The Rare Head-to-Head Conformation of Untethered Lopsided Ligands Discovered in Both Solution and Solid States of 1,5,6-Trimethylbenzimidazole Re(V) and Ru(II) Complexes

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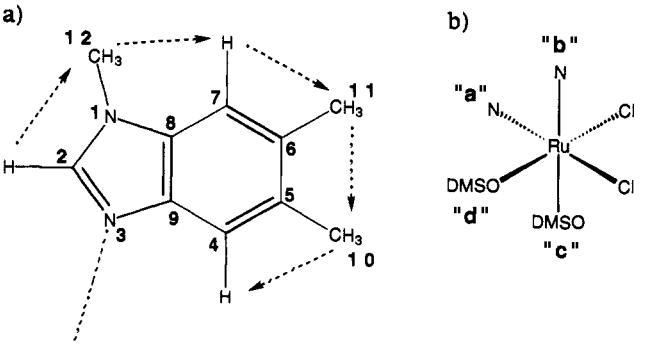
Metal ligation by N-donor ligands in biological systems involves heterocyclic ligands almost exclusively.[1] The two most common classes of such ligands are macrocycles (e.g., porphyrins) and lopsided bases (B, e.g., imidazoles). Ligation by two or more of the same type of B is widespread. For two cis B's, the corresponding atoms of each ligand can be on the same side or opposite sides of the N–M–N plane, giving the head-to-head (HH) and the head-to-tail (HT) orientations, respectively. The most lopsided B's are five–six bicyclic ligands, B_{5-6} (purines, benzimidazoles). The vast majority of *cis*-bis(B_{5-6}) complexes are HT.[2-4] The very few reported HH *cis*-bis(B_{5-6}) complexes are square-planar.[2,5-8] These HH *cis*-bis(Gua)Pt(II) complexes (Gua = guanine derivatives) are models for the principal adduct formed by the anticancer drug *cis*-$Pt(II)(NH_3)_2Cl_2$ with dGpG sites in the putative target, DNA.[2] However, for untethered lopsided ligands, there is only one report of HH species in solution and no report of such complexes in both solution and solid states.[2] Consequently, most factors controlling orientation are not well understood, although H-bonding and steric clashes of purine exocyclic groups influence conformation. Because Me_3Bzm (1,5,6-trimethylbenzimidazole) lacks exocyclic groups directed toward the metal, this B_{5-6} ligand serves as a prototype to gain insight into the behavior of nucleopurines.

We find the rare HH conformation in the crystalline[9] octahedral $Re_2O_3Cl_4(Me_3Bzm)_4$ (**1**) and *cis,cis,cis*-$RuCl_2(Me_2SO)_2(Me_3Bzm)_2$ (**2**) (Figures 1 and 2) prepared from $ReOCl_3(Me_2S)(OPPh_3)$ and *cis*-$RuCl_2(Me_2SO)_4$, respectively. The ^1H NMR spectra of both **1** and **2** in $CDCl_3$ exhibit features characteristic of highly fluxional species.

Chart 1. (a) NMR Numbering Scheme and NOE Connectivities for Me_3Bzm (The carbons are designated B for benzimidazole) and (b) Labeling Scheme for Ligand Positions



The ^1H NMR ROESY and EXSY (Figure 3, see Chart 1 for Me_3Bzm labeling) spectra of **2** reveal the presence of only two species (**I** and **II**), each with two nonequivalent Me_3Bzm's; **I** and **II** interchange readily, indicating that they are atropisomers and not geometric isomers. For cis,cis,cis complexes, four atropisomers

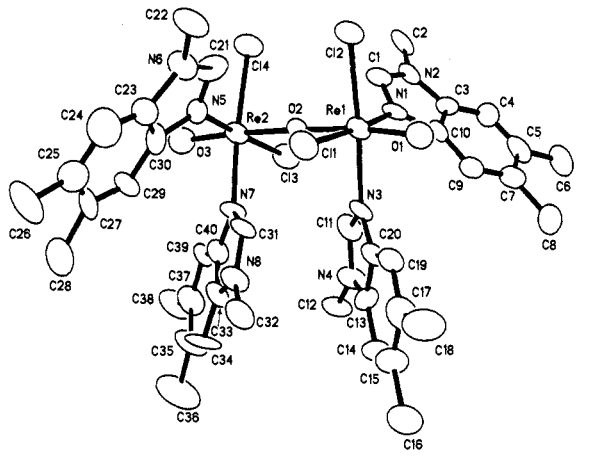


Figure 1. Molecular structure of $Re_2O_3Cl_4(Me_3Bzm)_4$ (**1**).

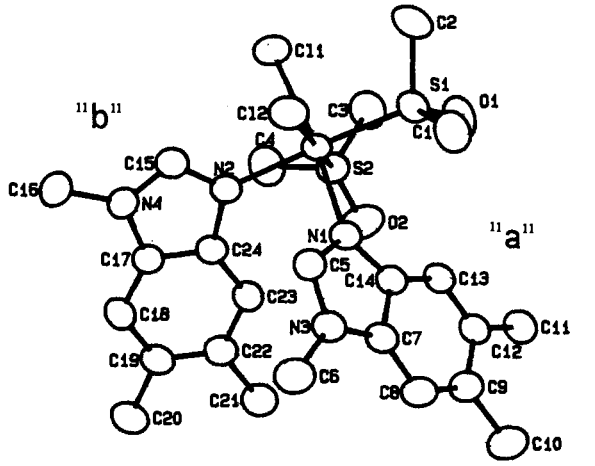


Figure 2. Molecular structure of *cis,cis,cis*-$RuCl_2(Me_2SO)_2(Me_3Bzm)_2$ (**2**).

