a]	CH_3	H
6[a]	CH_3	CH_3
7[a]	C_2H_5	C_2H_5
8[a]	$C_6H_5CH_2$	H
9[a]	$C_6H_5CH_2$	$C_6H_5CH_2$



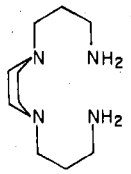
	R_1	R_2	R_3	R_4	R_5
2[c]	CH_3	H	H	H	H
3[a]	CH_3	CH_3	H	H	H
4[a]	H	H	CH_3	H	H
10[a]	H	H	H	CH_3	CH_3
11[a]	H	H	H	H	OH



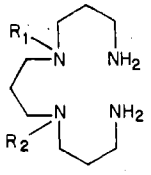
12[a]



13[a]

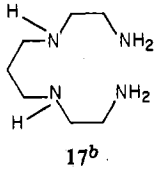


14[d]



15[e] H H

16[a] CH_3 CH_3



17[b]

[a] This work—see Experimental Section. [b] Eastman Kodak Co. [c] Reference 8. [d] Reference 11. [e] Reference 7.

5-Methyl-1,5,8,12-tetraazadodecane, 5, was prepared from 15 g (0.2 mol) of *N*-methylethylenediamine (Ames) and 21.2 g (0.4 mol) of acrylonitrile; bp 110 °C (0.04 mm); yield 29 g, 80%. NMR: τ 8.40 (m overlapping s) 9 H; 7.86 (s) 3 H; 7.2–7.8 (m) 12 H.

5,8-Dimethyl-1,5,8,12-tetraazadodecane, 6, was prepared from 25 g (0.28 mol) of *N,N'*-dimethylethylenediamine (Aldrich) and 30 g (0.57 mol) of acrylonitrile; bp 120 °C (0.01 mm); yield 31 g, 61%. NMR: τ 8.72 (s) 4 H; 8.46 (~quintet, J = 7 Hz) 4 H; 7.82 (s) 6 H; 7.64 (t, J = 7 Hz) 4 H; 7.60 (s) 4 H; 7.33 (t, J = 7 Hz) 4 H.

5,8-Diethyl-1,5,8,12-tetraazadodecane, 7, was prepared from 29 g (0.25 mol) of *N,N'*-diethylethylenediamine (Ames) and 26 g (0.50 mol) of acrylonitrile; bp 120 °C (0.1 mm); yield 29 g, 50%. NMR: τ 9.01 (*t*, J = 6 Hz) 6 H; 8.8 (s) 4 H; 8.44 (quintet, J = 6 Hz) 4 H; 7.54 (t, J = 7 Hz) 4 H; 7.52 (s) 4 H; 7.31 (t, J = 7 Hz) 4 H.

5-Benzyl-1,5,8,12-tetraazadodecane, 8, as the Nickel(II) Chloride Complex. A solution of 63.7 g (0.38 mol) of bis(cyanoethylated) ethylenediamine [$NCCH_2CH_2NHCH_2-]_2$[9] in 500 ml of absolute ethanol was cooled to ice temperature. While the mixture was stirred, 65.6 g (0.38 mol) of benzyl bromide was added dropwise over a period of 1 h. After complete addition of the halide, the solution was refluxed for 2 h. As the refluxing proceeded, a white precipitate began to form. After the required reaction time, the mixture was cooled to ca. 5 °C and the white precipitate was filtered off. The solid was the dihydrobromide salt of bis(cyanoethylated) ethylenediamine and it was discarded. The filtrate was evaporated to an oil, which was taken up in a mixture of 200 ml of water and 100 ml of $CHCl_3$. While the mixture was stirred vigorously, the pH of the solution was adjusted to 8. The $CHCl_3$ layer was separated and dried over anhydrous Na_2SO_4. The Na_2SO_4 was removed and the filtrate evaporated to an oil. The oil (ca. 40 g) was dissolved in 200 ml of absolute ethanol and saturated with NH_3 at ca. 5 °C. The solution was treated with ca. 10 g of Raney nickel and hydrogenated at 50 psi of H_2 for 24 h. After this time, the mixture was filtered and the filtrate evaporated to an oil.

Thirteen grams of the oil was dissolved in 100 ml of absolute methanol and treated with 10 g of $NiCl_2 \cdot 6H_2O$. The dark green solution was heated to boiling and filtered. The filtrate was evaporated to dryness leaving behind a gummy, green semisolid. The semisolid was taken up in 200 ml of $CHCl_3$ and shaken vigorously. The mixture was filtered and the $CHCl_3$ filtrate dried over anhydrous Na_2SO_4. After 2 h, the Na_2SO_4 was removed and the filtrate evaporated to dryness. The residue was taken up in 25 ml of absolute ethanol and allowed to stand undisturbed. After approximately 1 day fine blue crystals had separated; yield 2.0 g. Anal. Calcd for $NiC_{15}H_{28}N_4Cl_2$: Ni, 14.90; C, 45.72; H, 7.16; N, 14.22. Found: Ni, 14.50; C, 45.51; H, 7.25; N, 13.78.

No additional product was obtained from evaporating the ethanol solution. Complete evaporation yielded an oily, green uncharacterizable residue.

5,8-Dibenzyl-1,5,8,12-tetraazadodecane, 9, as the Nickel(II) Chloride Complex. A solution of 16.0 g (0.1 mol) of cyanoethylated ethylenediamine ($NC(CH_2)_2NH(CH_2)_2NH(CH_2)_2CN$)[9] in 150 ml of absolute ethanol was treated with 25.3 g (0.2 mol) of benzyl chloride. The solution was refluxed for 5–6 h, during which time a white solid separated from solution. The mixture was cooled in a refrigerator and the white solid filtered off. The solid was the dihydrochloride salt of bis(cyanoethylated) ethylenediamine and was discarded. The ethanol filtrate was evaporated to an oil which was taken up in a mixture of 150 ml of water and 100 ml of $CHCl_3$. While the solution was stirred vigorously, the pH was adjusted to 8. The $CHCl_3$ layer was collected and dried over anhydrous Na_2SO_4 for 2–3 h. The Na_2SO_4 was removed and the filtrate evaporated to an oil (21 g).

The oil was dissolved in 150 ml of acetic anhydride and treated with 6.0 g of anhydrous sodium acetate. Five grams of Raney nickel was washed thoroughly with two 20-ml portions of acetic anhydride and two 20-ml portions of ethanol and added to the reaction mixture. The mixture was hydrogenated at 50 psi of H_2 for 12 h. During the hydrogenation the temperature of the solution rose to ca. 60–70 °C. When hydrogen uptake had ceased, the mixture was filtered and the filtrate treated with 100 ml of water. Within minutes the solution became quite hot as the acetic anhydride hydrolyzed. The solution was evaporated to an oil which was taken up in 150 ml of 9 M HCl. The acid solution was refluxed for 12 h and then evaporated to yield a brownish solid. The solid was dissolved in 100 ml of 5 M NaOH and extracted with two 75-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined and dried over anhydrous Na_2SO_4. The Na_2SO_4 was removed and the filtrate evaporated to an oil. The oil was added to 200 ml of water containing 15 g of $NiCl_2 \cdot 6H_2O$. The solution was heated to 60–70 °C, held there for 15 min, filtered, and evaporated to dryness. The solid was taken up in $CHCl_3$ and filtered, and the filtrate was dried over anhydrous Na_2SO_4. The Na_2SO_4 was removed and the filtrate evaporated to yield a green solid. The solid was collected, washed with ether, and dried in vacuo; yield 13.6 g, 50%. The compound isolated proved very difficult to purify but was predominantly the desired product as determined from elemental analysis and conversion to macrocyclic product; vide infra.

