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# Structural Analysis of the Conformational Flexibility of Tris(pyrazolyl)borate Ligands and Their Analogues

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Database analysis and molecular mechanics were used to determine the conformational flexibility of tridentate scorpionate ligands. The tris(pyrazolyl)methane and tris(pyrazolyl)borate ligands act like molecular vises, opening their tripodal structure for larger metals and closing around smaller metal ions. Tris(3-*tert*-butylpyrazolyl)methane has significant preference for larger metal ions than its unsubstituted parent compound. Tris(pyrazolyl)methanes and tris(pyrazolyl)borates have similar conformational flexibilities. Placing sterically hindered groups on the central carbon or boron has only a minor effect on the geometry of the tris(pyrazolyl)methanes and tris(pyrazolyl)borates. However, it does influence the flexibility of the ligands, particularly when they have to open far from their ideal geometry, which commonly occurs.

## Introduction

Since poly(pyrazolyl)borates were first synthesized by Trofimenko in the late 1960s,[1,2] over 2000 papers have been published describing and/or using the ligands.[3,4] Figure 1 shows the structure of tris(pyrazolyl)borate, RB(pz)$_3$, which forms the basis of the class of ligands. Poly(pyrazolyl)borate ligands and their analogues are also known as scorpionate ligands. They form a very diverse group of compounds as they can bind almost any metal, the central atom can be boron, carbon, silicon, phosphorus, or gallium, the ligands can be mono-, bi-, tri-, or even tetradentate (bisbidentate binding two metals), and the coordinating atoms can be part of pyrazole, indazole, or imidazole heterocycles, which in turn can be substituted at the 3 (e.g. HB(3-CH$_3$pz)$_3$), 3,5 (e.g. HB(3,5-tBu$_2$pz)$_3$), or 4 (e.g. HB(4-CH$_3$pz)$_3$) positions. As a result, over 150 different scorpionate ligands have been synthesized, and more than 1500 crystal structures of pyrazolylborate ligands and their analogues have been released. The immense variability of the scorpionate ligands is partly responsible for their popularity.

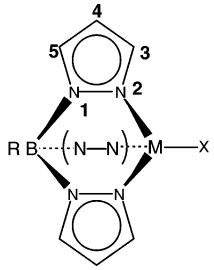

**Figure 1.** Tris(pyrazolyl)borate. In this paper ligands substituted at positions 3,4 and 5 with carbon or any other atom in place of the central boron and R = H, Me, and pz will be examined. ---(−N−N−)--- is meant to represent a pyrazolyl moiety that is perpendicular to the plane of the page.

Tris(pyrazoyl)borates and their analogues can be considered as the tripodal equivalent of cyclopentadiene ligands and have been used in catalysis, bioinorganic models systems, metal extraction, and biomedicine.[5−7] By changing the size of the substituents on the pyrazolyl ring, especially those at the 3 position, it is possible to decrease the access to the coordinated metal ion. Sterically hindered ligands such as HB(3,5-tBu$_2$pz)$_3$ limit both the side and frontal access to the metal ion and form a tight protective pocket around the metal ion. The steric blocking effect has been quantified using cone and wedge angles.[3,8,9] However, to date there have been no systematic examinations of the flexibility of poly(pyrazolyl)borate ligands.

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In his book on scorpionates Trofimenko states that, “Polypyrazolylborate ligands have generally been used as molecular vises to keep the metal ion in a firm tridentate ($C_{3v}$ symmetry) grip, so that chemical operations could be performed at the remaining coordination sites.”[3] In this paper we describe the use of molecular mechanical and database analyses to examine the flexibility of tris(pyrazolyl)borate and tris(pyrazolyl)methane ligands.

We have previously used database analysis and molecular mechanical methods to analyze the conformations of cobalt(III),[10] copper(II),[11] and nickel(II)[12] propanediamine and substituted propanediamine ring systems, in a way similar to that used to examine the flexibility of tris(pyrazolyl)borates in this paper.

## Experimental Section

All database searches and analyses were done using the Conquest and Vista programs associated with Cambridge Structural Database[13] (CSD) v5.24, which was released in Nov 2002 and contains 272 066 crystal structures.

