

Conformational Analysis of Cobalt(III), Copper(II), and Nickel(II) Six-Membered-Ring Systems

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Introduction

Cyclohexane and its organic derivatives have been extensively studied for more than 100 years. One of the first conformational analyses to be published was Sachse's 1890 article which proposed for the first time that cyclohexane preferably adopts chair conformations.¹ After many years, it was accepted that cyclohexane preferred a chair conformation over a planar one. It was mainly the work of Hueckel² in 1925 and the solution of the crystal structure of hexachlorocyclohexane³ in 1928 that convinced the chemists of the day that indeed the chair conformation was valid. In 1969, Barton won the Nobel prize for his work which established that equatorial substituents are more stable than axial cyclohexane substituents and that equatorial groups are generally more reactive than axial ones, as they are less sterically protected. Since then, cyclohexane and cyclohexane derivatives have been thoroughly studied.⁴ Six-membered rings such as cyclohexane can adopt chair (D_{3d}), boat (C_{2v}), twist-boat (D_2), half-chair (C_2), and sofa (C_3) geometries (see Figure 1), which can be uniquely defined by the six intraannular dihedral angles or, more efficiently, by the three Cremer–Pople⁵ or the three Haasnoot⁶ parameters.

The energy surface of cyclohexane is best described as an inverse Mexican hat potential. The chair conformation sits at the tip of the hat 26.4 kJ/mol lower in energy than the boat conformation, which is located on a slight bump on the rim of the hat 2.6 kJ/mol higher in energy than the twist-boat conformation that is also located on the rim.^{7,8} An energy barrier of 4.6 kJ/mol has been calculated for the interconversion between twist-boats, which passes through the boat form along the rim of the hat. The interconversion between the chair and the twist-boat form has to pass through the sofa or half-chair form with an energy barrier of 43.9 kJ/mol.⁹ A series of six articles using principal component and cluster analysis to distinguish among all the different conformations adopted by cyclohexane have been published.¹⁰ The conformations of cyclohexane have also been represented by a spherical map.¹¹ The two poles of the sphere correspond to the chair conforma-

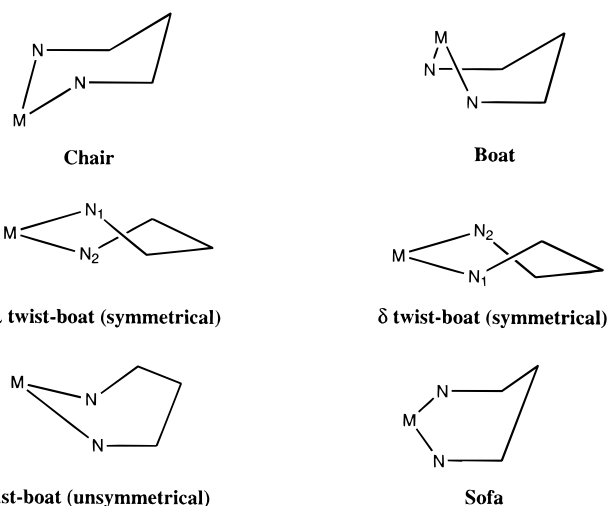


Figure 1. Common conformations adopted by six-membered chelate rings.

tions, while the twist-boat and boat conformations lie on the equator. Pseudorotational conformational changes are depicted horizontally (latitudinally) and symmetrical changes vertically (longitudinally).

In contrast to the interest in organic six-membered rings, very little attention has been paid to the conformation of six-membered rings in inorganic systems. Hancock has published many interesting papers in which he has analyzed the stability and bite size of five- and six-membered rings.¹² However, he only considered the six-membered chair conformation. Some molecular mechanical studies of six-membered rings incorporating cobalt(III) have also been published.^{13–16} We recently published conformational and cluster analyses of cobalt(III),¹⁷ nickel(II),¹⁸ and copper(II).¹⁹ We looked at all the metal systems individually, and in this note we compare the conformations of cobalt, nickel, and copper complexes containing six-membered rings.

Experimental Section

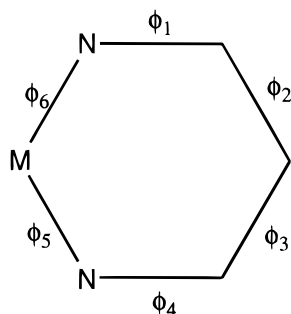
The Cambridge Structure Database (CSD)²⁰ V5.11 was searched for all six-membered rings having the substructure shown in Figure 2, where M is nickel(II), cobalt(III), or copper(II). All crystal structures containing the substructure with sp^3 -hybridized carbons and ligating atoms in the six-membered rings and having error-free atomic coordinate data and R factors less than 10.00% were retained. Version 5.11 of the CSD was released in April 1996 and contains 152 464 crystal structures. All the hits were stored and converted to MacroModel

