Articles

Structural Analysis of All the Nickel 14-Membered Tetraaza Macrocycles in the Cambridge Structural Database

Maria A. Donnelly and Marc Zimmer*

Chemistry Department, Connecticut College, New London, Connecticut 06320

Received August 3, 1998

One hundred and thirty-nine nickel complexes containing the 1,4,8,11-tetraazacyclotetradecane backbone were found in the Cambridge Structural Database. Cluster analysis was used to separate the structures according to their macrocyclic configurations, using their conformations as a separation criteria. The most commonly found configuration was the trans III configuration. The amount of trans I macrocycles relative to trans III macrocycles was found to be higher for square-planar complexes than octahedral ones. Molecular mechanical conformational searches were done for select structures found in the Cambridge Structural Database.

Introduction

Macrocyclic complexes are thermodynamically more stable and more selective metal ion binders than their open-chain analogues. These facts have led to a large amount of research involving such systems.[1−6] The 14-membered macrocycle 1,4,8,11-tetraazacyclotetradecane (cyclam, 14-aneN_4) is one of the most commonly studied and used macrocycles. Cyclam was first synthesized in 1937,[7] and new uses for this macrocycle and its derivatives continue to be found. They have applications in a variety of areas, including catalysis, bioinorganic, biomimetic, and coordination chemistry.[8] The tight coordinations found in metal-containing molecules of cyclam and its derivatives allow them to be used as metal ion binding sites in medical techniques such as MRI and radioimmunotherapy.[9−11] The macrobicyclic hexaamine sar has gained importance through its ability to create dissociation resistant complexes by coordinating to many metal ions as a hexadentate ligand.[12,13] Many of the derivatives of cyclam can also be used as catalysts in redox reactions.[14] For example, nickel-containing tetraaza macrocycles are used to produce CO through the photochemical and electrochemical reduction of CO_2.[15,16] Even in H_2O, $[Ni(cyclam)]^{2+}$ catalyzes this reaction selectively and efficiently.[15] In addition, a fluorescent sensor capable of sensitively and selectively monitoring heavy metal ion concentrations has been synthesized by linking cyclam to 4-(*N*,*N*-dimethylamino)benzonitrile.[17]

It has become apparent that the substituents on the rings of cyclam derivatives, especially when those functional groups are bonded to one or more of the nitrogens, have a very important affect on the chemistry of the macrocycles.[18,19] Changes in substituents can cause important alterations in both structural and chemical properties.[19] For example, the lability of 1,4,8,11-tetrakis(2-hydroxyethyl)-1,4,8,11-tetraazacyclotetradecane in many reactions is greatly increased by complete *N*-hydroxyethylation,[19] while the addition of electron-withdrawing groups, such as fluorine, has been observed to reduce ligand field strengths and amine basicities.[8] (Tetramethylcyclam)nickel has been used as a model for F430, the prosthetic group of methyl coenzyme M reductase.[20] In the transport of Ni^{II} across a bulk liquid membrane, Tscyclam is a much more efficient carrier than lipophilic cyclam, which is too strongly coordinating for the metal to be released into the aqueous phase.[21] Substituents which provide additional chelating sites can also promote redox

---

(1) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, U.K., 1989.
(2) Martell, A. E.; Hancock, R. D. Metal Complexes in Aqueous Solutions. *Modern Inorganic Chemistry*; Fackler, J. P., Ed.; Plenum: New York, 1996.
(3) Cabbiness, D. K.; Margerum, D. W. *J. Am. Chem. Soc.* **1969**, *91*, 6540.
(4) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
(5) Ciampolini, M.; Nardi, N.; Vantancoli, B.; Micheloni, M. *Coord. Chem. Rev.* **1992**, *120*, 223.
(6) Lindoy, L. *Pure Appl. Chem.* **1997**, *69*, 2179.
(7) van Alphen, J. *Rec. Trav. Chim.* **1937**, *56*, 343.
(8) Shionoya, M.; Kimura, E.; Iitaka, Y. *J. Am. Chem. Soc.* **1990**, *112*, 9237 and references therein.
(9) Konig, B.; Pelka, M.; Zieg, H.; Jones, P. G.; Dix, I. *J. Chem. Soc., Chem. Commun.* **1996**, 471.
(10) Aime, S.; Botta, M.; Crich, S. G.; Giovenzana, G. B.; Jommi, G,; Pagliarin, R.; Sisti, M. *J. Chem. Soc., Chem. Commun.* **1995**, 1885.
(11) Norman, T. J.; Parker, D.; Smith, F. C.; King, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1879.
(12) Bernhardt, P. V.; Harrowfield, J. M.; Hockless, D. C. R.; Sargeson, A. M. *Inorg. Chem.* **1994**, *33*, 5659.
(13) Comba, P.; Sargeson, A. M.; Engelhardt, L. M.; Harrowfield, J. M.; White, A. H.; Horn, E.; Snow, M. R. *Inorg. Chem.* **1985**, *24*, 2325.
(14) Barefield, E. K.; Freeman, G. M.; Van Derveer, D. G. *Inorg. Chem.* **1986**, *25*, 552.
(15) Szalda, D. J.; Fujita, E.; Sanzenbacher, R.; Paulus, H.; Elias, H. *Inorg. Chem.* **1994**, *33*, 5855 and references therein.
(16) Kimura, E.; Haruta, M.; Koike, T.; Shionoya, M.; Takenouchi, K.; Iitaka, Y. *Inorg. Chem.* **1993**, *32*, 2779.
(17) Collins, G. E.; Choi, L.-S.; Callhan, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 1474.
(18) Barefield, E. K.; Bianchi, A.; Billo, E. J.; Connolly, P. J.; Paoletti, P.; Summers, J. S.; Van Derveer, D. G. *Inorg. Chem.* **1986**, *25*, 4197.
(19) Kang, S.-G.; Kim, M.-S.; Choi, J.-S.; Whang, D.; Kim, K. *J. Chem. Soc., Dalton Trans.* **1995**, 363.
(20) Ram, M. S.; Riordan, C. G.; Ostrander, R.; Rheingold, A. L. *Inorg. Chem.* **1995**, *34*, 5884.

10.1021/ic980918f CCC: $18.00

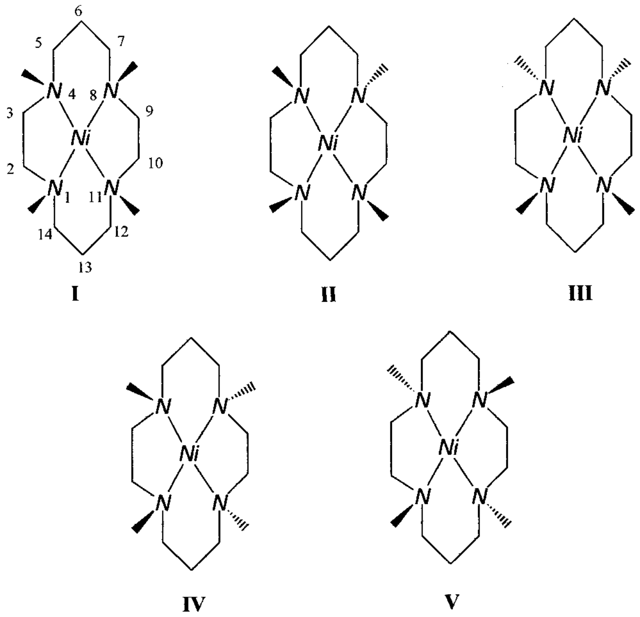

Figure 1. Fourteen-membered tetraaza macrocycles can adopt the 5 different configurations shown above in both a planar (trans) and a folded (cis) geometry. The CSD search was conducted for any nickel complex having the macrocyclic backbone with any substituents on the any of the positions. However, the macrocycles with double bonds in their backbone were rejected.

reactions.[22] These pendant arm donors can force some metals, which would normally be square planar, into a five or six coordinate geometry,[22−24] thereby facilitating those processes which require an octahedral geometry.[22,24]