To determine the ideal metal−nitrogen distance of $HC(pz)_3M(H_2O)_3$, $HC(3\text{-}tBupz)_3M(H_2O)_3$, $CH_3C(pz)_3M(H_2O)_3$, and $pzC(pz)_3M(H_2O)_3$ the molecular mechanics method of Hancock[14−16] was used. The ideal metal−nitrogen distance in the AMBER* force field of MacroModel v8.0[17] was increased systematically from 1.50 to 2.80 Å with 0.05 Å increments. A force constant of 128 kJ/(mol·Å$^2$) was used for the bond stretching interaction. All structures were energy minimized with 500 iterations and no solvent.

## Results and Discussion

There are many structures in the CSD that have a common backbone, e.g. scorpionates, porphyrins, or 14-membered macrocycles. Analyses of such congeneric families are very useful as they can reveal the different conformations the backbone structure can adopt in the different environments found in the crystals. This can provide information about the conformations available to the backbone, how the conformers can interconvert, and the environmental factors that are responsible for certain conformations.[18−23] Use of a sufficiently large data set can “average out” random effects that are common to all data points across a series.

Table 1 gives the number of compounds in the Cambridge Structural Database that have the tris(pyrazolyl)borate substructure shown in Figure 1. There are 436 $RB(pz)_3$ complexes with no substituents on the pyrazole and 49 tris(pyrazolyl)methane complexes with no substituents on the pyrazole, $RC(pz)_3$, in the CSD.

**Table 1.** Distribution of $HB(pz)_3$ Ligands in the CSD[a]

| substitution | $RC(pz)_3$ | $RB(pz)_3$ | $RX(pz)_3$ |
|---|---|---|---|
| unsubstituted | 49 | 436 | 499 |
| substituted | 89 | 1624 | 1735 |

[a] X is any atom, “unsubstituted” have hydrogens at positions 3,4 and 5, while “substituted” can have any group at positions 3,4 and 5, including hydrogens.

The shortest metal−nitrogen distance found in a search performed of all substituted and unsubstituted metal-$RB(pz)_3$ complexes was 1.78 Å (CSD refcode = JOVPAL,[24] M = Be) and the longest was 2.93 Å (CSD refcode = NEBKOU,[25] M = K), while for M-$RC(pz)_3$ complexes it was 1.96 Å (CSD refcode = XAMNII,[26] M = Fe) and 2.94 Å (CSD refcode = ZUBRAP,[27] M = Tl). This shows that the tridendate scorpionate ligands examined are quite flexible and can bind a variety of metals with a metal−nitrogen distance range of at least 1.0 Å.

**What Is the Ideal Metal−Nitrogen Distance for Tris(pyrazolyl)borate?** Unfortunately, we cannot determine the ideal metal−nitrogen distance for tris(pyrazolyl)borates because there are no force field parameters for boron in the AMBER* force field. However, it is possible to calculate the ideal M−N distance in $HC(pz)_3M(H_2O)_3$, $HC(3\text{-}tBupz)_3M(H_2O)_3$, $CH_3C(pz)_3M(H_2O)_3$, and $pzC(pz)_3M(H_2O)_3$ complexes and to determine the effect substituents on the ligand have on the metal−nitrogen distance. Molecular mechanical calculations were used for this purpose. In molecular mechanics, it is common practice to drive a certain parameter, for example, a torsion angle, through a series of fixed values to obtain the strain energy as a function of the parameter. A curve of the strain energy versus the M−N bond distance can similarly be obtained by systematically increasing the ideal M−N distance in the force field and calculating the strain after each increase. The minimum of such a graph occurs at the ideal M−N bond length, because the strain energy is at a minimum when the ligand bite size perfectly matches the metal size.[14,15] The ideal M−N bond length therefore represents the metal to nitrogen distance of a hypothetical metal that would best fit the ligand in its lowest energy conformation. Molecular mechanics calculations of this type were used to find the ideal metal−nitrogen distance for tris(pyrazolyl)methane ligands and not tris(pyrazolyl)borates, because we could not find reliable boron molecular mechanics parameters.