3,3,10,10-Tetramethyl-1,5,8,12-tetraazadodecane, 10. A solution of 63.7 g (0.65 mol) of 1,3-diamino-2,2-dimethylpropane in 300 ml of 95% ethanol was cooled to ice temperatures and treated with 24 g (0.13 mol) of 1,2-dibromoethane added dropwise over a period of 1 h. The solution was brought to reflux temperature and held there for 2 h. Upon cooling, the solution was treated with 25 g of KOH and refluxed for an additional 30 min. The mixture was then cooled and the precipitated KBr filtered off. The KBr was washed thoroughly with absolute ethanol. The filtrate was evaporated to an oil which was distilled under reduced pressure until all of the excess 1,3-diamino-2,2-dimethylpropane was removed. The remaining oil was dissolved in 50–100 ml of ether and filtered. The filtrate was evaporated to an oil and the oil distilled under reduced pressure. The fraction boiling at 132 °C (0.2 mm) was collected; yield 14.7 g, 50%. NMR: τ 9.14 (s) 12 H; 8.76 (s) 6 H; 7.62 (s) 4 H; 7.50 (s) 4 H; 7.34 (s) 4 H.

3,10-Dihydroxy-1,5,8,12-tetraazadodecane, 11. This amine was prepared by the same prodedure as the 3,3,10,10-tetramethyl analogue, **10**, using 81 g of 1,3-diamino-2-propanol and 28 g of 1,2-dibromoethane in 500 ml of ethanol. After removal of KBr and ethanol, the excess 1,3-diamino-2-propanol was removed by vacuum distillation during which the pot temperature was raised to ca. 120 °C. We were unable to distill the product. The NMR spectrum of the material was reasonably consistent with the desired product so that it was used for subsequent reactions as it was obtained.

1,2-Bis(3-aminopropoxy)ethane, 12. This material was prepared by hydrogenation of 1,2-bis(3-cyanoethoxy)ethane;[9] bp 82 °C (0.05

mm); yield 79%. NMR (60 MHz): τ 8.80 (s) 4 H; 8.32 (~quintet, J = 6 Hz) 4 H; 7.26 (t, J = 6 Hz) 4 H; 6.46 (s, overlapping triplet at ~6.48, $J \approx 6$ Hz) 8 H.

1,12-Diaza-5,8-dithiadodecane, 13. A three-necked flask fitted with condenser and nitrogen inlet system, magnetic stirring bar, dropping funnel, and thermometer was charged with 400 ml of ethanol and 9.2 g (0.4 mol) of sodium. After the sodium had dissolved, the flask was cooled in an ice bath (<5 °C) and 26 g (0.2 mol) of solid $(H_3NCH_2CH_2CH_2SH)Cl$[10] was added. A homogeneous solution was never obtained—only a change in the appearance of the suspended solid. The dropping funnel was loaded with 8.6 ml (18.8 g, 0.1 mol) of dibromethane and this was slowly added to the stirred cold solution. After addition was complete, the ice bath was removed and the mixture was refluxed for 1.5 h. After cooling, the sodium halides were removed by filtration and the ethanol was evaporated under reduced pressure. The residue that remained was extracted with ether and the dried (Na_2SO_4) extracts were evaporated to yield 10 g of a pale yellow oil; yield 50%. NMR: τ 8.32 (quintet, J = 7 Hz) 4 H; 8.15 (s) 4 H; 7.42 (t, J = 7 Hz) 4 H; 7.31 (s) 4 H; 7.28 (t, J = 7 Hz) 4 H. No further purification was necessary.

5,9-Dimethyl-1,5,9,13-tetraazatridecane, 16, was prepared from 46 g (0.45 mol) of *N,N'*-dimethyl-1,3-propanediamine and 48 g (0.91 mol) of acrylonitrile; bp 100–110 °C (0.1 mm); yield 49 g, 50%. NMR: τ 8.77 (s) 4 H; 8.44 (quintet, J = 7 Hz) 8 H; 7.84 (s) 6 H; 7.52–7.82 (overlapping triplets) 8 H; 7.32 (t, J = 7 Hz) 4 H.

Glyoxal Cyclization Reactions. Unless otherwise stated the following procedure was followed. Generally 0.1–0.5 mol of $NiCl_2 \cdot 6H_2O$ or $Ni(ClO_4)_2 \cdot 6H_2O$ was dissolved in 70–200 ml of water and was treated with 1 equiv of the appropriate tetradentate ligand. The resulting orange-brown solution was treated with a slight excess of glyoxal (30 or 40% in water) and allowed to stand for about 12 h (reaction times as short as 3 h were sometimes used and longer reaction times have no effect). After cooling of the reaction mixture to ~5 °C, 2 equiv of sodium borohydride was added, slowly to avoid frothing of the reaction mixture. This was added either as a solid or in a minimum amount of 1:1 ethanol–water. After addition of the borohydride the solution was heated to near boiling and filtered. The filtrate was cooled slightly and neutralized with concentrated $HClO_4$. Further cooling of the solution generally yielded crystalline product, and in some cases this was collected and recrystallized to yield pure material. An alternative and often better method involved extraction of the neutralized solution with nitromethane followed by drying of the extracts with sodium sulfate and evaporation of solvent to yield the crude product. Recrystallization was generally from hot water. A few drops of concentrated $HClO_4$ was generally added to reduce the solubility of the complex and thus speed up the crystallization process. Subsequent to the completion of most of this work, we found that catalytic hydrogenation (as utilized in the original preparation) gives yields equal to the borohydride method when the hydrogenation reaction is conducted at 50 psi of H_2 and 60–70 °C. In two preparations (0.05-mol scale) of **1a** (one utilizing $Ni(ClO_4)_2 \cdot 6H_2O$ as starting material, the other $NiCl_2 \cdot 6H_2O$), isolated yields of 70% were obtained. This is the only procedure by which **15c**, 1,5,9,13-tetraazacyclopentadecane, has been prepared.

Caution! We have prepared many samples of these nickel(II) complexes without an accident by observing the simple precaution of never heating them or their solutions with an uncontrolled heat source (such as a hot plate). We earlier had two terrific explosions when solutions of perchlorate salts of other nickel–amine complexes evaporated to dryness on a hot plate.

2-Methyl-1,4,8,11-tetraazacyclotetradecanenickel(II) perchlorate, 2a, was prepared from **2**; yield 70%. Anal. Calcd for $NiC_{11}H_{26}N_4Cl_2O_8$: Ni, 12.42; C, 27.93; H, 5.54; N, 11.86. Found: Ni, 12.18; C, 28.08; H, 5.42; N, 11.63.

2,2-Dimethyl-1,4,8,11-tetraazacyclotetradecanenickel(II) perchlorate, 3a, was prepared from **3**; yield 55%. Anal. Calcd for $NiC_{12}H_{28}N_4Cl_2O_8$: Ni, 12.08; C, 29.64; H, 5.81; N, 11.53. Found: Ni, 11.71; C, 29.92; H, 5.83; N, 11.61.