Knowledge of the effects of substitution has made it possible to develop macrocycles that can be used for very specific purposes.[25] As a result, a number of azamacrocycles containing *N*-substituents have been synthesized.[26]

Fourteen-membered tetraaza macrocycles, such as cyclam and its derivatives, are fairly flexible and can adopt any of the five configurations, see Figure 1, in both folded (cis) and planar (trans) geometries. The energies of the different configurations have been estimated on the basis of molecular models[27,28] and calculated using molecular mechanics,[29−32] semiempirical methods,[33] and local density functional theory.[33]

The Cambridge Structural Database (CSD)[34,35] contains more than 170 000 solid-state structures. Cluster analysis was used to find all the conformations adopted by all 14-membered nickel tetraaza macrocycles in the CSD. Cluster analysis uses algorithms to place objects into groups such that the similarities found within the groups are significantly greater than those between them. Recently four programs have been released that cluster molecules on the basis of their conformations; two were written primarily for the analysis of structures generated in molecular dynamics simulations,[36,37] one was written primarily for conceptual database analysis,[38] and one for the contraction of conformational space in the multiconformational analysis of solution NOE data.[39,40] For this study, the agglomerative, hierarchical, single-link method found in the Xclusters[41] program was used. At the first clustering level, Xcluster[41] considers each object as a single cluster. The first structure is chosen randomly and all the others are ordered according to their conformational proximity to the first structure. It then takes those that are most similar and joins them together, at times combining whole clusters. Each time a structure or group of structures is joined, a higher level is reached. This process continues until the final clustering level, in which all the objects are in a single group, is reached. After the program has completed the clustering process, it provides three useful tools, separation ratio, distance map, and clustering mosaic, which can be used to predict potentially significant clustering levels.

Experimental Section

A search of the CSD[34] v5.14 was performed to find all the nickel complexes containing the 1,4,8,11-tetraazacyclotetradecane backbone. All substituents, including hydrogens, were removed from the macrocycles. The atoms of every structure were then renumbered such that the corresponding atoms of each ring were given the same number.

Proximity matrixes were obtained by determining the pairwise distances between 14-membered rings using the root-mean-squared deviation (rms) differences between corresponding external dihedral angles (i.e. the dihedral angles not involving the nickel ion), the rms differences between corresponding internal dihedral angles (i.e. the dihedral angles of the five- and six-membered rings that make up the macrocycle), and the rms displacement between pairs of identically numbered atoms after optimal rigid-body superimposition. Cluster analysis was performed using the program Xcluster.[41]

The MM2* force field in MacroModel[42] v 5.5 was used for the molecular mechanical analysis of the nickel(II) macrocycles. The nickel(II) parameters were identical to those used by us previously[43] with one exception: bend interactions around nickel(II) high-spin atoms were modeled using a points on a sphere model.[44] Unless specified, the chirality of all chiral centers except the four asymmetric amines was retained by the use of improper torsions.

Conformational searches were conducted using the Monte Carlo torsional and molecular position variation method.[45,46] All the external torsion angles (i.e. dihedrals not involving the metal ion) were varied between 0 and 180°. Metal and monodentate ligands (if present) were translated by between 0 and 0.5 Å, ring closure atoms were defined with default constraints, and all bonds to the metal were broken to

---

(21) Calligaris, M.; Carugo, O.; Crippa, G.; De Santis, G.; Di Casa, M.; Fabbrizzi, L.; Poggi, A.; Seghi, B. *Inorg. Chem.* **1990**, *29*, 2964.

(22) McAuley, A.; Subramanian, S. *Inorg. Chem.* **1991**, *30*, 371.

(23) Fortier, D. G.; McAuley, A. *Inorg. Chem.* **1989**, *28*, 655.

(24) Martell, A. E.; Hancock, R. D. *Comments Inorg. Chem.* **1986**, *6*, 737

(25) Freeman, G. M.; Barefield, E. K.; Van Derveer, D. G. *Inorg. Chem.* **1984**, *23*, 3092.

(26) Alcock, N. W.; Benniston, A. C.; Grant, S. J.; Omar, H. A. A.; Moore, P. *J. Chem. Soc., Chem. Commun.* **1991**, 1573.

(27) Bosnich, B.; Poon, C. K.; Tobe, M. L. *Inorg. Chem.* **1965**, *4*, 1102.

(28) Warner, L. G.; Busch, D. H. *J. Am. Chem. Soc.* **1969**, *91*, 4092.

(29) Thom, V. J.; Fox, C. C.; Boeyens, J. C. A.; Hancock, R. D. *J. Am. Chem. Soc.* **1984**, *106*, 5947.

(30) Connolly, P. J.; Billo, E. J. *Inorg. Chem.* **1987**, *26*, 3224.

(31) Adam, K. R.; Antolovich, M.; Atkinson, I. M.; Brigden, L. G.; Lindoy, L. F. *J. Mol. Struct.* **1994**, *323*, 223. Adam, K. R.; Antolovich, M.; Brigden, L. G.; Lindoy, L. F. *J. Am. Chem. Soc.* **1991**, *113*, 3346.

(32) Hambley, T. W. *J. Chem. Soc., Dalton Trans.* **1986**, 565.

(33) Adam, K. R.; Atkinson, I. M.; Lindoy, L. F. *J. Mol. Struct.* **1996**, *384*, 183.

(34) Allen, F. H.; Davies, J. E.; Galloy, J. J.; Johnson, O.; Kennard, O.; Macrae, C. F.; Mitchell, E. M.; Mitchell, G. F.; Smith, J. M.; Watson, D. G. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 187.

(35) Allen, F. H.; Kennard, O. *Chem. Des. Autom. News* **1993**, *1*, 31.

(36) Shenkin, P. S.; McDonald, D. Q. *J. Comput. Chem.* **1994**, *15*, 899.

(37) Torda, A. E.; Van Gunsteren, W. F. *J. Comput. Chem.* **1994**, *12*, 1331.

(38) Conklin, D.; Fortier, S.; Glasgow, J. I.; Allen, F. H. *Acta Crystallogr.* **1996**, *B52*, 535.

(39) Landis. C. R.; Allured, V. S. *J. Am. Chem. Soc.* **1991**, *113*, 9493.

(40) Giovannetti, J. S.; Kelly, C. M.; Landis, C. R. *J. Am. Chem. Soc.* **1993**, *115*, 4040.

(41) Shenkin, P. S.; McDonald, D. Q. *J. Comput. Chem.* **1994**, *15*, 899.

(42) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, C.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(43) Norenberg, K. M.; Shoemaker, C. M.; Zimmer, M. *J. Chem. Soc., Dalton Trans.* **1997**, 1521.

(44) Hay, B. P. *Coord. Chem. Rev.* **1993**, *126*, 177.

(45) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(46) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419.