The ideal metal−nitrogen distance for a metal ion with an octahedral coordination was found to be 1.88 Å for $pzC(pz)_3M$, 1.90 Å for $CH_3C(pz)_3M$, 1.95 Å for $HC(pz)_3M$, and 2.5 Å for the $HC(3\text{-}tBu(pz)_3)M$ complexes; see Figure 2. Unsubstituted tris(pyrazolyl)methane, $HC(pz)_3$, has an

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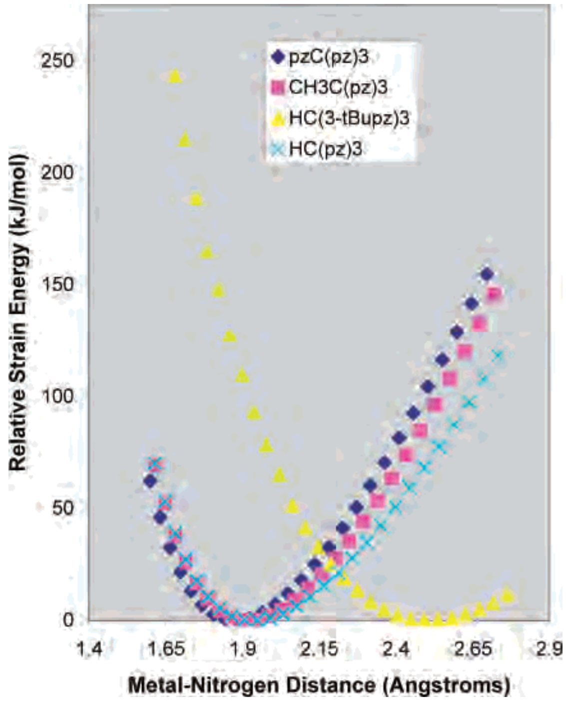

**Figure 2.** Relative strain energy vs the imposed ideal metal to nitrogen distance used in the AMBER* force field calculations.

idealmetal to nitrogen distance of 1.95 Å, as expected, and adding a t-Bu group at the 3-position on each pyrazole ring increases the ideal metal−nitrogen distance of the ligand substantially; this is due to the repulsions between the tertiary butyl groups opening up the tris(pyrazolyl) tripod. Placing substituents on the central carbon closes the tripod marginally and the ideal M−N distance is decreased: the larger the substituent, the shorter the M−N distance. The same effect should be observed in the tris(pyrazolyl)borates. This would explain why the $HB(pz)_3$ and $HB(3,5\text{-}(CH_3)_2pz)_3$ ligands bind the large lead ion in a tridentate manner, while $pzB(pz)_3$ with its preference for smaller metal ions binds lead in a bidentate fashion.[28] It might also explain why $pzB(pz)_3$ is the first chelating ligand which can extract $Mg^{2+}$ quantitatively around neutral pH but can barely extract $Ca^{2+}$ and why the small Be ion prefers $pzB(pz)_3$ over $HB(pz)_3$.[29] According to Figure 2 the effect of placing substituents at the 3-position of the pyrazolyl ring is much larger than changing the substituent on the central carbon. But the effect of the steric groups on the central atom increases with larger metal ions. Figure 2 clearly shows that $HC(pz)_3$ opens up to accept metals that are larger than its ideal size with less steric strain than $CH_3C(pz)_3$ does; e.g., to open up to a metal−nitrogen distance of 2.60 Å $HC(pz)_3$ has to undergo deformations that cause an increase in steric strain of 87 kJ/mol vs 120kJ/mol for $CH_3C(pz)_3$.

All the energy-minimized structures with imposed M−N distances between 1.6 Å and 2.8 Å that were used to generate Figure 2 were kept and analyzed to determine how the $HC(pz)_3$ and $HC(3\text{-}tBupz)_3$ ligands respond to increasing M−N distance. Did the tripodal ligand open and close like a jellyfish swimming in the water or did it rigidly retain its shape? An overlap of all the $HC(pz)_3$ structures shows that the tripodal $HC(pz)_3$ ligand opens up as the M−N distance increases; see Figure 3.