5,14-Dimethyl-1,4,8,11-tetraazacyclotetradecanenickel(II) perchlorate, 4a, was prepared from **4** using nitromethane to extract the product after reduction and acidification of the reaction mixture. Two isomers were formed since **4** is a mixture of diastereomers (two asymmetric carbon centers). Thin-layer chromatograms (microcrystalline cellulose, 6:1:2:1 1-butanol–ethanol–water–concentrated HCl) of the reaction mixture indicated that two isomers were indeed present (R_f 0.802, 0.63) in roughly equal amounts. After drying of the nitromethane extracts and evaporation of them to dryness, an orange oil remained which did not crystallize but could be induced to solidify by trituration with ethanol. Yields were typically 50%. The isomer having the greatest R_f value could be crystallized from the mixture by slow evaporation of an aqueous solution. Anal. Calcd for $NiC_{12}H_{28}N_4(ClO_4)_2$: Ni, 12.08; C, 29.66; H, 5.81; N, 11.52. Found: Ni, 12.23; C, 29.78; H, 5.80; N, 11.54. This complex exhibited a single methyl resonance in its NMR spectrum (trifluoroacetic acid solution, TMS) at τ 8.7 which occurred as a broad singlet rather than the expected doublet. In fact the entire spectrum was broad and featureless and it appeared that there was a small amount of a paramagnetic species present. Several attempts to obtain the spectrum produced similar results except that the bandwidths varied from sample to sample. The second isomer proved to be impossible to crystallize as the perchlorate salt even from fractions obtained from preparative-scale chromatography. Only oils were obtained. NMR spectra obtained on such oils contained doublets ($J \approx 6$ Hz) at τ 8.72 and 8.17 that are assigned to the methyl groups in this complex.

1-Methyl-1,4,8,11-tetraazacyclotetradecanenickel(II) perchlorate, 5a, was prepared from **5**; yield 70%. Anal. Calcd for $NiC_{11}H_{26}N_4Cl_2O_8$: Ni, 12.42; C, 27.93; H, 5.54; N, 11.86. Found: Ni, 12.53; C, 27.80; H, 5.42; N, 11.72.

1,4-Disubstituted Complexes 6a, 7a, and 9a. As described in the text there are two possible orientations of the two *N*-alkyl substituents, on the same side (eclipsed) or on opposite sides (staggered) of the coordination plane; thus there are two possible stereoisomeric complexes possible for **6a**, **7a**, and **9a**. The eclipsed form has C_s symmetry and the staggered C_2 symmetry; these will be so designated in the following discussions.

1,4-Dimethyl-1,4,8,11-tetraazacyclotetradecenenickel(II) Perchlorate, 6a. Three experiments were performed, twice each. The second trial was identical with the first except the quantity of all reagents used was half that of the first trial. Ratios of isomers were determined by NMR using relative peak heights of the methyl resonances. The C_2 isomer methyl resonance occurs at τ 3.0; the C_s resonance at τ 2.72.

Experiment 1. To a solution of 7.3 g (0.02 mol) of $Ni(ClO_4)_2 \cdot 6H_2O$ in 100 ml of H_2O was added 4.0 g (0.02 mol) of **6**. After mixing, the solution was cooled to room temperature with tap water (elapsed time about 5 min). To this solution was added 4 ml of 40% glyoxal and after mixing well it was allowed to stand undisturbed for 3 h at room temperature. After cooling of the solution in an ice bath to at least 5 °C, 1.42 g (0.04 mol) of $NaBH_4$ dissolved in ~50 ml of ethanol was slowly added with vigorous stirring. After the addition was complete, the solution was heated to near boiling and then gravity filtered to remove some black solid. After the solution cooled, it was acidified (pH ~3) with concentrated $HClO_4$ and then extracted with three 50-ml portions of nitromethane. After drying these extracts with sodium sulfate, the drying agent was removed and the nitromethane evaporated under reduced pressure to yield an orange complex. Trial 1: yield 7.2 g, 75%; C_2:C_s = 1.18. Trial 2: yield 4.1 g, 85%; C_2:C_s = 1.18. Crude materials from such experiments did not always give totally acceptable analyses. However a single recrystallization gave very good recovery of material with adequate analyses.

Experiment 2. The procedure was identical with that of experiment 1 except that the reaction time after addition of glyoxal was 24 h. Trial 1: yield 7.59 g, 78%; C_2:C_s = 7. Trial 2: yield 3.9 g, 80%; C_2:C_s = 5.7.

Experiment 3. The procedure here was identical with that described in experiment 1 except the solution of Ni^{2+} + **6** was allowed to stand 4 h before addition of glyoxal. The reaction time after addition of glyoxal was 3 h. Trial 1: yield 6.15 g, 67%; C_2:C_s = 0.98. Trial 2: yield 3.9 g, 80%; C_2:C_s = 1.18. Extraction of products from experiment 1 with acetone left behind the C_s isomer (by NMR) as deep orange crystals which were recrystallized from water. Anal. Calcd for $NiC_{12}H_{28}N_4Cl_2O_8$: Ni, 12.08; C, 29.64; H, 5.81; N, 11.53. Found: Ni, 12.20; C, 29.53; H, 5.89; N, 11.50. Pure C_2 isomer was best obtained by recrystallization of the product from experiment 2.

1,4-Diethyl-1,4,8,11-tetraazacyclotetradecenenickel(II) Perchlorate, 7a. Again three experiments were performed as described above using 3.5 g (0.015 mol) of $NiCl_2 \cdot 6H_2O$ and 3.5 g (0.015 mol) of **7** in 60–70 ml of H_2O, 3 ml of 40% glyoxal, and 1.2 g of $NaBH_4$.

Experiment 1. Five minutes after mixing of Ni^{2+} with **7**, glyoxal was added and 5.5-h reaction time was allowed before reduction; yield 6 g, 77%; C_2:C_s = 1.9.

Experiment 2. This was the same as experiment 1 except 22 h was allowed for glyoxal reaction; yield 5.2 g, 67%; C_2:C_s = 4.4.

Experiment 3. Ni^{2+} + **7** were allowed to stand for 24 h before addition of glyoxal. Reaction time was then 5.5 h before reduction; yield 5.4 g, 70%; C_2:C_s = 1.8. Recrystallization of material from experiment 2 gave pure C_2 isomer. Anal. Calcd: Ni, 11.42; C, 32.70; H, 6.27; N, 10.90. Found: Ni, 11.36; C, 32.84; H, 6.47; N, 10.85. Fractional crystallization of products of experiment 1 from water gave a small amount of pure C_s isomer as the more soluble fraction.

1,4-Dibenzyl-1,4,8,11-tetraazacyclotetradecanenickel(II) Perchlorate, 9a. This cyclization was conducted using 10 g (0.02 mol) of dichloro-5,8-dibenzyl-1,5,8,12-tetraazadodecanenickel(II) and 2.9 ml of glyoxal in 200 ml of H_2O. After a reaction period of 12 h the reaction mixture was treated as described for the dimethyl and diethyl complexes; yield 5.5 g, 50%. The infrared and NMR spectra were identical with those of a sample prepared by dibenzylation of [Ni(cyclam)]$^{2+}$ and is the isomer having C_2 symmetry.[6b]

1-Benzyl-1,4,8,11-tetraazacyclotetradecanenickel(II) Perchlorate, 8a. This cyclization reaction was conducted according to the previously described procedure starting with 1.7 g (4.3 mmol) of dichloro-5-benzyl-1,5,8,12-tetraazadodecanenickel(II) and 0.62 ml of 40% glyoxal in 50 ml of water; yield 1.3 g, 60%. Anal. Calcd for $NiC_{17}H_{30}N_4Cl_2O_8$: Ni, 10.71; C, 37.23; H, 5.54; N, 10.33. Found: Ni, 10.39; C, 37.55; H, 5.54; N, 10.33.