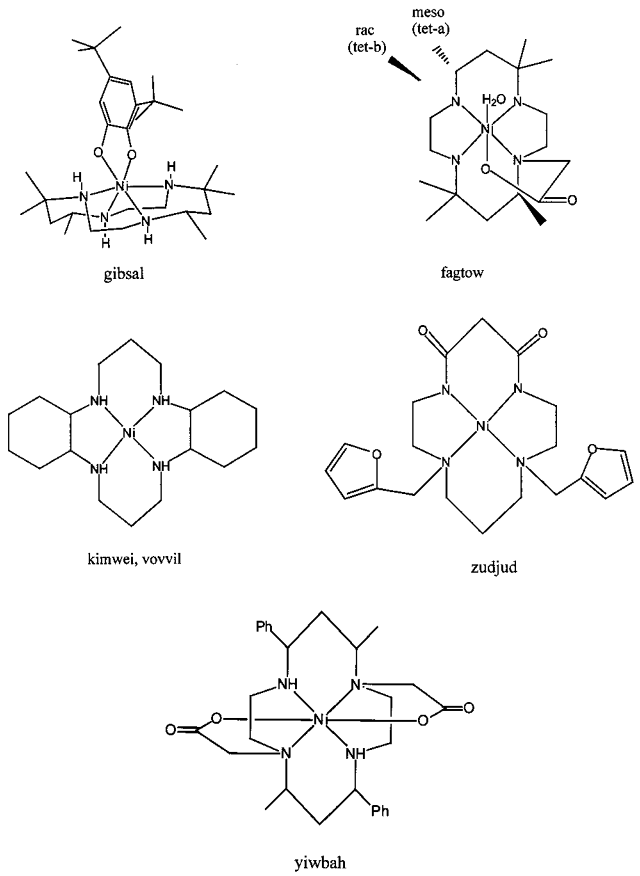

Figure 2. Structures of gibsal,[49] fagtow,[47] kimwei,[66] zudjud,[50] and yiwbah.[48]

Table 1. Distribution of Nickel Stereochemistries[68]

	% Oct	% Spl	% Spy	% Tbp
overall	54.7	40.0	2.67	0.667
low-spin Ni^{2+}	0.0	100	0.0	0.0
high-spin Ni^{2+}	92	1.3	5.3	1.3
Ni^{3+}	77.8	22.2	0.0	0.0
Ni^{+}	0.0	100	0.0	0.0

generate the macrocycle, metal, and monodentate ligand (if present) fragments that were translated. Structures found in the conformational search were considered unique if the least-squared superimposition of equivalent non-hydrogen atoms found one or more pairs separated by 0.25 Å or more.

Results and Discussion

Cambridge Structural Database. One hundred and thirty-nine nickel complexes containing the 1,4,8,11-tetraazacyclotetradecane backbone were found in the Cambridge Structural Database. Examples of these structures are shown in Figure 2. Five structures contained two or three tetraaza rings. These rings were separated so that they could be evaluated individually, resulting in 150 structures. One hundred and thirty-nine of the complexes were nickel(II), while only nine were nickel(III) and two were nickel(I).

Table 1 lists the distribution of the nickel stereochemistries found in the $14AneN_4$ complexes. Nickel(II) is a d^8 system, which can adopt high-spin and low-spin forms; high-spin nickel(II) is found in six-coordinate (octahedral), five-coordinate (trigonal-bipyramidal (tbp) and square-pyramidal (spy)), and four-coordinate (tetrahedral) geometries, while low-spin complexes have been found in five-coordinate (tbp, spy) and four coordinate (square-planar) geometries. Nickel(II) low-spin has an ideal Ni−N distance of 1.89 Å, while that of nickel(II) high-spin is 2.10 Å. The histogram of the Ni−N distances, Figure 3, shows that there are two distinct sets of Ni−N distances among the structures found in the CSD search. The nickel(II) low-spin complexes have Ni−N distances of less than 2.02 Å, while the high-spin complexes have distances of greater than 2.05 Å. Using the Ni−N distance as a criteria for separation we divided the structures into 64 low-spin and 75 high-spin complexes. As Table 1 shows, most of the high-spin complexes are octahedral and all the low-spin complexes are square-planar.

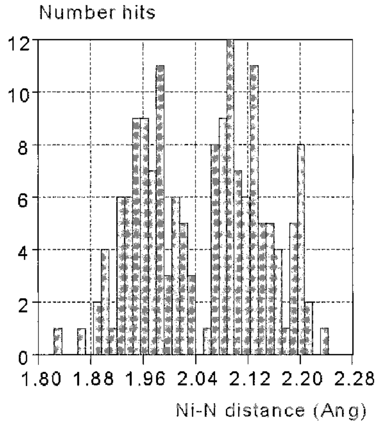

Figure 3. Histogram showing the distribution of Ni−N distances among the structures found in the CSD search. The nickel(II) low-spin complexes have Ni−N distances of less than 2.02 Å, while the high-spin complexes have distances of greater than 2.05 Å.

The properties of 1,4,8,11,-tetraazacyclotetradecane metal complexes can be altered by adding pendant arms to the macrocycle. These arms can bind to the metal raising the denticity of the macrocycle. Fifteen of the macrocycles bound the metal through one arm (e.g. fagtow[47] in Figure 2) and 14 bound with two pendant arms (e.g. yiwbah[48] in Figure 2). There were five macrobicyclic complexes.

There were 17 complexes with bidentate counterions, such as gibsal[49] which is shown in Figure 2. They all had a cis V configuration. Eleven structures, such as zudjud[50] which is shown in Figure 2, have one or more than one amide group.

Cluster Analysis. In previous work we have used cluster analysis to establish the factors responsible for the conformations of first-row transition metal complexes containing six-membered rings.[51] Since the different amine configurations give rise to different conformations, we have used similar clustering methods to separate all the different conformations and therefore configurations of the 14-membered macrocycles. All hydrogens and substituents were removed from the 1,4,8,11,-tetraazacyclotetradecane backbone so that each structure was composed of one nickel, four nitrogens, and ten carbons. Xcluster[41] was used to perform three separate cluster analyses on the 150 structures. Each analysis was based on a different clustering criteria. The most successful attempt clustered the macrocycles according to the rms displacement between identically numbered atomic pairs after rigid body superimposition. The other two

---

(47) Yujuan, L.; Shisheng, N.; Jide, X. *Jiegou Huaxue (J. Struct. Chem.)* **1986**, *5*, 5.

(48) Yu-Juan, L.; Li-Qin, C.; Shi-Sheng, N.; Ji-De, X. *Jiegou Huaxue (J. Struct. Chem.)* **1995**, *14*, 44.

(49) Benelli, C.; Dei, A.; Gatteschi, D.; Pardi, L. *Inorg. Chem.* **1988**, *27*, 2831.

(50) Bu, X. H.; Cao, X. C.; Zhang, Z. H.; Zhu, Z. A.; Chen, Y. T.; Shionoya, M.; Kimura, E. *Polyhedron* **1996**, *15*, 1203.

(51) DaCruz, M. F.; Zimmer, M. *Inorg. Chem.* **1996**, *35*, 2872. DaCruz, M. F.; Zimmer, M. *Inorg. Chim. Acta* **1997**, *261*, 181. Norenberg, K. M.; Shoemaker, C. M.; Zimmer, M. *J. Chem. Soc., Dalton Trans.* **1997**, 1521. DaCruz, M. F.; Zimmer, *M. Inorg. Chem.* **1998**, *2*, 366.

Table 2. Membership, Conformations, and Configurations for the Macrocyclic Backbones in the 27 Clusters Found at Clustering Level 124[a]