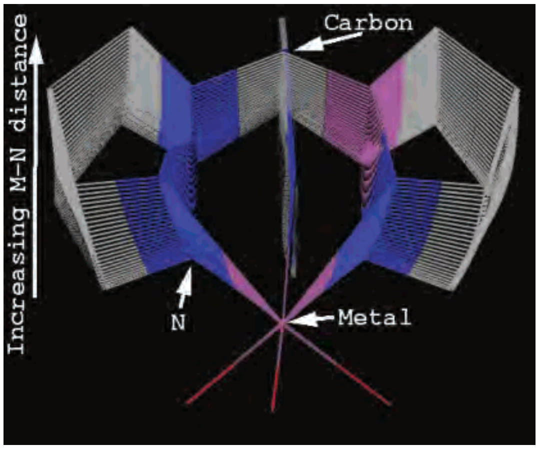

**Figure 3.** Overlap of all the $HC(pz)_3$ structures that were minimized to obtain the graph shown in Figure 2, showing that as the M−N distance increases the N−M−N angle increases and the $HC(pz)_3$ ligand flattens out. All the metal ions and oxygen (aqua) atoms were overlapped.

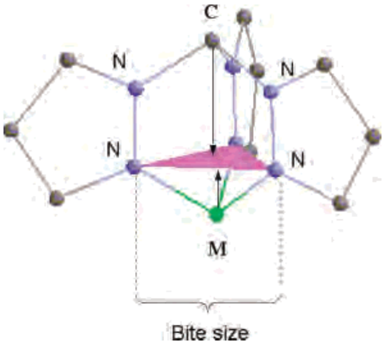

**Figure 4.** Parameters examined in this study: shortest distance from the metal to the plane; shortest distance from the central atom, carbon in this case, to the plane; metal−nitrogen distance; nitrogen−metal−nitrogen angle; bite size.

Solid-state structures in the CSD were examined to establish whether the scorpionate ligands in the database exhibit the same flexibility as calculated by molecular mechanics and to find structural parameters to describe changes associated with binding to different size metals.

Three parameters have been used to describe the structure of scorpionate ligands in the literature: bite size; cone angle; wedge angles.[3,8,9] The latter two have been devised to quantify the size of the protective pocket the scorpionate ligand forms around the metal ion. The smaller the cone angle, and the larger the wedge angle, the easier it is for other ligands to coordinate the metal.[3] They are not measures of the ligand flexibility and were not considered in this analysis.

The bite size of $RX(pz)_3$ ligands has been defined as the average distance between the coordinating nitrogens; see Figure 4.

What is the relationship between bite size and metal−nitrogen distance? Sohrin et al.[29,30] have suggested that $pzB(pz)_3$ ligands do not form tridentate complexes if the bite

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**Table 2.** Structural Parameters (Å, deg) Defining the Flexibility of All $RC(pz)_3$ Ligands from XAMNII and RIBSOK[a]

| param | shortest $RC(pz)_3$ (XAMNII[26]) | longest $RC(pz)_3$ (RIBSOK[31]) | ideal M−N 1.95 Å | av in CSD |
|---|---|---|---|---|
| M−N | 1.96 | 2.78 | 1.95 | 2.23 |
| bite size | 2.70 | 3.04 | 2.65 | 2.85 |
| N−M−N | 87.2 | 67.8 | 85.8 | 80.3 |
| C plane | 1.82 | 1.74 | 1.87 | 1.79 |
| M plane | 1.18 | 2.05 | 1.20 | 1.49 |

[a] The structures were found in a search of the CSD, looking for all structures $RC(pz)_3$ with hydrogens at positions 3,4 and 5 of the pyrazolyl ligands. "Shortest $RC(pz)_3$" refers to the structure with the shortest M−N distance that was found in the search. Ideal M−N (1.95 Å) refers to the calculated structure with the ideal metal to nitrogen distance for $HC(pz)_3$. Averages in the CSD are the average parameters for all structures found in the search.

**Table 3.** Structural Parameters (Å, deg) Defining the Flexibility of All $RC(pz)_3$ Ligands from XAMNII and ZUBRAP[a]

| param | shortest $RC(pz)_3$ |  | ideal M−N 2.50 Å | av in CSD |
|---|---|---|---|---|
|  | XAMNII[26] | ZUBRAP[27] |  |  |
| M−N | 1.96 | 2.94 | 2.50 | 2.25 |
| bite size | 2.70 | 3.37 | 3.15 | 2.89 |
| N−M−N | 87.2 | 70.2 | 77.9 | 80.5 |
| C plane | 1.82 | 1.56 | 1.66 | 1.77 |
| M plane | 1.18 | 2.24 | 1.72 | 1.50 |

[a] The structures were found in a search of the CSD, looking for all structures $RC(pz)_3$ with any groups at positions 3,4 and 5 of the pyrazolyl ligands, including hydrogens.