6,6,13,13-Tetramethyl-1,3,8,11-tetraazacyclotetradecanenickel(II) perchlorate, 10a, was prepared from **10**. Trial experiments indicated that the nickel complex of **10** reacted very slowly with glyoxal at room temperature. Thus reactions were ultimately conducted at 50 °C for 6 h. After reduction, the reaction mixture was treated with 2 equiv of NaSCN. The violet precipitate that formed was extracted with $CHCl_3$; the extracts were dried with Na_2SO_4 and, after filtration, evaporated to dryness. The large amount of violet precipitate obtained was largely the bis(thiocyanate) complex of the linear tetramine; however, after extraction of the precipitate with dilute HCl (which dissolved the linear amine complex), some violet material remained which was the bis(thiocyanate) of the cyclized product, albeit in low yield. This material was converted to the perchlorate salt with $AgClO_4$ in water. After removal of the precipitated AgSCN by filtration, the filtrate was acidified to yield the bis(perchlorate) salt as orange crystals; yield 3–5%. Anal. Calcd for $NiC_{14}H_{32}N_4Cl_2O_8$: Ni, 11.42; C, 32.69; H, 6.27; N, 10.90. Found: Ni, 11.40; C, 32.64; H, 6.26; N, 10.68.

Dithiocyanato-6,13-dihydroxy-1,4,8,11-tetraazacyclotetradecanenickel(II), 11a, was prepared from **11** on a 0.02-mol scale using a hydrogenation technique (Raney Ni catalyst). After removal of catalyst, NaSCN was added to precipitate a pale violet solid. This solid was collected, recrystallized from boiling water, washed with ethanol, and dried in vacuo to give 2 g of product; yield 25%. Anal. Calcd for $NiC_{12}H_{24}N_6O_2S_2$: Ni, 14.42; C, 35.40; H, 5.94; N, 20.64. Found: Ni, 14.23; C, 35.28; H, 6.0; N, 20.25. The infrared spectrum contained the expected absorptions for N–H, OH, and NCS functions.

1,5,9,13-Tetraazacyclopentadecane, 15b. A solution consisting of 15.6 g (43 mmol) of $Ni(ClO_4)_2·6H_2O$ (or an equivalent amount of $NiCl_2·6H_2O$), 8 g (43 mmol) of **15** and 8 ml of glyoxal in 150–200 ml of water was heated at ~60 °C for 2 h. Raney nickel catalyst was added and the solution was shaken at 60–70 °C under 50 psi of H_2 for 12–14 h. After removal of the catalyst, the solution was treated with 10 g of sodium cyanide and warmed until the orange color of $Ni(CN)_4^{2-}$ was obtained. The pH of the solution was adjusted to >12 with NaOH and six 50-ml extractions were made with $CHCl_3$. Evaporation of the $CHCl_3$ yielded an off-white solid that was recrystallized from hot THF by addition of pentane. After collection of the first crop, a second was obtained by evaporation of the filtrate and addition of more pentane; yield 45%. Anal. Calcd for $C_{11}H_{26}N_4$: C, 61.63; H, 12.22; N, 26.18. Found: C, 61.36; H, 12.32; N, 26.18. Note the material is hygroscopic and probably forms a hydrate.

1-Methyl-1,4,8,11-tetraazacyclotetradecane Tetrahydrochloride Monohydrate, 5b. A mixture of 2 g of **5a** and 0.5 g of NaCN in 50 ml of water was refluxed for 1 h, cooled, made very basic with NaOH, and extracted with $CHCl_3$ (three 25-ml portions). After drying of the extracts with Na_2SO_4, the $CHCl_3$ was evaporated to leave an oil which did not crystallize after several weeks. The oil was dissolved in ethanol and concentrated HCl was added to precipitate a white solid. This solid was collected, washed with ether, and dried in vacuo for 2.5 days. The infrared spectrum still showed that water was present in the sample; yield 1.3 g, 81%. Anal. Calcd for $C_{11}H_{26}N_4·4HCl·H_2O$: C, 34.94; H, 8.52; N, 14.81; Cl, 37.49. Found: C, 35.46; H, 8.68; N, 14.81; Cl, 37.42. NMR (D_2O, DSS, 60 MHz): τ 7.8 (multiplet) 4 H; 7.0 (s) 3 H; 6.46–6.71 (multiplet) ~8 H; 6.4 (s) ~4 H; 6.3 (s) ~4 H.

1,4-Dimethyl-1,4,8,11-tetraazacyclotetradecane Tetrahydrochloride Dihydrate, 6b. This amine salt was obtained in the same fashion as the monomethyl analogue; yield 85%. Anal. Calcd for $C_{12}H_{28}N_4·4HCl·2H_2O$: C, 35.13; H, 8.84; N, 13.66; Cl, 34.57. Found: C, 34.84; H, 8.68; N, 13.54; Cl, 35.34. NMR (D_2O, DSS, 60 MHz): τ 7.8 (multiplet) 4 H; 7.0 (s) 6 H; 6.45–6.7 (multiplet) ~8 H; 6.4 (s) 3 H; 6.35 (s) 3 H.

Isolation of Products from Reaction 1. Fourteen-Membered Ring. NCS Derivative. Slow addition of 2 equiv of thiocyanate to a reaction mixture comprised of 0.02 mol of $Ni(ClO_4)_2·6H_2O$, 0.02 mol of **1**, and 4 ml of 40% glyoxal resulted in precipitation of a tan solid which was insoluble in most ordinary solvents. This solid was washed well with methanol and dried at 100 °C (0.1 mm) for 18 h. The infrared spectrum showed an –OH stretch (3350 cm^{-1}), an NH stretch (3210 cm^{-1}), a C≡N stretch (2080 cm^{-1}), and an absorption at 1670 cm^{-1} that was assigned to a C=N stretch. Anal. Calcd for $NiC_{12}H_{20}N_6S_2·1.5H_2O$: Ni, 14.73; C, 36.19; H, 5.82; N, 21.10. Found: Ni, 14.73; C, 36.54; H, 5.85; N, 21.43.

$ZnCl_4$ Derivative. Addition of 2.2 equiv of $ZnCl_2$ to a reaction mixture similar to that described above except using $NiCl_2·6H_2O$ followed by filtration and slow evaporation of the dark brown solution under a stream of air gave a dark brown microcrystalline material. This complex was washed with methanol and dried at 100 °C (0.1 mm) for 18 h. The infrared spectrum showed an –OH stretch (3350 cm^{-1}) and an NH stretch (3140 cm^{-1}) (b)). No imine absorption could be assigned in this case. Anal. Calcd for $NiC_{10}H_{20}N_4ZnCl_4·H_2O$: Ni, 12.23; Zn, 13.61; C, 25.01; H, 4.62; N, 11.67. Found: Ni, 12.12; Zn, 14.14; C, 25.01; H, 4.62; N, 12.12.

Fifteen-Membered Ring. NCS Derivative. Addition of 2 equiv of NaSCN to reaction mixtures of Ni^{2+}, **15**, and glyoxal after heating for 2 h at 60 °C resulted in the precipitation of red-brown solids. Recrystallization of these from methanol yielded red-brown crystals whose infrared spectra contained absorptions for NH (3270, 3220 cm^{-1} (w)) and C=N (1654, 1600 cm^{-1}). Anal. Calcd for $NiC_{13}H_{22}N_6S_2$: Ni, 15.24; C, 40.53; H, 5.76; N, 21.81. Found: Ni, 15.14; C, 40.56; H, 5.85; N, 21.72.