cluster level	conformation		membership	
1	trans III	c c λ δ	azcyni^{68}	meazni 01^{90}
			azcyni^{68}	yownon^{91}
			fehyew^{69}	pimhau^{92}
			pertip^{16}	maznib^{78}
			zufdin^{70}	fucmof^{93}
			badsaa 10^{71}	vopsic^{94}
			yewzuv^{15}	**jimnoi**^{22}
			tehtab^{72}	dojzux^{95}
			cafhum^{73}	hanmak^{96}
			comrif^{63}	doncak^{14}
			defkaa^{74}	tmtzni^{97}
			zegcap^{75}	dukpuu^{98}
			emtzni^{76}	**behfez**^{99}
			jiztuh^{77}	zufdin^{70}
			maznia^{78}	fagtow^{47}
			pikpoo^{79}	fagtow 10^{100}
			dmzcni^{76}	**zudgua**^{101}
			fibhed^{80}	yimnaj^{19}
			saspad^{81}	gehcur^{102}
			fiskex^{82}	gehcur 10^{100}
			ocmeni 01^{83}	aztdni^{103}
			comvef^{29}	carwat^{104}
			tazdnc 01^{84}	carwat 10^{25}
			ziqxom^{85}	donceo^{14}
			ditvor^{84}	aztdni^{103}
			yewzop^{15}	dohxih^{105}
			kikjap^{8}	*zimwun*^{20}
			pehxab^{86}	fucyil^{106}
			mipzni 10^{87}	cucrib^{25}
			zegcet^{75}	vovvux^{64}
			mipzni 01^{87}	dugtee^{107}
			factni^{88}	foxbav^{108}
			jadgok^{89}	zimxau^{20*}
			fehyew^{69}	jucpig^{109}
			vovwae^{64}	vovveh^{64}
			yexbae^{15}	tojtan^{110}
			meazni^{90}	tojtan^{110}
				zendur^{111}
	amide			yutziw^{112}
	amide			limxou^{52}
	amide			zudjud^{50}
	amide			laljox^{113}
	amide			gamcec^{114}
	amide			gamcig^{114}
27	cis V	t t λ δ	lafxof^{135}	
2	trans 1	c c λ δ	jagbic^{23}	nibtet^{62}
			libpob^{115}	tabzax^{117}
			seldiw^{116}	
3	trans 1	b c λ δ	pehxef^{86}	
			pertel^{16}	
4	trans I	c c λ λ	cucrat^{25}	
5	trans I	b c λ δ	yewtoj^{12}	
6	trans V	$^{1}/_{2}$c $^{1}/_{2}$c δ δ	fagwal^{18}	niatet^{62}
		t t δ δ	yuvbas^{112}	
7	amide		yutzoc^{112}	yutzui^{112}
8	trans I	c c λ λ	ocmeni^{118*}	
9	amide		yutzui^{112*}	
10	trans I	c c δ δ	debful^{119*}	tispeq^{121*}
			fiwrei^{120*}	zadsay^{122*}
11	amide		yuvbas^{112}	
12	trans I	c c λ δ	tabyok^{117}	libpuh^{115}
			vovvil^{64}	ticcox^{54}
			jodnof^{26*}	tmcazn^{123*}
		c c δ δ	ditmuo^{32*}	dohxed^{105*}
			kimwei^{66*}	
13	trans I	c c δ δ	tispiu^{121*}	
14	trans I	c c λ λ	zimxey^{20*}	
15	trans I	c b λ δ	yewtid^{12}	
16	trans I	t t δ δ	yewtup^{12}	
17	trans I	c c λ λ	**zopcow**^{9*}	
18	amide		**vixlix**^{53*}	
19	cis V	c c δ δ	fagvue^{18}	pajzab^{125}
			jesdam^{21}	fowzum^{108}
			gibsal^{49}	kigler^{126}
			tetnia^{124}	
20	cis V	c t δ δ	hazdni^{55}	
21	cis V	b b λ λ	lafxiz^{127}	
22	cis V	c c λ λ	lavyuc^{60}	vadtoj^{128}
			lavyuc^{60}	rablux^{129}
			lavyuc^{60}	rablux^{129}
23	trans III	b b δ δ	pehwoo^{86}	pehwuu^{86}
		b b λ λ	febzuh 10^{86}	febzuh^{130}
24	cis V	c c δ δ	bismul^{58}	vadtoj^{128}
			divyai^{131}	hewkav^{133}
			dikwez^{132}	tedhuf^{134}
25	cis V	c c λ λ	carvum^{104}	duccuz^{59}
			carvum 10^{25}	somxun^{61}
26	cis V	t c λ δ	dedgoi^{56}	yiwbah^{48}
			dedgoi 10^{57}	

[a] c = chair; $^{1}/_{2}$c = $^{1}/_{2}$ chair; b = boat; t = twist boat; italics = Ni^{+}; bold = Ni^{3+}; * = domed.

attempts, which based the clustering on the rms differences between the internal and external torsion angles, had trouble separating cis and trans structures. All discussions about cluster analysis from this point onward are based on the clustering with pairwise atomic overlap used as the clustering criteria.

The clustering mosaic and distance map, shown in Figures 4 and 5, respectively, and the separation ratio indicated that the most significant clustering was at level 124.

The distance map (Figure 5) shows a matrix in which conformational similarity is indicated by the color of the cross-peaks; the more similar two structures are, the darker the cross-peak. Since all the diagonal elements indicate the similarity between identical conformations, they should be black; however, they have been changed to white to increase the clarity of the map. Table 2 shows the membership, conformations, and configurations for the macrocyclic backbones in the 27 clusters found at level 124.

Figures 4 and 5 and Table 2 show that cluster 1 is the largest cluster. It has 81 structures. They are all trans III configurations. All but two of the members of cluster 1 had both of their six-membered rings in the stable chair conformation and a λ and a δ five-membered ring. The two exceptions to the general conformation were the last two macrocycles in the cluster. Limxou[52] and zudjud[50] both had one chair and one boat.

Besides the trans III macrocycles located in cluster 1, there were also four macrocycles with a trans III configuration in cluster 23. All four had both of their six-membered rings in the boat conformation. They are located in a separate cluster from the other trans III macrocycles because the clustering is based on the macrocyclic conformation and not configuration.

All the macrocycles in clusters 2−17 are in the trans I and trans V configuration. Cluster 18 contains tetraazacyclotetradecan-2,5,7,10,13-pentanone (vixlix[53]). It cannot be assigned a configuration as its amide nitrogens are deprotonated. Every macrocycle in clusters 19−27 was in the cis V configuration, except those in cluster 23 which had trans III configurations. No trans II or IV or cis I, II, III, or IV macrocycles were found.

The agglomerative, hierarchical, single-link method used to cluster the nickel(II) macrocyclic complexes was effective in separating different configurations and conformations.

Conformational Analysis. Table 3 lists the distribution of the different macrocyclic configurations found for the nickel-

---

(52) Moran, J. K.; Olmstead, M. M.; Meares, C. F. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1995**, *51*, 621.

(53) Collins, T. J.; Nichols, T. R.; Uffelman, E. S. *J. Am. Chem. Soc.* **1991**, *113*, 4708.

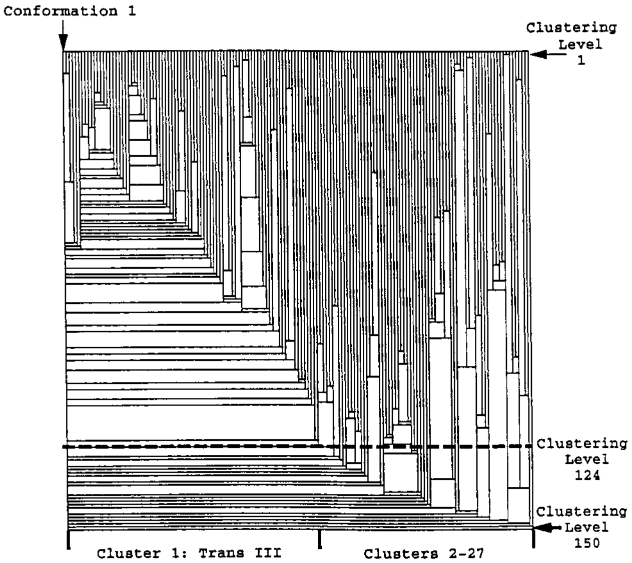

Figure 4. At the top of the clustering mosaic, each narrow band corresponds to one of the 150 structures, each of which is in its own cluster. The first structure (on the far left) was chosen randomly, and all the others are ordered according to their conformational proximity to the first structure. In each following level the two closest clusters are joined, so that in clustering level N there are $150 - N$ clusters. The clusters joined at low clustering levels and, shown near the top of the figure, contain conformationally similar macrocycles, whereas those joined at higher levels are not very similar. At the bottom of the mosaic, there is one long band, corresponding to the final clustering level, in which all the structures are joined into one cluster. Clustering level 124 is indicated by a dashed line, and each block along the line is one of the level's 27 clusters.