**Table 4.** Structural Parameters (Å, deg) Defining the Flexibility of All $RB(pz)_3$ Ligands from ZAWJAI and RUGNUC[a]

| param | shortest $RB(pz)_3$ (ZAWJAI[30]) | longest $RB(pz)_3$ (RUGNUC[32]) | av $RB(pz)_3$ |
|---|---|---|---|
| M−N | 1.89 | 2.80 | 2.22 |
| bite size | 2.73 | 2.97 | 2.90 |
| N−M−N | 94.3 | 66.5 | 82.2 |
| C plane | 1.98 | 1.82 | 1.88 |
| M plane | 1.08 | 1.95 | 1.45 |

[a] The structures were found in a search of the CSD, looking for all structures $RB(pz)_3$ with hydrogens at positions 3,4 and 5 of the pyrazolyl ligands.

**Table 5.** Structural Parameters (Å, deg) Defining the Flexibility of All $RB(pz)_3$ Ligands from JOVPAL and NEBKOU[a]

| param | shortest $RB(pz)_3$ (JOVPAL[24]) | longest $RB(pz)_3$ (NEBKOU[25]) | av $RB(pz)_3$ |
|---|---|---|---|
| M−N | 1.78 | 2.93 | 2.22 |
| bite size | 2.73 | 3.17 | 2.95 |
| N−M−N | 100 | 67.3 | 84.0 |
| C plane | 1.92 | 1.65 | 1.86 |
| M plane | 0.82 | 2.08 | 1.41 |

[a] The structures were found in a search of the CSD, looking for all structures $RB(pz)_3$ with any groups at positions 3,4 and 5 of the pyrazolyl ligands, including hydrogens.

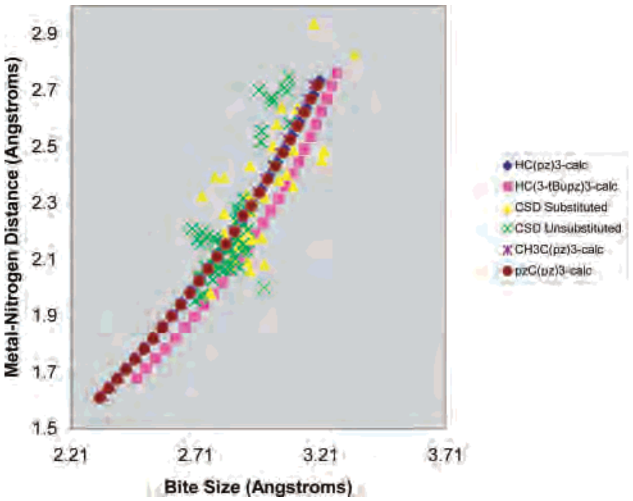

**Figure 5.** Plot of the bite size vs the metal−nitrogen distance for all the structures generated in the calculations to produce Figure 2, as well as all the $RC(pz)_3$ structures in the CSD.

size is 3.1 Å or greater. If the scorpionate ligands are completely rigid the bite size will stay constant with changing M−N distance. However, in Figure 3, which is based on our molecular mechanics calculations, we can see that the scorpionate ligands examined are not rigid. Our CSD analysis confirms this. Tables 2−5 show that the bite size between different $HX(pz)_3$ ligands can vary a lot. In both the substituted and unsubstituted tris(pyrazolyl)borate and the tris(pyrazolyl)methane ligands it spans a range of about 1.00 Å. As the M−N distance increases the ligand opens up the bite size increases; see Figure 5 and Tables 2−5.

Figure 5 shows that the effect of placing sterically hindered groups on the central atom is negligible. As the metal−nitrogen distance increases the bite size of $HC(pz)_3$, $CH_3C(pz)_3$, and $pzC(pz)_3$ are all the same and increase in exactly the same manner. The steric bulk of the tertiary butyl groups at position 3 of the pyrazolyl rings has a much larger effect on the bite size, and they prevent the tripod from closing. Therefore, the bite size of $HC(3\text{-}tBupz)_3$ is constantly larger than that of the other ligands examined. However, although the bite size is larger for $HC(3\text{-}tBupz)_3$, it responds to changing metal−nitrogen distances in a manner similar to that for the other ligands studied. The structures found in the CSD exhibit similar behavior.