***trans*-Dichloro-1,4,8,11-tetraazacyclotetradecanecobalt(III) Perchlorate.** To a solution of 16.87 g (0.046 mol) of $Co(ClO_4)_2·6H_2O$ in 125 ml of oxygen-free water was added under nitrogen 8.1 g (0.046 mol) of **1**. Glyoxal (7.7 ml, 40%) was added with good stirring and the solution was allowed to stand overnight (3–14 h produced identical results) after which time a deep wine red solution was present. After cooling of the solution to ~5 °C, 3.4 g of $NaBH_4$ was slowly added in small portions. Some metallic cobalt appeared during the addition. The solution was heated to near boiling and then, after cooling somewhat, acidified with concentrated HCl and filtered *in the air*. Upon cooling, green crystals formed. These were collected, washed with ethanol and ether, and air-dried; yield 6 g, 25%. Anal. Calcd for $CoC_{10}H_{24}N_4Cl_3O_4$: Co, 13.71; C, 27.95; H, 5.63; N, 13.04. Found: Co, 13.79; C, 27.56; H, 5.24; N, 12.89. The infrared spectrum of this product was identical with that of a sample prepared from **1b** by the literature procedure.[3]

In other experiments it was possible to isolate an unsaturated complex by passing air through the wine red solution, at the stage before addition of borohydride, and, after a short time, acidifying with concentrated HCl. The yield was no better than 10% for several attempts.

Cyclization of 1 with Glyoxal Using Cu(II) as the Template Ion. Two reactions were run using 3.7 g (0.01 mol) of $Cu(ClO_4)_2·6H_2O$ and 1.74 g (0.01 mol) of **1** in 50 ml of H_2O. Two milliliters of 40% glyoxal was added to the blue solution and it was allowed to stand for 5 h. During this time some Cu metal precipitated and the solution changed color slightly. After filtration, the solution was treated with 2 equiv of NaSCN and the mixture was cooled to ~5 °C. After a short while a green crystalline solid formed; it was collected, washed with ethanol and ether, and dried in vacuo; yield 2.2–2.5 g. Analyses on samples from these two preparations gave the following results (ratios are given in parentheses and are based on N = 6): Cu, 17.16, 17.78 (1.04, 1.14); C, 37.14, 36.70 (11.94, 12.48); H, 5.36, 5.03 (20.54, 20.38); N, 21.75, 20.57 (6, 6). Calcd for the α-diimine structure $CuC_{12}H_{20}N_6S_2$: Cu, 16.89; C, 38.32; H, 5.36; N, 22.35.

NMR spectra of **5a**, **6a** (both isomers), and **9a** are given in ref **6b**. Spectra of **2a**, **3a**, **4a** (both isomers), **7a** (both isomers), and **8a** are

given as supplementary material to this paper. Complex **10a** was too insoluble to obtain an NMR spectrum.

Results and Discussion

Preparation of Linear Tetradentate Ligands. As a part of this study, a number of linear tetradentate ligands were prepared, several for the first time, for testing in the nickel ion assisted cyclization reaction with glyoxal. A complete list of ligands is given in Chart I; syntheses and properties of new ligands are described in the Experimental Section. Most of the ligands were prepared by cyanoethylation of the appropriate difunctional compound as shown in eq 4, followed by

$$\begin{matrix} XH \\ | \\ (CH_2)_n \\ | \\ XH \end{matrix} + 2CH_2{=}CHCN \rightarrow \begin{matrix} XCH_2CH_2CN \\ | \\ (CH_2)_n \\ | \\ XCH_2CH_2CN \end{matrix} \qquad (4)$$

X = O, S, NH, NR; n = 2, 3

catalytic reduction of the nitrile groups. Nitrile intermediates were not purified; their identity was determined before hydrogenation by spectroscopy (ir, NMR). In general, yields were quite good. Exceptions were **3**, which was one of several components in the mixture obtained from the hydrogenation reaction, and **4**. Addition of crotonitrile to ethylenediamine proved difficult, and a fairly low yield of the latter compound was obtained. The identity of the tetradentates (and an estimate of their purity) was established by NMR. Generally, product from a single distillation was pure enough for use in the cyclization reaction; however, in cases where problems were encountered, the nickel(II) perchlorate complex was prepared and purified prior to carrying out the cyclization reaction. In particular, this proved helpful in the case of **5**.

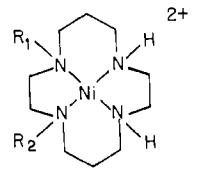
Some amines could not be prepared by the cyanoethylation route. N-Benzylated ethylenediamines did not add to acrylonitrile, even under forcing conditions. Thus ligands **8** and **9** were prepared by an alternate route that involved mono- and dibenzylation, respectively, of *N,N'*-bis(2-cyanoethyl)-1,2-diaminoethane and reduction of the nitrile groups. These amines were isolated as their nickel(II) chloride complexes. These procedures are not satisfactory for the preparation of quantities of these materials.

Tetramines **7** and **11** cannot be prepared by a cyanoethylation route. These amines were prepared by a standard nucleophilic displacement[12] route from 2,2-dimethyl-1,3-diaminopropane and 1,2-dibromethane and from 1,3-diamino-2-propanol and 1,2-dibromoethane, respectively. The dihydroxytetramine **11** could not be distilled, nor did acid salts crystallize readily. The impure material was used for all cyclization experiments. The N_2S_2 ligand **12** was prepared by reaction 5 in satisfactory yield.

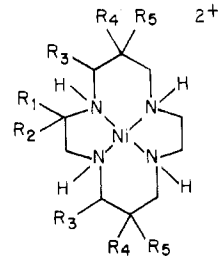
$$2H_2NCH_2CH_2CH_2S^- + BrCH_2CH_2Br \rightarrow (H_2NCH_2CH_2CH_2SCH_2{-})_2 + 2Br^- \qquad (5)$$

Nickel Ion Assisted Cyclization Reactions. Fourteen-Membered Systems. Eleven successful cyclization reactions of linear tetramines and glyoxal were conducted and the products isolated, after reduction, as nickel(II) complexes. Structures of these complexes are shown in Chart II. Complex **1a** has been known for about 10 years although a truly satisfactory procedure for its preparation was only recently developed.[2] Complexes **5a**, **6a**, and **9a** were recently reported by us as products of alkylation reactions of **1a**;[6b] however, such alkylation reactions are not satisfactory methods for the preparation of **5a** and **6a**. Yields of most products obtained by the glyoxal cyclization reaction were greater than 50% and some were obtained in yields as high as 75–80%. Exceptions to this were **10a** and **11a**, which were both obtained in quite low yields. Characterization of products was by analysis and infrared and NMR spectroscopy as appropriate. Perchlorate salts were generally obtained by crystallization from the reaction mixture or by extraction with nitromethane. Nitromethane was a very good solvent for most of the complexes prepared. Again **10a** and **11a** were exceptions as they were both isolated as thiocyanato complexes.

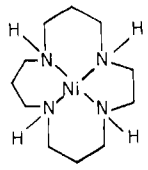
Chart II. Complexes Prepared by the Nickel(II)-Assisted Cyclization with Glyoxal



	R_1	R_2
1a	H	H
5a	CH_3	H
6a[a]	CH_3	CH_3
7a[a]	C_2H_5	C_2H_5
8a	$C_6H_5CH_2$	H
9a[b]	$C_6H_5CH_2$	$C_6H_5CH_2$



	R_1	R_2	R_3	R_4	R_5
2a	CH_3	H	H	H	H
3a	CH_3	CH_3	H	H	H
4a[c]	H	H	CH_3	H	H
10a	H	H	H	CH_3	CH_3
11a[d]	H	H	H	H	OH



15a

[a] Two isomers are formed in the cyclization reaction; the ratio depends on the reaction conditions. [b] Only one of the two possible isomers was isolated. [c] Two isomers are formed because of the diastereoisomeric composition of the starting tetramine; these were separable by chromatography or crystallization. [d] Two isomers are formed because of the diastereoisomeric composition of the starting tetramine; these were not separated.

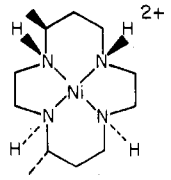
In our first successful use of this metal ion assisted cyclization reaction, for the preparation of **1a**,[1] the unsaturated intermediate was catalytically reduced at room temperature with hydrogen using Raney nickel catalyst. Later sodium borohydride was utilized with a substantial improvement in yield.[2] Most of the preparations reported here were done using sodium borohydride as the reducing agent; however, as outlined in the Experimental Section, catalytic hydrogenation *conducted at 60–70 °C* was equally effective and gave a cleaner product. Either method should be adequate for most preparations.