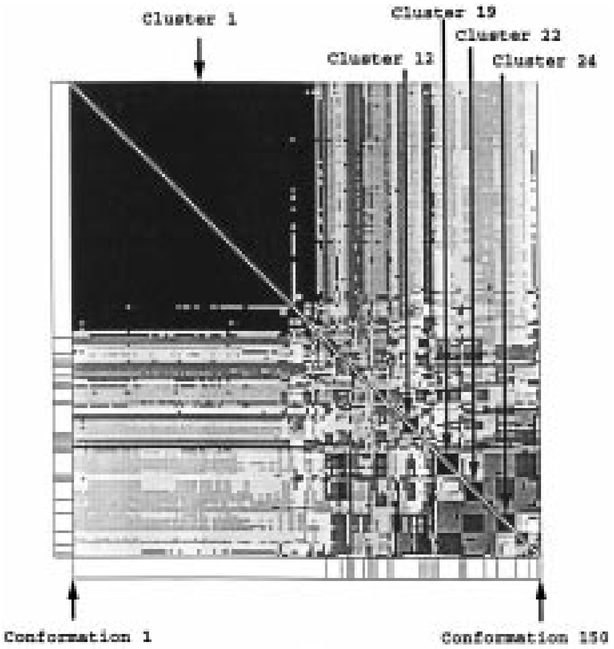

Figure 5. Distance map showing clusters 1, 12, 19, 22, and 24. The cross-coordinates of conformationally similar macrocycles are darkly colored, while dissimilar structures are lightly colored.

Table 3. Configurational Distribution[a] (Amide-Containing Macrocycles Not Included)[137]

config	overall %	Oct %	Spl %	Spy %	Tbp %	Ni(II) l.s.	Ni(II) h.s.
no. of structs	138	75	58	4	1	54	74
trans I	20.3	9.33	29.3	75.0	100	29.6	14.9
trans III	57.2	52.0	67.2	25.0	0.00	66.7	45.9
trans V	1.45	0.00	3.45	0.00	0.00	3.70	0.0
cis V	21.0	38.7	0.00	0.00	0.00	0.00	39.2

[a] Oct = octahedral; Spl = square-planar; Spy = square-pyramidal; Tbp = trigonal bipyramidal.

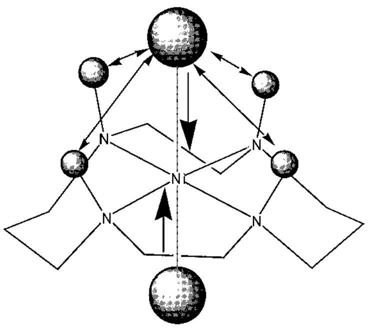

Figure 6. Trans I configuration becomes less stable relative to the trans III configuration as axial ligands bind in going from square-planar to octahedral geometry.

Table 4. Configurational and Conformational Distribution of 1,4,8,11-Substituted 1,4,8,11-Tetraazacyclotetradecane Macrocycles

	octahedral	Spl, Spy, and Tbp[a]
trans III	77.8	26.7
trans I	22.3	73.3

(II) complexes analyzed in this study. The most commonly found configuration was the trans III configuration, which is the lowest energy configuration available to nickel(II) cyclam. Molecular mechanics calculations have shown that the trans I configuration becomes more stable relative to the trans III configuration in going from octahedral nickel(II) cyclam complexes to their square-planar analogues.[30] Even though most of the complexes found in the CSD search were substituted nickel(II) cyclam complexes, it was not surprising that the trans III configuration was the most common configuration and that the relative amount of trans I macrocycles was higher for square-planar complexes than for octahedral complexes. This is due to the nonbonded interactions between the atoms/substituents at positions 1, 4, 8, and 11 and the nonmacrocyclic coordinating ligands (see Figure 6). This effect is enhanced for 1,4,8,11-substituted macrocycles; see next section.

N-Substitution. The CSD search found 24 1,4,8,11-substituted 1,4,8,11-tetraazacyclotetradecane macrocycles. The majority of octahedral nickel(II) complexes with a 1,4,8,11-substituted 1,4,8,11-tetraazacyclotetradecane backbone adopted a trans III configuration, while most square-planar, square-pyramidal, and trigonal-bipyramidal complexes are trans I; see Table 4. For the square-planar, square-pyramidal, and trigonal-bipyramidal molecules, the situation was reversed. Only 26.7% adopted the trans III configuration, while 73.3% had the preferred trans I configuration. These preferences support the molecular mechanical calculations that the trans I configuration is the most stable configuration of square-planar 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane nickel(II), while trans III is favored by the octahedral complex.[32]

C-Substitution on the Six-Membered Rings. Table 5 gives the relative energies of all the configurations within 25 kJ/mol of the lowest energy conformation for all the macrocycles found in our CSD search that had methyl substituents on the six-membered rings. In cases where substitution resulted in chiral centers the chirality of the solid-state structure was used and retained in the search. In all cases the lowest energy conformation matched the solid-state conformation. The trans III configuration was the lowest energy configuration for all the methyl-substituted macrocycles studied except for *C-rac-*

Table 5. Relative Energies of All the Configurations within 25 kJ/mol of the Lowest Energy Conformation for All the Macrocycles Found in the CSD Search with Methyl Substituents on the Six-Memebered Rings

	5*R*,12*R* (dmzcni)	5*SR*,7*RS*,12*RS*,14*RS* (zendur, zegcap)	tet-a Spl	tet-a Oct (fagtow)	tet-b Spl	tet-b Oct (bismul)
trans I	22.86	11.95			5.80	
trans II	15.77	2.45	11.87		0.00	
trans III	0.00	0.00	0.00	0.00	15.89	
trans V	21.94	8.66	20.59		0.00	
cis V	*b*	*b*	*b*	14.94	*b*	0.00

[a] 5*R*,12*R*: 5,12-dimethyl-1,4,8,11-tetraazacyclotetradecane. 5*SR*,7*RS*,12*RS*,14*RS*: 5,7,12,14-tetramethyl-1,4,8,11-tetraazacyclotetradecane. tet-a: *C-meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane. tet-b: *C-rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane. [b] Square-planar compounds cannot adopt a cis configuration.

Table 6. Structural Properties of All the Nickel(II) Complexes of 5,5,7,12,12,14-Hexamethyl-1,4,8,11-tetraazacyclotetradecane and the Rms after the Overlap of the Solid-State Structure with the Lowest Energy Conformation Found in the Conformational Search

CSD refcode	isomer	configurn	geometry	rms overlap (Å)	color
badsaa10	meso	trans III	spl	0.059	orange
dukpuu	meso	trans III	spl	0.088	brick-red
fibhed	meso	trans III	spl	0.091	orange
maznia	meso	trans III	spl	0.043	orange
meazni	meso	trans III	spl	0.106	orange
meazni01	meso	trans III	spl	0.076	orange
ocmeni01	meso	trans III	spl	0.082	orange
pimhau	meso	trans III	spl	0.071	red
yownon	meso	trans III	spl	0.062	purple
ticcox	meso	trans I	spl		orange
hazdni	meso	cis V	oct		
dedgoi	meso	cis V	oct		violet
dedgoi10	meso	cis V	oct		violet
behfez	meso	trans III	oct	0.155	
factni	meso	trans III	oct	0.114	pale violet
fagtow	meso	trans III	oct	0.097	
fagtow10	meso	trans III	oct	0.097	light violet
gehcur	meso	trans III	oct	0.131	
gehcur10	meso	trans III	oct	0.131	light reddish
jadgok	meso	trans III	oct	0.153	
maznib	meso	trans III	oct	0.132	violet
zudgua	meso	trans III	oct	0.126	light pink
niatet	rac	trans V	spl	0.146	
nibtet	rac	trans I	spl		
ocmeni	rac	trans I	spl		orange
bismul	rac	cis V	oct	0.094	blue
dikwez	rac	cis V	oct	0.135	violet
divyai	rac	cis V	oct	0.079	blue-violet
duccuz	rac	cis V	oct	0.880[a]	
gibsal	rac	cis V	oct	0.138	black-green
hewkav	rac	cis V	oct	0.166	blue
lavyuc	rac	cis V	oct	0.850[a]	
pajzab	rac	cis V	oct	0.192	blue-violet
rablux	rac	cis V	oct	0.202	green
somxun	rac	cis V	oct	0.873[a]	
tedhuf	rac	cis V	oct	0.165	blue
tetnia	rac	cis V	oct	0.162	

[a] See text for reasons for bad overlap.