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Table 1. Dihedral Angles, Numbered As Shown in Figure 2, of Representative Structures of Each of the Eight Clusters at Clustering Level 762, Their Conformations, Number of Members in Each Cluster, and the Percentage of Ni(II), Cu(II), and Co(III) Six-Membered Rings That Adopt the Conformation

cluster no.	ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ϕ_6	conformn	no. of members	% Ni	% Cu	% Co
1	57	-68	68	-56	39	-40	chair	657	82.9	96.0	79.8
2	-9	-60	59	11	-58	58	boat	70	11.5	2.9	9.6
3	-65	22	47	-72	28	36	δ -twist-boat	17	2.8	0.6	2.4
4	46	-87	47	16	-36	3	λ -twist-boat	4	0.77	0	0.5
5	-43	-25	76	-45	-12	59	δ -twist-boat	1	0	0	0.5
6	46	-68	21	38	-47	5	λ -twist-boat	1	0	0	0.5
7	11	-62	71	-26	-11	20	sofa	1	0.3	0	0
8	68	-38	-27	66	-35	-29	λ -twist-boat	18	0.8	0.6	6.7

**Figure 2.** The substructure used in the Cambridge Structural Database search. M = nickel(II), copper(II), or cobalt(III), and all nitrogens as well as the carbons are sp^3 hybridized.

format using the *csdconv* utility.²¹ All atoms that were not part of the fragment shown in Figure 2 were removed with the *draw* function in *MacroModel*.²² Atoms were renumbered so that all six-membered rings were numbered in the same way and placed into a masterfile for cluster analysis. The *Xcluster*³ program was used for cluster analysis. Proximity matrices were obtained by determining the pairwise distances between six-membered rings using the rms differences between corresponding dihedral angles. In order to prevent a misalignment of torsional sequences, all the atom labels in the rings were reflected through the plane created by the metal ion and the carbon atom directly opposite it. A 6-fold rotation such as the one required for six-membered carbocycles²³ is not needed due to the C_{2v} symmetry created by the metal diamine moiety of the six-membered rings. The energies of the different conformations were obtained as a function of the metal–ligand distance using the method of Hancock²⁴ and Wiberg.²⁵

Results and Discussion

A total of 769 six-membered rings containing the substructure in Figure 2 with nickel(II), cobalt(III), and copper(II) were obtained from the CSD search. Three hundred and eighty-seven of the rings were found with nickel(II), 174 for copper(II), and 208 for cobalt(III).

Clustering algorithms attempt to find groupings such that the similarities within the groups are significantly greater than those between the groups. There are many different methods of clustering data. Recently four programs were released that cluster molecules on the basis of their conformations; two were written primarily for the analysis of structures generated in

molecular dynamics simulations,^{26,27} one was written primarily for conceptual database analysis,²⁸ and one was written for the contraction of conformational space in the multiconformational analysis of solution NOE data.²⁹ In this study, we used the *Xcluster* program,³ which is an agglomerative, hierarchical, single-link method. Some reservations have been expressed that single-link methods can link dissimilar clusters that contain bridging outlying members. However, this was not found to be a problem in our study. One of the difficulties in an agglomerative, hierarchical, single-link method is to choose between all the clustering levels and find a level, or levels, at which the clusters are significantly different. We have found that the separation ratio³ and visual inspection of both the distance maps and clustering mosaics are the best indicators of a significant clustering level. On the basis of the clustering mosaic, distance map, and separation ratio, we judged clustering level 762 to be the level at which the individual clusters were separated most effectively. At this clustering level, there are eight distinct conformational families; see Table 1.

Although the same clusters were obtained at high clustering levels when atomic overlap or torsional differences were used as similarity criteria, at lower clustering levels there were noticeable differences. The reason for this is fairly obvious; when the dihedral angles are used as a measure of similarity, the lengths of the Ni–N, Cu–N, and Co–N bonds are not important. However, if the difference in Cartesian coordinates between identical pairs of atoms is used, then differing bond lengths will result in larger differences and therefore in different clusters. The fact that the same clusters are obtained at the more important higher clustering levels indicates that the agglomerative, hierarchical, single-link clustering method is a fairly robust technique.

As expected the chair conformation is the most common conformation for all three metal ions. For cobalt(III) and nickel(II), there are more boat conformations than one would expect on the basis of the potential energy surface, which has the boat conformation as a transition state higher in energy than either the twist-boat or chair. In fact, minimizing a cobalt, nickel, or copper propanediamine moiety that is in the boat conformation always results in a twist-boat energy-minimum structure. Although some boat conformations are found for copper(II), there are significantly less than there are for cobalt(III) and nickel(II). In order to establish whether this could be due to the difference in metal ion sizes we performed some bite-size calculations on hypothetical cobalt(III), nickel(II), and copper-

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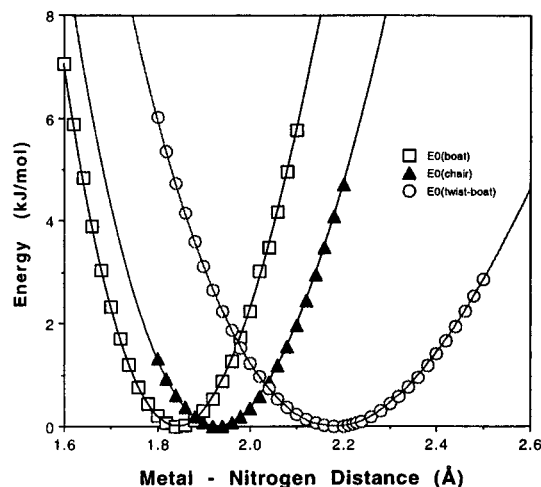


Figure 3. Plot of “relative energy” as a function of the metal–nitrogen distance in a metal propanediamine complex. The energies of the different conformations cannot be compared in these calculations as the boat conformation had to be constrained, while the other two conformations were not. For this reason, we took the minimum energy of each conformation as having 0.00 kJ/mol relative energy.