The low yield of **10a**, which was obtained in three attempts, is probably due to a low rate of reaction of Ni(tetramine)$^{2+}$ with glyoxal. The tetramine complex formed with **1** reacted completely with glyoxal in 2.5 h as shown by the absence of further change in the absorption spectrum of the reaction mixture after this time. However, in the case of **10**, the reaction with glyoxal did not occur to an appreciable extent after 2 days at room temperature. Heating the reaction mixture at 50 °C for a few hours increased the extent of reaction (judging by the color of the solution) but produced

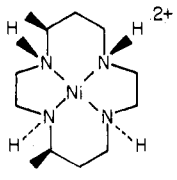
some insoluble material. A low rate of dissociation of primary amine groups in the complex may be responsible for the low rate of reaction. A free amino group is required for the Schiff base reaction but the tetramine complex of **10** may be considerably less prone to dissociation than complexes of amines not substituted in the 3 and 10 positions. It is known that 2,2-dimethyl-1,3-propanediamine forms Ni(II) and Cu(II) complexes that are more stable than those of the unsubstituted diamine.[13] The low yield obtained for **11a** is most likely due to the fact that the tetramine used was not pure, although the hydroxy groups might also have had an effect.

Attempts to utilize tetradentate ligands **12** and **14** in the cyclization reaction were unsuccessful because of the low stability of their nickel complexes in aqueous solution. One to one ratios of Ni^{2+} and **12** or **14** produced copious quantities of nickel hydroxide in water. A low stability constant for the Ni^{2+} complex of **14** compared with those for other tetramines has been recognized.[14] The S_2N_2 ligand, **13**, yields a stable complex with nickel ion in water and a reaction between this complex and glyoxal occurs. However, attempts to reduce the complex with sodium borohydride were unsuccessful. So much of the nickel was reduced to the metallic form that the reaction solution was nearly colorless after filtration. Since none of these three systems appeared at all promising, no further work was done with them.

Some interesting stereochemical aspects of these cyclization reactions merit discussion. The 14-membered ligand complexes contained in Chart II can be divided into three groups for the purposes of this discussion. The first of these groups consists of **2a**, **3a**, **5a**, **8a**, and **10a**. These complexes are expected to have the cyclam-like set of nitrogen donor configurations[15] and no other stereoisomeric possibilities (other than optical). The second group consists of **4a** and **11a**. Tetramines **4** and **11** consist of diastereoisomers and thus the macrocyclic ligand complexes will also exist in diastereoisomeric form. These complexes should have the cyclam-like set of nitrogen donor configurations. Complex **4a**, which was separated into its isomeric forms, should have the structures[16] I and II. NMR data obtained on these two isomers (see



I



II

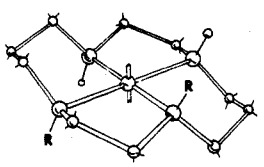
Experimental Section) are consistent with these structures.[17] No separation of **11a** was attempted. The third group consists of **6a**, **7a**, and **9a**. Cyclization reactions of 1,5,8,12-tetraazadodecanes that have substituents in the 5 and 8 positions, such as **6**, **7**, and **9**, may produce stereoisomeric products. If only the 5 and 8 substituents are considered, then there are two possible products. One of these has both substituents on the same side of the nickel–nitrogen donor plane (eclipsed) and the other has the two substituents located on opposite sides of the plane (staggered).

In fact, we found that preparations using tetramines **6** and **7** yielded mixtures of the stereoisomers. Both isomers of **6a** showed a single methyl resonance in their NMR spectrum. This observation alone confirmed that the N–H groups in the staggered form must have the expected cyclam-like configurations and hence the complex must have C_2 symmetry. In order for the methyl groups in the eclipsed form to exhibit isochronous behavior both N–H groups must be located on the same side of the coordination plane. These protons could be on the same side of the coordination plane as the methyl groups or on the opposite side. However, it is obvious that the former has the lower energy set of ring conformations.[3a,16] This structure has C_s symmetry. Idealized structures for the staggered and eclipsed isomers are shown below.

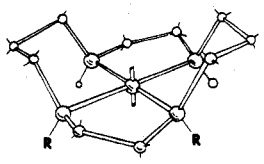
Table I. Product Distribution in Cyclization Reactions of 5,8-Disubstituted Tetramines

Tetramine	Reaction times[a] Ni^{2+} + tetramine	Reaction times[a] [Ni(tetramine)]$^{2+}$ + glyoxal	Product ratio C_2:C_s	Total yield, %
6[b]	5 min	3 h[c]	1.2	75
	5 min	24 h	6.4	80
	4 h	3 h	1.1	72
7[d]	5 min	5.5 h[e]	1.9	77
	5 min	22 h	4.4	67
	24 h	5.5 h	1.8	70
9	*f*	12 h	*g*	55

[a] All reactions were conducted at room temperature. [b] Product ratio and yield are averages of two experiments; the amount of C_2 isomer represents an upper limit because of overlap of methyl resonance with methylene resonances in the NMR spectrum. [c] After this time there was no further change in the intensity of bands that were assigned to the unsaturated product of the cyclization reaction when reaction mixtures were followed spectrophotometrically. [d] The amount of C_s represents an upper limit because of overlap of methyl group patterns in the NMR spectrum of the mixtures. [e] After this time rapid changes in the absorption spectra of reaction mixtures ceased to occur. [f] Preformed Ni(tetramine)Cl_2 was used as starting material. [g] Only the C_2 isomer was obtained.



C_2

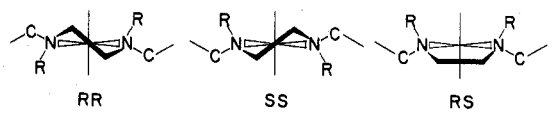


C_s

The stereoisomers of **6a** were separated by extraction with acetone. The identity of the least soluble dimethyl isomer as the one of C_s symmetry was determined by conversion of the two compounds to *N*-tetramethyl complexes of known structure,[6b] although the same result could be obtained on the basis of data given below.

The relative amounts of C_2 and C_s isomers formed from cyclization reactions of **6** and **7** depended upon the reaction time for the reaction of the nickel–tetramine complex with glyoxal. Table I shows the results of several experiments using amines **6** and **7** for cyclization reactions. These results show that the distribution of products in both cases is determined by the Ni(tetramine)$^{2+}$ + glyoxal reaction time. As the reaction time increased, so did the amount of the C_2 isomer at the expense of the C_s form, with the total yield of macrocyclic complexes remaining essentially constant.