5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane (tet-b) macrocycles.

The *C-meso* (tet-a) and *C-rac* (tet-b) isomers of 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane, Figure 2, have two chiral carbon centers which, together with the five possible nitrogen configurations, give rise to 20 configurations available to the nickel complexes of these macrocycles. The configurations of all the nickel(II) hexamethylcyclam complexes found in the CSD are given in Table 6.

A conformational search of square planar *C-meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane nickel(II) found the trans III configuration to be the most stable configuration, Table 5. All but one of the square-planar *meso* solid-state structures are in the trans III configuration, and they all have a conformation similar to the lowest energy conformation (rms between 0.043 and 0.106 Å), Table 6. The lowest energy conformation has both six-membered rings in a chair conformation with equatorial 7,14-methyl groups and $\lambda\delta$ five-membered rings. Ticcox[54] has a trans I configuration which is 14 kJ/mol higher in energy than the lowest energy conformation. The lowest trans I configuration found in the conformational search overlaps fairly well with the solid-state structure of ticcox[54] (rms = 0.225 Å); the only difference between the two trans I structures is that the calculated structure has two $\lambda\lambda$ five-membered rings, while the solid-state structure has $\lambda\delta$ rings.

The most stable configuration of octahedral *C-meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane nickel(II) complexes is trans III. A conformational search of fagtow,[47] Figure 2, found that the only other configuration within 25 kJ/mol of the lowest energy configuration is a cis V form, Table 5. According to Table 6 all the solid-state structures of octahedral (*C-meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane)nickel(II) complexes, except hazdni,[55] dedgoi,[56] and dedgoi10[57] have trans III configurations. Hazdni[55] has a cis V configuration which is due to the bidentate acetylacetonato counterion enforcing a folded configuration. We have found no thermodynamic reasons for dedgoi[56] or dedgoi10[57] adopting a cis V configuration. All the trans III structures have the same conformation as the most stable conformation found in the conformational search of fagtow[47] (rms deviations from 0.097 to 0.155 Å). This conformation has both six-membered rings in the chair conformation, $\lambda\delta$ five-membered rings, and the 7,14-methyls equatorially orientated.

Cis V is the only configuration found, within 25 kJ/mol of the lowest conformation, in a conformational search of bismul,[58] *cis*-diaqua(*C-rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane)nickel(II). The next lowest configuration, trans III, is more than 40 kJ/mol higher in energy. This configuration has a severely distorted six-membered ring that is adopted so that the 5-methyl group is equatorial and is responsible for the higher strain energy. All but three of the octahedral *rac* isomers found in our CSD search are in the cis V configuration, which has both its six-membered rings in a chair conformation with equatorial 7,14-methyl groups and $\delta\delta$ five-membered rings. Duccuz,[59] lavyuc,[60] and somxun[61] adopt a cis V conformation

---

(54) Wang, A.; Lee, T.-J.; Chen, B.-H.; Yuan, Y.-Z.; Chung, C.-S. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1996**, *52*, 3033.

(55) Curtis, N. F.; Swann, D. A.; Waters. T. N. *J. Chem. Soc., Dalton Trans.* **1973**, 1408.

(56) Yujuan, L.; Shisheng, N.; Jide, X. *Jiegou Huaxue (J. Struct. Chem.)* **1985**, *4*, 42.

(57) Ji-De, X.; Shi-Sheng, N.; Yu-Juan, L. *Inorg. Chim. Acta* **1986**, *111*, 61.

(58) Ito, H.; Sugimoto, M.; Ito, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1971.

(59) Bencini, A.; Caneschi, A.; Dei, A.; Gatteschi, D.; Zanchini, C.; Kahn, O. *Inorg. Chem.* **1986**, *25*, 1374.

(60) Mitsumi, M.; Okawa, H.; Sakiyama, H.; Ohba, M.; Matsumoto, N.; Kurisaka, T.; Wakita, H. *J. Chem. Soc., Dalton Trans.* **1993**, 2991.

with λλ five-membered rings that is 14 kJ/mol higher in energy than the lowest cis V conformation.

There are only three solid-state structures of square-planar complexes of the *rac* isomer; two have a trans I configuration and one has a trans V configuration. The square-planar *rac* isomer has two lowest energy configurations, one is trans V and the other is trans II, Table 5. Niatet[62] has a trans V configuration containing two six-membered rings in a twist-boat conformation with equatorial methyls and δδ five-membered rings. It compared well with the lowest energy, trans V, configuration (rms = 0.146 Å). The trans I conformation adopted by nibtet[62] is nearly 6 kJ/mol higher in energy than the most stable configurations.

The distribution of the solid-state structures in the CSD, Table 6, and the configuration of the low energy conformations of (*meso*- and (*rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane)nickel(II), Table 5, show that a small change in substitution (*meso* vs *rac*) can result in the adoption of completely different low-energy configurations.

C-Substitution on the Five-Membered Rings. We have undertaken conformational searches for the nickel(II) complexes of 2,9-dimethylcyclam (comrif[63]), 2,3,9,10-tetramethylcyclam (yewzuv[15]), and 2,2,3,3-tetramethylcyclam (vovvux[64]). The results are summarized in Table 7. The trans III configuration is the lowest energy configuration found for all three complexes, and all three crystal structures have the same conformation as the most stable configuration (rms values are 0.043 Å for comrif,[63] 0.042 Å for yewzuv,[15] and 0.081 Å for vovvux[64]).

Table 7. Relative Energies of the Most Stable Configurations of Nickel(II) 1,4,8,11-Tetraazacyclotetradecane Complexes with Methyl Substitution in Their Five-Membered Rings

configurn	2,9-dimethyl-cyclam (comrif)	2,3,9,10-tetramethyl-cyclam (yewzuv)	2,2,3,3-tetramethyl-cyclam (vovvux)
trans I	13.98	15.91	18.91
trans II	17.74	9.09	7.15
trans III	0.00	0.00	0.00
trans V	21.78	7.05	4.31

Table 8. All the Low-Energy Conformations Found within 25 kJ/mol of the Lowest Energy Conformation in a Conformational Search of Square-Planar Nickel(II) 2,3,9,10-Dicyclohexano-1,4,8,11-tetraazacyclotetradecane

tetraaza configurn	cyclam-ring conformations	cyclohexane conformations	cyclohexane stereochem	rel energy (kJ/mol)
trans II	c t λ λ	c c	dl-trans-trans	0.00
trans II	c t δ δ	c c	dl-trans-trans	0.00
trans I	c c λ δ	c c	meso-trans-trans	1.11
trans II	c t λ λ	c c	cis-trans	5.04
trans V	t t λ λ	c c	cis-trans	9.56
trans V	t t δ δ	c c	cis-trans	9.56
trans II	c t λ λ	c c	cis-trans	10.24
trans I[a]	c c λ δ	c c	cis-syn-cis	12.88
trans II	c t λ δ	c c	meso-trans-trans	14.51
trans II	c t λ λ	c c	cis-syn-cis	15.08
trans II	c t δ δ	c c	cis-syn-cis	15.08
trans I[b]	c c δ δ	c c	cis-syn-cis	15.23
trans V	t t λ λ	c t	dl-trans-trans	19.39
trans V	t t δ δ	c t	dl-trans-trans	19.39
trans II	c t λ δ	c c	cis-trans	19.84

[a] Conformation adopted by vovvil. [b] Conformation adopted by kimwei.