(II) propanediamine complexes (i.e., Co(pn), Ni(pn), and Cu(pn)). The energies of the different conformations were obtained as a function of the metal–ligand distance using the method of Hancock.²⁴ Similar results were obtained with Wiberg’s method.²⁵ Ideally, we would have used constraints in place of restraints,³⁰ but we did not have access to the software. Since minimizing the boat conformation always results in a twist-boat conformation, we had to constrain the M(pn) to a boat by fixing the intraannular dihedral angles. The results from the bite-size calculations are shown in Figure 3. The boat conformation has the smallest bite size with an ideal metal–nitrogen distance of 1.84 Å, the chair has an ideal metal–nitrogen distance of 1.92 Å, and the twist-boat prefers metal–nitrogen distances of 2.18 Å. The twist-boat conformation has the broadest parabola in Figure 3, which indicates that it is the most flexible conformation.

The energy differences between the different conformations (ΔE ’s) are not very useful in these calculations as the boat conformation had to be constrained, while the other two conformations were not. Luckily, the difference in the energies of the different conformations of the three metals ($\Delta\Delta E$) can be compared to see for which metal ion the difference in energy between the chair and boat conformations is the greatest. At 1.89 Å, which corresponds to the ideal nickel–nitrogen distance, the boat conformation is 42.76 kJ/mol higher in energy than the chair, at 1.93 Å (cobalt), the difference is 1.31 kJ/mol greater than for nickel, and at 2.03 Å (copper), the energy difference between the boat and the chair conformations is 3.3 kJ/mol larger than for six-membered nickel(II) rings. This energy difference between the three metal ions indicates that low-spin nickel(II) is more likely to adopt a boat conformation than copper(II).

As shown before,¹⁸ the boat conformations are only found when the six-membered rings are forced into the boat conformation by other parts of the compound; such compounds all have the substructures shown in Figure 4. The fact that cobalt and nickel form six-membered rings with boat conformations in the solid state more often than copper can be attributed to two factors. First, the copper–nitrogen distance is slightly longer than the distances for the other two metal ions and

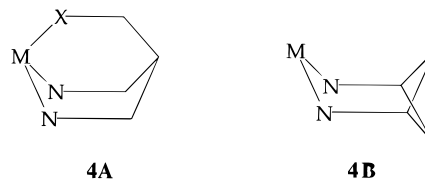


Figure 4. Structural motifs responsible for all the boat and twist-boat conformations.

therefore the energy difference between the boat and chair conformations is larger. Second, the boat conformations are only found in compounds having the substructure shown in Figure 4; compounds having these substructures are most commonly prepared by template syntheses and copper does not lend itself to all template syntheses. Furthermore, copper(II) undergoes a Jahn–Teller distortion, which lengthens the axial bonds beyond 2.10 Å, further decreasing the chances of forming boat conformations in compounds having the substructure shown in Figure 4A.

Encapsulated transition metal compounds are good illustrations of how these factors influence the formation of boat conformations. A search of the Cambridge Structural Database found 24 complexes of cobalt(III) with octahedral encapsulating ligands, 3 nickel(II) complexes, and 1 copper(II) complex. The reason for this is that cobalt(III) is a “good” templating center, while copper and nickel are not.³¹ The copper and nickel complexes that have been crystallized were formed either in very low yield or from the reaction with the free ligand that is not easily synthesized.³² Even though a copper hexaamine macrobicyclic complex has been crystallized,³² the structure is not rigid enough to force the six-membered rings to adopt boat conformations, and although they have the substructure shown in Figure 4A, they adopt strained twist-boats.

Conclusion

We have shown that cluster analysis is a very robust method that is able to find all the common conformations of six-membered rings, especially if the difference in pairwise dihedrals is used as a similarity criterion. As expected, the chair conformation is the most common conformation for nickel(II), copper(II), and cobalt(III) containing six-membered rings. Although some boat conformations are found for copper(II), there are significantly less than there are for cobalt(III) and nickel(II). The fact that cobalt and nickel form six-membered rings with boat conformations in the solid state more often than copper can be attributed to two factors. First, the copper–nitrogen distance is slightly longer than the distances for the other two metal ions, especially if one considers the Jahn–Teller elongation present in copper(II) complexes, and therefore the energy difference between the boat and chair conformations is larger. Second, the boat conformations are only found in compounds having the substructure shown in Figure 4, compounds having these substructures are most commonly prepared by template syntheses and copper does not lend itself to all template syntheses.

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