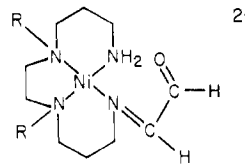
The above observations provide some information about the mechanism of the cyclization reaction and about the relative energies of the staggered and eclipsed forms of the unsaturated intermediate. Work on the Co(III) complexes of linear tetramine **1** indicated that under equilibrium conditions this ligand prefers a planar geometry with an *RR* or *SS* set of secondary nitrogen donor configurations with essentially none of the *RS* form. The Ni(tetramine)$^{2+}$ species derived from



RR SS RS

6 or **7** should also exist predominantly in the *RR* (*SS*) form as well. Thus the nearly equal amounts of the C_2 and C_s isomers that are found early in the cyclization reaction must

be a result of a faster rate of reaction of the equilibrium amount of the *RS* isomer with glyoxal. This requires the rate of *RR* (*SS*) → *RS* conversion in Ni(tetramine)$^{2+}$ to be greater than the rate for reaction of the *RR* (*SS*) isomer with glyoxal. This is not an unreasonable expectation for a labile metal such as nickel(II) although specific rate constants for such an isomerization are not available. Thus the initial isomer distribution in the unsaturated intermediate is a result of kinetic control, and reduction with borohydride "traps the system" as the saturated macrocyclic ligand complex. When the reaction Ni(tetramine)$^{2+}$ + glyoxal is allowed to approach equilibrium, the C_s isomer is slowly converted to the more stable C_2 form. This presumably occurs via a ring-opened species such as III. If isomerization does occur via this



III

intermediate, then kinetic control of the initial product ratio requires that the *RS* tetramine complex react more rapidly than *RR* (*SS*) form to form the above intermediate and that ring closure to form the second imine (or carbinolamine) is much faster than isomerization. No evidence for stepwise formation of product was obtained from spectra taken on reaction mixtures. In all cases only an increase in the intensity of the band assigned to the product of reaction 1 was observed in the early stages of the reaction.

The single preparation of **9a** that was performed was done prior to the discovery of the time dependence of the isomer distribution described above for **6a** and **7a**. Twelve hours was allowed for reaction 1 and only a single stereoisomer was obtained. Its identity as the C_2 form rests on a comparison with a sample prepared by an alternative route, alkylation of [Ni(cyclam)]$^{2+}$.[6b] With the exception of the 22-h reaction with tetramine **7**, whose product analysis may be substantially in error, the data given in Table I suggest that the larger the size of the 5 and 8 substituents in the tetraazadodecane, the smaller the amount of the C_s isomer that is formed at any stage of the reaction. This is reasonable since one expects that steric interactions between groups would increase as the size of the groups increases and that this should decrease the stability of the *RS* form of the nickel–tetramine complex and perhaps decrease the rate of *RR* (*SS*) ⇌ *RS* interconversion. Both results should decrease the amount of the C_s isomer formed in the initial stages of the cyclization reaction.

As described earlier, cyclam, **1b**, can be obtained in high yield by decomposition of **1a** with cyanide ion.[2] This decomposition may be performed without isolation of the nickel complex with no loss in yield. In fact, if the free base is the desired product, this procedure is saving in time. Cyanide decomposition of the other complexes shown in Chart II should be equally feasible and thus should provide an easy route to a variety of substituted ligands of the cyclam type. We earlier demonstrated that complex **9a** was readily decomposed with cyanide ion[6b] and we have since shown that **5a** and **6a** can be decomposed with cyanide and that the amines are readily isolated as hydrochloride salts (see Experimental Section).

Fifteen- and Thirteen-Membered Systems. The reaction of glyoxal with the nickel complex of **14** proceeded slowly at room temperature and a few days was required to develop the deep orange-brown color that is typical of reaction mixtures for the 14-membered systems. However, when the reaction mixture was heated at 60–70 °C, the reaction was greatly accelerated and the intense color expected for the intermediate unsaturated complex rapidly formed. Borohydride reduction of the intermediate complex was not successful, as copious quantities of black metallic nickel precipitated with every attempt at this reaction. However, after a 2-h reaction period at 60–70 °C, catalytic hydrogenation (Raney nickel, 50 psi of H_2, 60–70 °C) proceeded smoothly and moderate yields (40–45%) of the 15-membered tetramine were isolated by extraction after treatment of the solution with excess cyanide. Isolation of the free amine was much easier than isolation of the nickel complex. The latter could be simply prepared from the amine as required. Although the yield of the tetraazacyclopentadecane is not as high as for the 14-membered tetramines, it is still the best procedure presently available for its synthesis.[18] Attempts to prepare 1,5-dimethyltetraazacyclopentadecane from **16** were frustrated by the instability of the nickel complex of **16** in aqueous solution. No other reactions of tetraazatridecanes were attempted.

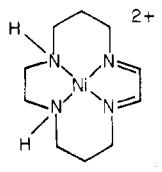
All of our attempts to prepare 13-membered rings by the glyoxal condensation reaction with the nickel complex of **17** were unsuccessful. Judging from the color of the solution there was little reaction with glyoxal at room temperature. When reaction mixtures were heated at 60–70 °C, a darker color somewhat like that expected was produced but attempts at catalytic reduction of these species did not yield cyclized products. Addition of NaSCN to the reaction mixture after attempted reduction yielded only the bis(thiocyanato) complex of the linear tetramine.

Other Metal Ions. Both Co(II) and Cu(II) have been utilized to a limited extent as replacements for Ni(II) in reaction 1. Deep violet solutions rapidly formed when Co(II) was used as the template ion for the cyclization reaction with tetramine **1**. Although quantitative measurements were not made, this reaction appeared to be complete in about half the time required when nickel was used. The color of the complex formed is similar to that of the complex obtained from the condensation reaction of biacetyl and **1**.[19] The violet species formed in reaction 1 was very air sensitive in solution. Addition of sodium tetraphenylborate resulted in precipitation of a pink solid, but it was also very air sensitive and it was not characterized. Air oxidation of the violet product followed by addition of HCl and $HClO_4$ produced very low yields of a complex that contained a cyclic ligand (see next section). Reduction of the violet product with sodium borohydride (which produced a considerable amount of metal) followed by air oxidation and acidification gave a low yield (maximum 25%) of [Co(cyclam)Cl_2]ClO_4.[3a]

When Cu(II) was used as the template ion, the deep blue solution of the tetramine complex generated with ligand **1** slowly became redder. After 2–3 h some copper metal formed in the flask. After filtration, addition of sodium thiocyanate produced a deep green product in high yield. The product apparently contained a macrocyclic α-diimine ligand (see next section) but attempts to reduce the unsaturated complex with either sodium borohydride or hydrogen–Raney nickel resulted in complete reduction of Cu(II) to metal.

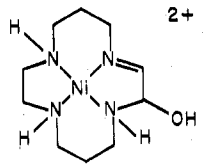
No further investigations were made with either of these metals as template ions as it seemed unlikely that either of them could replace nickel as the reagent of choice for the production of saturated macrocyclic tetramine ligands.

Products of Reaction 1. We had earlier assumed that the complex formed in reaction 1 contained the α-diimine ligand,[1] IV. Such species have been isolated from analogous reactions



IV

that involved biacetyl as the α-dicarbonyl reagent.[5] Our first attempts to isolate the product formed from tetramine **1** were unsuccessful; however, we were ultimately able to obtain both $ZnCl_4^{2-}$ and thiocyanato derivatives of a complex from the glyoxal reaction mixture. In each case, after drying at 100 °C in vacuo for several hours, the infrared spectra of these derivatives showed strong –OH stretching absorptions and the analytical data were consistent with the presence of 1 and 1.5 mol of water, respectively. NMR spectra obtained on concentrated sulfuric and trifluoroacetic acid solutions did contain resonances for vinylic protons. Spectra obtained on freshly prepared trifluoroacetic acid solutions show two vinylic proton resonances; one of these disappeared as the solution aged. The spectra obtained on sulfuric acid solutions showed only one resonance for vinylic protons regardless of age. Although these data are not unambiguous, we believe that the species isolated is probably an imine–carbinolamine complex, V. Such a



V

species would be rapidly dehydrated in concentrated sulfuric acid and probably in trifluoroacetic as well; however, the rate of dehydration in the latter acid should be slower. The presence of two types of =C—H resonances in spectra obtained on freshly prepared solutions may be attributed to the presence of imine–carbinolamine and α-diimine complexes. Loss of water from the carbinolamine function, which is the final step to Schiff base formation, could occur after reduction of the existing imine function. The product obtained from the S_2N_2 ligand **13** was also hydrated and may also contain a carbinolamine function.