Conformational searches of inorganic systems and of linked cyclic systems are notoriously difficult.[65] A conformational search of (2,3,9,10-dicyclohexanocyclam)nickel(II) was conducted in order to establish how effective the search procedure described in the Experimental Section is in dealing with complex inorganic systems. A search to find all the low-energy conformations of (2,3,9,10-dicyclohexanocyclam)nickel(II) was conducted without constraining the chirality of any of the stereo-

---

(61) Vicente, R.; Escuer, A.; Ribas, J.; Dei. A.; Solans, S.; Calvet, T. *Polyhedron* **1990**, *9*, 1729.
(62) Curtis, N. F.; Swann, D. A.; Waters, T. N. *J. Chem. Soc., Dalton Trans.* **1973**, 1963.
(63) Urbanczyk-Lipkowska, Z.; Krajewski, J. W.; Gluzinski, P.; Parkanyi, L. *Pol. J. Chem.* **1983**, *57*, 85.
(64) Kobiro, K.; Nakayama, A.; Hiro, T.; Suwa, M.; Tobe, Y. *Inorg. Chem.* **1992**, *31*, 676.
(65) Comba, P.; Hambley, T. W. In *Molecular Modeling of Inorganic Compounds*; VCH: Weinheim, Germany, 1995.
(66) Kobiro, K.; Nakayama, A.; Hiro, T.; Suwa, M.; Kakiuchi, K.; Tobe, Y.; Odaira, Y. *Chem. Lett.* **1990**, 1979.
(67) Zimmer, M. Manuscript in preparation.
(68) A search of CSD v5.15 found 3 new nickel 14-membered macrocyclic complexes. Addition of these 3 complexes to this table does not significantly change the conclusions.
(69) Barefield, E. K.; Chueng, D.; Van Derveer, D. G.; Wagner, F. *J. Chem. Soc., Chem. Commun.* **1981**, 302.
(70) McAuley, A.; Subramanian, S.; Whitecombe, T. W. *J. Chem. Soc., Chem. Commun.* **1987**, 539.
(71) Kido, H.; Takada, M.; Suwabe, M.; Yamaguchi, T.; Ito, T. *Inorg. Chim. Acta* **1995**, *228*, 133.
(72) Lee, T.-J.; Lu, T. H.; Liang, B. F.; Chung, C.-S.; Lee, T.-Y. *J. Chin. Chem.* **1981**, *28*, 191.
(73) Choi, K.-Y.; Kim, J. C.; Jensen, W. P.; Suh, I.-H.; Choi, S.-S. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1996**, *52*, 2166.
(74) Prasad, L.; McAuley, A. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1983**, *39*, 1175.
(75) Yamashita, M.; Toriumi, K.; Ito, T. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1985**, *41*, 1607.
(76) Hay, R. W.; Jeragh, B.; Ferguson, G.; Kaitner, B.; Ruhl, B. L. *J. Chem. Soc., Dalton Trans.* **1982**, 1531.
(77) Krajewski, J.; Urbanczyk-Lipkowska, Z.; Gluzinski, P. *Bull. Acad. Pol. Sci., Sci. Chim.* **1977**, *25*, 853.
(78) Adam, K. R.; Antolovich, M.; Brigden, L. G.; Leong, A. J.; Lindoy, L. F.; Baillie, P. J.; Uppal, D. K.; McPartlin, M.; Shah, B.; Prosperio, D.; Fabbrizzi, L.; Tasker, P. A. *J. Chem. Soc., Dalton Trans.* **1991**, 2493.
(79) Ito, T.; Toriumi, K. *Acta Crystallogr., Sect B* **1981**, *37*, 88.
(80) McAuley, A.; Palmer, T.; Whitecombe, T. W. *Can. J. Chem.* **1993**, *71*, 1792.
(81) Drew, M. G. B.; Mok, K. F. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1987**, *43*, 666.
(82) Toriumi, K.; Wada, T.; Mitani, T.; Bandow, S.; Yamashita, M.; Fujii, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2341.
(83) Prasad, L.; Nyburg, S. C.; McAuley, A. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1987**, *43*, 1038.
(84) Ferguson, G.; Lough, A. J.; Bembi, R. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1990**, *46*, 213.
(85) Ito, T.; Kato, M.; Ito, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2641.
(86) Mochizuki, K.; Kondo, T. *Inorg. Chem.* **1995**, *34*, 6241.
(87) Curtis, N. F.; Gainsford, G. J.; Siriwardena, A.; Weatherburn, D. C. *Aust. J. Chem.* **1993**, *46*, 755.
(88) Krajewski, J. W.; Urbanczyk-Lipkowski, Z.; Gluzinski, P. *Pol. J. Chem.* **1980**, *54*, 2189.
(89) Toriumi, K.; Ito, T. *Acta Crystallogr., Sect. B* **1981**, *37*, 240.
(90) Yamashita, M.; Miyamae, H. *Inorg. Chim. Acta* **1989**, *156*, 71.
(91) Ito, T.; Toriumi, K.; Ito, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1096.
(92) Munoz, M. C.; Cano, J.; Ruiz, R.; Lloret, F.; Faus, J. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1995**, *51*, 873.
(93) Ruiz, R.; Julve, M.; Cano, J.; Soto, J.; Martinez-Manez, R.; Munoz, C.; Paya, J. *Transition Met. Chem.* **1993**, *18*, 523.
(94) Miyamura, K.; Kohzuki, M.; Narushima, R.; Saburi, M.; Gohshi, Y.; Tsuboyama, S.; Tsuboyama, K.; Sakurai, T. *J. Chem. Soc., Dalton Trans.* **1987**, 3093.
(95) Chapman, J.; Ferguson, G.; Gallagher, J. F.; Jennings, M. C.; Parker, D. *J. Chem. Soc., Dalton Trans.* **1992**, 345.
(96) Iitaka, Y.; Koike, T.; Kimura, K. *Inorg. Chem.* **1986**, *25*, 402.
(97) Oshio, H. *Inorg. Chem.* **1993**, *32*, 4123.
(98) Krajewski, J.; Urbanczyk-Lipkowski, Z.; Gluzinski, P. *Pol. J. Chem.* **1978**, *52*, 1513.
(99) Lee, T.-Y.; Hsieh, M.-Y.; Lee, T.-J.; Chen, J.-W.; Chung, C.-S. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1986**, *42*, 1001.
(100) Zeigerson, E.; Bar, I.; Bernstein, J.; Kirschenbaum, L. J.; Meyerstein, D. *Inorg. Chem.* **1982**, *21*, 73.
(101) Jide, X.; Shisheng, N.; Yujuan, L. *Inorg. Chem.* **1988**, *27*, 4651.
(102) Colacio, E.; Dominquez-Vera, J. M.; Escuer, A.; Kivekas, R.; Klinga, M.; Romerosa, A. *Acta Chem. Scand.* **1996**, *50*, 178.

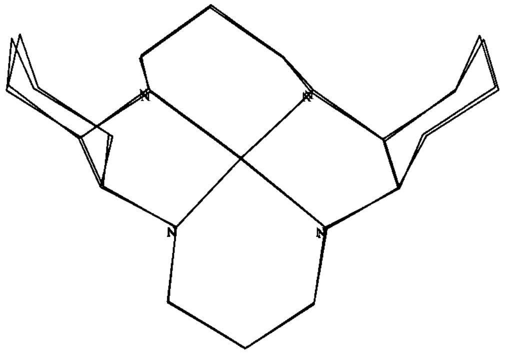

Figure 7. Overlap of the lowest energy conformation of vovvil[64] with the solid-state structure of vovvil.[64] (Rms overlap of all the non-hydrogen atoms is 0.078 Å.) The conformation is described in Table 8.

centers. We chose (2,3,9,10-dicyclohexanocyclam)nickel(II) because it has two five-membered rings, four six-membered rings and eight chiral centers, see Figure 2, and because the CSD contains two (*cis*,*syn*,*cis*-2,3,9,10-dicyclohexanocyclam)-nickel(II) complexes with differing conformations (vovvil,[64] kimwei[66]). The lowest energy conformation found in the search had a trans II configuration with both fused cyclohexanes in a trans configuration; see Table 8. Unfortunately there are no solid-state structures in the CSD of any *trans*,*trans*-2,3,9,10-dicyclohexanocyclam transition metal complexes to check this finding. The lowest energy configuration with the two cyclohexanes in a cis-syn-cis arrangement is trans I, which is the configuration found in the solid-state structures (vovvil,[64] kimwei[66]). The conformation found in the crystal structure of vovvil[64] corresponds to that of the lowest energy conformation for the cis-syn-cis configuration; see Figure 7. Kimwei[66] has a conformation that is 2.35 kJ/mol higher in energy (rms = 0.071 Å). This conformation, which was also found in the conformational search, differs from the lowest energy conformation in the orientation of its five-membered rings ($\delta\delta$ vs $\lambda\delta$). The conformational search method used was effective, because in one search we were able to find all the low energy conformations of all the configurations available to 2,3,9,10-dicyclohexanocyclam.[67]

Conclusion

The agglomerative hierarchical single-link clustering method used is very effective at separating the different configurations of 14-membered macrocycles. Because pairwise atomic superimposition was used as a clustering criteria, the analysis was able to separate macrocycles with identical configurations but different six-membered ring conformations.