Figure 5 and Table 2 also show that there are no crystal structures with metal−nitrogen distances of 1.95 Å or less, which is the ideal metal−ligand distance for the tris(pyrazolyl)methane ligand with no substituents on the pyrazole rings. Most of the structures found in the CSD have much longer metal−nitrogen distances; in fact, the average distance for unsubstituted $RC(pz)_3$ complexes is 2.23 Å.

An analysis of all the parameters shown in Figure 4 and presented in Tables 2−5 shows that as the metal to nitrogen distance increases the bite size and shortest distance between the plane and metal increases, while N−M−N angle and shortest distance between the central atom and the plane shorten. Trofimenko is correct; the poly(pyrazolyl)methane ligands act like molecular vises, opening the tripod for larger metals and closing around smaller metal ions.

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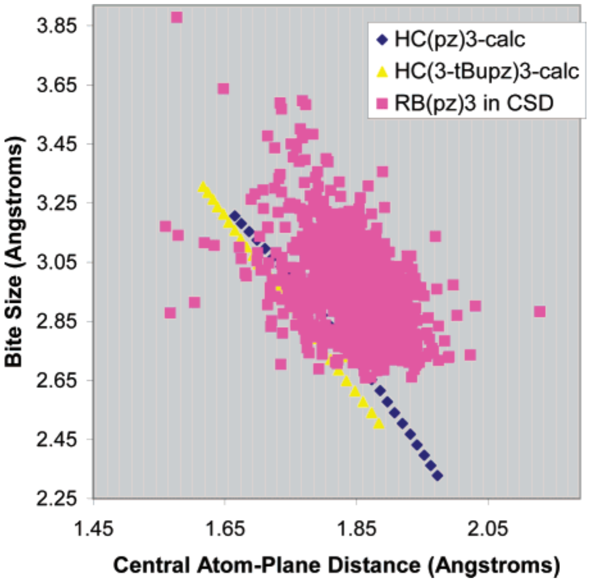

**Figure 6.** Plot of the shortest distance between the central atom to plane and the bite size distance for all the structures generated in the calculations to produce Figure 2, as well as all the RB(pz)$_3$ structures in the CSD.

To establish the effect of replacing the central carbon in tris(pyrazolyl)methane with boron, we compared the tris(pyrazolyl)methane and tris(pyrazolyl)borates structures in the CSD with the calculated tris(pyrazolyl)methane structures. Figure 6 is a typical plot. It shows that for all the tripodal scorpionates examined the carbon to plane distance decreases as the bite size increases and that the carbon to plane distance is larger for the tris(pyrazolyl)methanes than for the tris(pyrazolyl)borates. In response to changing metal sizes the tris(pyrazolyl)borates undergo structural changes similar to those for tris(pyrazolyl)methane, except they are slightly more dome shaped (concave) than the flatter tris(pyrazolyl)methanes.

## Conclusions

Using molecular mechanics and database analysis, it has been shown that tripodal scorpionate ligands can accommodate a variety of metal sizes by opening up the ligand. It undergoes deformations similar to that of a jellyfish swimming through the water; with small metals the mouth of the ligand contracts (short bite size) and the body lengthens (large carbon to plane distance). Large metals cause the ligand to open its mouth (large bite size) and contract its body (short carbon to plane distance).

Placing sterically hindered groups on the central carbon or boron has a small effect on the geometry of the tris(pyrazolyl)methanes and tris(pyrazolyl)borates. However, they do influence the flexibility of the ligands particularly when they have to open far from their ideal geometry, which commonly occurs. Large groups tend to close the mouth of the ligand and result in a preference for shorter metal—nitrogen distances. Substitution at position 3 of the pyrazole ring has a much more obvious effect; see Figure 2. The large groups, such as tertiary butyl groups, force open the mouth of the ligand and increase the ideal metal—nitrogen distance.

Tris(pyrazolyl)methanes and tris(pyrazolyl)borates have similar geometries and conformational flexibilities. The major difference is that tris(pyrazolyl)borates have longer bodies (i.e. longer carbon to plane distances; see Figure 4).

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