Previously mentioned products that were obtained via reaction 1 using Cu(II) and Co(II) were equally difficult to characterize. The bis(thiocyanato)copper complex was never obtained in analytically pure form; although the C, H, and N elemental ratios were always correct for an α-diimine species, the amount of copper was always high and the insolubility of the complex precluded purification. No infrared absorptions for –OH were observed but absorptions for an α-diimine function[20] were not clearly defined either, so the nature of the product remains uncertain. The cobalt complex was obtained as a hydrated material. Again it was not possible to dehydrate samples by heating in vacuo and the actual structure is unknown.

The 15-membered ring product that was obtained from reaction 1 with tetramine **15** was the only α-diimine complex that could be definitively characterized. The red-brown product obtained by addition of thiocyanate to reaction mixtures of Ni^{2+}, **15**, and glyoxal exhibited absorptions for C=N (1654, 1600 cm^{-1}) as well as NH (3270 (w), 3220 cm^{-1}) in its infrared spectrum. Analytical data were also consistent with an α-diimine structure.

Conclusion

The results presented in this paper clearly demonstrate the general synthetic utility of cyclization reactions between linear tetramines and glyoxal, using nickel as a template ion, in the synthesis of complexes of saturated 14- and at least one 15-membered macrocyclic tetramines. The simplicity of the procedures required to conduct these preparations and the ease with which the ligands can be isolated makes the method a practical route to a variety of cyclic tetramines. It appears likely that almost any substituted 1,5,8,12-tetraazadodecane that is available can be utilized in the cyclization reaction. Most tetramines of this class are fairly easily prepared. The situation with regard to the use of 1,5,9,13-tetraazatridecanes is less obvious. It is apparent that substituents in both the 5 and 8 positions cause the nickel complex to be too unstable; presumably C-substitution would have a much smaller, and perhaps negligible, effect on the stability of the metal complex.

In principle, any metal that forms linear tetramine complexes of a stability similar to that of the nickel(II) complexes and which has an ionic radius about the same as that of Ni(II) should serve as a template ion for the condensation reaction (reaction 1). It seems that both Co(II) and Cu(II) do function well in this regard, although the products were not fully characterized. However, the unsaturated complexes cannot be successfully reduced to their saturated forms by either of the methods that were used for reduction of the nickel complexes.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. The assistance of Mr. Jay Corwin in the synthesis of tetramine ligands was most helpful.

Registry No. **2a**, 58815-23-9; **3**, 58770-16-4; **3a**, 58815-21-7; **4**, 58770-17-5; **4a**(I), 58802-50-9; **4a**(II), 58864-84-9; **5**, 58770-18-6; **5a**, 57379-01-8; **5b**, 53118-96-0; **6**, 999-22-4; **6a**(C_2), 57379-03-0; **6a**(C_5), 57427-03-9; **6b**, 58770-19-7; **7**, 58770-20-0; **7a**(C_2), 58846-41-6; **7a**(C_5), 58802-48-5; **8**·$NiCl_2$, 58801-83-5; **8a**, 58802-46-3; **9**·$NiCl_2$, 58802-44-1; **9a**, 57378-99-1; **10**, 58770-21-1; **10a**, 58801-91-5; **11**, 58770-22-2; **11a**, 58801-76-6; **12**, 2997-01-5; **13**, 7058-57-3; **15**, 4605-14-5; **15b**, 15439-16-4; **16**, 999-41-7; *trans*-dichloro-1,4,8,-11-tetraazacyclotetradecanecobalt(III) perchlorate, 15220-75-4; 1,2-diamino-2-methylpropane, 811-93-8; ethylenediamine, 4433-65-2; *N*-methylethylenediamine, 109-81-9; *N,N'*-dimethylethylenediamine, 110-70-3; *N,N'*-diethylethylenediamine, 111-74-0; $[NCCH_2CH_2NHCH_2-]_2$, 3217-00-3; 1,3-diamino-2,2-dimethylpropane, 7328-91-8; 1,3-diamino-2-propanol, 616-29-5; 1,2-bis(3-cyanoethoxy)ethane, 3386-87-6; $(H_3NCH_2CH_2CH_2SH)Cl$, 7211-54-3; *N,N'*-dimethyl-1,3-propanediamine, 111-33-1; acrylonitrile, 107-13-1; crotonitrile, 4786-20-3; benzyl bromide, 28807-97-8; benzyl chloride, 25168-05-2; 1,2-dibromoethane, 106-93-4; glyoxal, 107-22-2.

Supplementary Material Available: NMR spectra of **2a**, **3a**, **4a**, **7a**, and **8a** (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) E. K. Barefield, *Inorg. Chem.*, **11**, 2273 (1972).
(2) E. K. Barefield, F. Wagner, A. W. Herlinger, and A. R. Dahl, *Inorg. Synth.*, **16** 220 (1975).
(3) (a) B. Bosnich, C. K. Poon, and M. L. Tobe, *Inorg. Chem.*, **4**, 1102 (1965); (b) H. Stetter and K. H. Mayer, *Chem. Ber.*, **94**, 1410 (1961).
(4) J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, **96**, 2268 (1974).
(5) E. K. Barefield, Ph.D. Thesis, The Ohio State University, 1969.
(6) (a) F. Wagner, M. T. Mocella, M. J. D'Aniello, Jr., A. H.-J. Wang, and E. K. Barefield, *J. Am. Chem. Soc.*, **96**, 2625 (1974); (b) E. K. Barefield and F. Wagner, *Inorg. Chem.*, **15**, 408 (1976).
(7) I. M. Israel, J. S. Rosenfield, and E. J. Modest, *J. Med. Chem.*, **7**, 710 (1964).
(8) L. J. Dehayes and D. H. Busch, *Inorg. Chem.*, **12**, 2010 (1973).
(9) H. A. Bruson, *Org. React.*, **5**, 79 (1949).
(10) T. C. Owen, *J. Chem. Soc. C*, 1373 (1967).
(11) L. C. Baker, J. E. Kirby, R. N. McDonald, and C. W. Todd, *J. Am. Chem. Soc.*, **68**, 1296 (1946).
(12) H. G. Hamilton, Jr., and M. D. Alexander, *Inorg. Chem.*, **5**, 2060 (1966).
(13) G. B. Hares, W. C. Fernelius, and B. E. Douglas, *J. Am. Chem. Soc.*, **78**, 1816 (1956); M. S. Newman, D. H. Busch, G. E. Cheney, and C. R. Gustafson, *Inorg. Chem.*, **11**, 2890 (1972).
(14) W. Wind and D. E. Goldberg, *J. Inorg. Nucl. Chem.*, **31**, 575 (1969).
(15) B. Bosnich, R. Mason, P. J. Pauling, G. B. Robertson, and M. L. Tobe, *Chem. Commun.*, 97 (1965).
(16) L. G. Warner and D. H. Busch, *J. Am. Chem. Soc.*, **91**, 4092 (1969).
(17) Both isomers of the 5,12-dimethyl analogue of **4a** have been prepared by reduction of the 4,11-diene complex: R. A. Kolinski and B. Korybut-Daszkiewicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **17**, 13 (1969).
(18) L. Y. Martin, L. J. Dehayes, L. J. Zompa, and D. H. Busch, *J. Am. Chem. Soc.*, **96**, 4046 (1974).
(19) S. C. Jackels, K. Farmery, E. K. Barefield, N. J. Rose, and D. H. Busch, *Inorg. Chem.*, **11**, 2893 (1972).
(20) L. T. Taylor, N. J. Rose, and D. H. Busch, *Inorg. Chem.*, **7**, 785 (1968).