The trans III configuration which is the lowest energy configuration of nickel cyclam is the most commonly found configuration. The CSD search confirmed that the trans I configuration becomes more stable relative to the trans III configuration in going from octahedral nickel(II) cyclam complexes to their square-planar analogues.[30] The number of trans I macrocycles relative to the trans III macrocycles was higher for square-planar complexes than for octahedral complexes.

In some cases the addition and/or location of substituents on the macrocyclic backbone can change the identity of the lowest energy configuration; this was most dramatically shown for (5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane)-nickel(II) complexes. The lowest energy configuration found in a conformational search of nickel(II) tet-b was cis V, which was more than 40 kJ/mol lower in energy than the next lowest configuration, trans III. All the octahedral nickel(II) tet-b complexes found in our CSD search were in the cis V configuration. On the other hand, all but 3 octahedral nickel-(II) tet-a complexes were found in the trans III configuration, and a conformational search found that the trans III configuration was about 15 kJ/mol lower in energy than the cis V configuration.

The conformational searches showed that the Monte Carlo torsional and molecular position variation method, in which the dihedral angles in the macrocycle are varied as well as the

---

(103) Yujuan, L. *Jiegou Huaxue (J. Struct. Chem.)* **1988**, *7*, 107.
(104) Wagner, F.; Mocella, M. T.; D'Aniello, M. J., Jr.; Wang, A. H.-J.; Barefield, E. K. *J. Am. Chem. Soc.* **1974**, *96*, 2625.
(105) Barefield, E. K.; Freeman, G. M.; Van Derveer, D. G. *J. Chem. Soc., Chem. Commun.* **1983**, 1358.
(106) Kato, M.; Ito, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 285.
(107) Hay, R. W.; Pujari, M. P.; Moodie, W. T.; Craig, S.; Richens, D. T.; Perotti, A.; Ungaretti, L. *J. Chem. Soc., Dalton Trans.* **1987**, 2605.
(108) Kimura, E.; Koike, T.; Nada, H.; Iitaka, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1322.
(109) Kimura, E.; Shionoya, M.; Mita, T.; Iitaka, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1712.
(110) Krajewski, J. W.; Gluzinski, P.; Korybut-Daszkiewicz, B.; Kemme, A.; Misnyov, A. *Bull. Pol. Acad., Sci. Chem.* **1991**, *39*, 279.
(111) Mochizuki, K.; Manaka, S.; Takeda, I.; Kondo, T. *Inorg. Chem.* **1996**, *35*, 5132.
(112) Tahirov, T. H.; Lu, T.-H.; Liu, G.-S.; Chi, T.-Y.; Chung, C.-S. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1995**, *51*, 2018.
(113) Dumas, S.; Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3368.
(114) Chinn, P.; Busch, D. H.; Alcock, N. W. *Acta Crystallogr., Sect. C (Cryst. Struct. Commun.)* **1993**, *49*, 1284.
(115) Kimura, E.; Koike, T.; Nada, H.; Iitaka, Y. *Inorg. Chem.* **1988**, *27*, 1036.
(116) McAuley, A.; Fortier, D. G.; Macartney, D. H.; Whitecombe, T. W.; Xu, C. *J. Chem. Soc., Dalton Trans.* **1994**, 2071.
(117) Kimura, E.; Wada, S.; Shionoya, M.; Takahashi, T.; Iitaka, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 397.
(118) Hancock, R. D.; Ngwenya, M. P.; Wade, P. W.; Boeyens, J. C. A.; Dobson, S. M. *Inorg. Chim. Acta* **1989**, *164*, 73.
(119) Ito, T.; Ito, H.; Toriumi, K. *Acta Crystallogr., Sect. B* **1981**, *37*, 1412.
(120) Lincoln, S. F.; Hambley, T. W.; Pisaniello, D. L.; Coates, J. H. *Aust. J. Chem.* **1984**, *37*, 713.
(121) Crick, I. S.; Gable, R. W.; Hoskins, B. F.; Tregloan, P. A. *Inorg. Chim. Acta* **1986**, *111*, 35.
(122) Schmid, C. L.; Kempf, C.; Taubert, A.; Neuberger, M.; Zehnder, M.; Kaden, T. A.; Bujno, K.; Bilewicz, R. *Helv. Chim. Acta* **1996**, *79*, 1011.
(123) Oberholzer, M. R.; Neuberger, M.; Zehender, M.; Kaden, T. A. *Helv. Chim. Acta* **1995**, *78*, 505.
(124) D'Aniello, M. J., Jr.; Mocella, M. T.; Wagner, F.; Barefield, E. K.; Paul, I. C. *J. Am. Chem. Soc.* **1975**, *97*, 192.
(125) Whimp, P. O.; Bailey, M. F.; Curtis, N. F. *J. Chem. Soc. A.* **1970**, 1956.
(126) Escuer, A.; Vicente, R.; Ribas, J.; Costa, R.; Solans, X. *Inorg. Chem.* **1992**, *31*, 2627.
(127) Kimura, E.; Kotake, Y.; Koike, T.; Shionoya, M.; Shiro, M. *Inorg. Chem.* **1990**, *29*, 4991.
(128) Clark, I. J.; Creaser, I. I.; Engelhardt, L. M.; Harrowfield, J. M.; Krausz, E. R.; Moran, G. M.; Sargeson, A. M.; White, A. H. *Aust. J. Chem.* **1993**, *46*, 111.
(129) Battaglia, L. P.; Bianchi, A.; Corradi, A. B.; Garcia-Espana, E.; Micheloni, M.; Julve, M. *Inorg. Chem.* **1988**, *27*, 4174.
(130) Escuer, A.; Vicente, R.; El Fallah, M. S.; Solans, X.; Font-Bardia, M. *J. Chem. Soc., Dalton Trans.* **1996**, 1013.
(131) Curtis, N. F.; Gainsford, G. J.; Hambley, T. W.; Lawrance, G. A.; Morgan, K. R.; Siriwardina, A. *J. Chem. Soc., Chem. Commun.* **1987**, 295.
(132) Ito, H.; Ito, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2133.
(133) Ito, H.; Ito, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1755.
(134) Colacio, E.; Dominguez-Vera, J. M.; Escuer, A.; Kivekas, R.; Romerosa, A. *Inorg. Chem.* **1994**, *33*, 3914.
(135) Colacio, E.; Dominguez-Vera, J. M.; Romerosa, A.; Kivekas, R.; Klinga, M.; Escuer, A. *Inorg. Chim. Acta* **1995**, *234*, 61.
(136) Engelhardt, L. M.; Harrowfield, J. M.; Sargeson, A. M.; White, A. H. *Aust. J. Chem.* **1993**, *46*, 127.
(137) A search of CSD v5.15 found 3 new nickel 14-membered macrocyclic complexes. Addition of these 3 complexes to this table does not significantly change the conclusions.

positions of the nickel and monodentate ligands (if present), is very effective at generating all the configurations and conformations of complicated inorganic systems, in one search.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. M.A.D. thanks the Keck Foundation for a Keck Summer Research Fellowship.

IC980918F