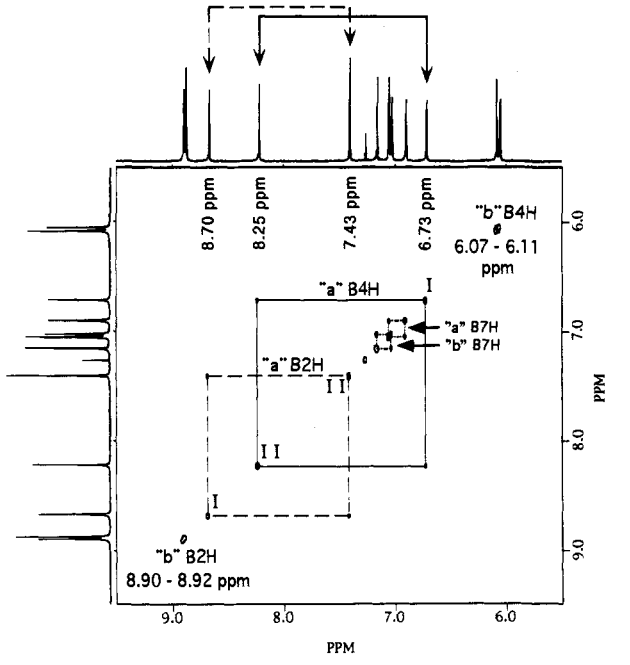


Figure 3. Downfield region of 2D ^1H EXSY spectrum of **2**. The exchange paths for Me_3Bzm "a" between **I** and **II** are depicted by the solid (B4H) and dashed (B2H) lines.

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(2 HH + 2 HT) are possible since each Me_3Bzm can flip between two orientations. The intra- and interligand NOE peaks allowed us to assign the ^1H signals and coordination positions of the two Me_3Bzm ligands in **I** and **II**. The B2H shifts of the Me_3Bzm "b" (trans to DMSO) for both atropisomers and of Me_3Bzm "a" (trans to Cl) for **I** are normal (~8.9 ppm). However, the "a" B2H shift for **II** is far upfield at 7.4 ppm.

A large upfield shift of one of the two five-membered-ring ^1H signals of one atropisomer, as found for **II**, is a hallmark of HH Gua atropisomers.[2] We now report marked shift effects for a six-membered-ring signal (B4H) and find that they are particularly informative. Remarkably, of the four B4H signals, *only* the "a" B4H signal of **II** has a normal shift; the other *three* are far upfield.

The large upfield shifts require that (i) the slightly more abundant atropisomer **II** is the solid-state HH form (Figure 2) and (ii) **I** is the HT species formed by flipping Me_3Bzm "a" of **II** while Me_3Bzm "b" remains fixed. (In models, a flipped Me_3Bzm "b" has B4H-Cl clashes, which destabilize the two atropisomers not observed.) In the HH atropisomer **II**, "a" B2H (C5H, Figure 2) is directed toward the shielding region of Me_3Bzm "b", resulting in the upfield shift of the "a" B2H signal. In the HT form **I** with Me_3Bzm "a" flipped, the "a" B4H is directed toward the shielding region of Me_3Bzm "b", explaining the upfield "a" B4H signal. For both atropisomers, B4H in Me_3Bzm "b" is in the shielding region of Me_3Bzm "a" (Figure 2, C23H is "b" B4H of **II**), and indeed the "b" B4H signal is upfield at ~6.1 ppm for both **I** and **II**.

Previously, HH atropisomers of untethered B_{5-6} ligands found in solids were too fluxional to be identified in solution, and HH atropisomers found only in solution were minor forms. For **2**, however, the evidence for the rare HH form in both solid and solution states is compelling. Furthermore, although there is only one set of signals for the two inequivalent types of Me_3Bzm of **1** at ambient temperature, at −60 °C two sets of signals were found; the shifts are consistent with the HH species found in the solid (Figure 1), using the arguments presented for **2**.

Since there are no relevant HH octahedral purine complexes, we compare **1** and **2** with HH square-planar complexes using the base/metal coordination plane dihedral angles (B/M and B′/M)[4] shown in Figure 4 and the supplementary material. In *cis*-$[Pt(NH_3)_2\{d(pGpG)\}]$,[5] both bases are nearly perpendicular to the PtN_4 plane (B/M and B′/M ~ 90°). In a related complex, *cis*-$[Pt(NH_3)_2\{d(CpGpG)\}]$,[6] only one Gua has a B/M ~ 90°. Model HH *cis*-$[Pt(NH_3)_2(9\text{-EtGua})_2]X$[7,8] salts usually have one B/M ~ 90°. Modeling of HH octahedral complexes[5] predicted severe steric clashes with axial Cl and OH ligands if B/M ≅ 90°. Given the relatively low bulk of Me_3Bzm, the small B/M and B′/M values (38–51° for **1** and **2**) support the predictions of steric clashes between Gua nucleobases and non-H-bonding axial ligands of octahedral HH complexes.[5] When present, small B/M dihedral angles in *cis*-bis(Gua)Pt(II) complexes are generally supported by interligand H-bonds.[5,7,8] It is interesting that octahedral anticancer drugs are less effective, in general, than square-planar ones. However, Ru(II) complexes are among the most active, and modeling suggests that a H-bonding axial ligand such as H_2O is necessary for B/M to be ~90°.[10] Further experimentation is needed to clarify this issue and to understand the factors influencing the conformations adopted by lopsided ligands in other biological systems.

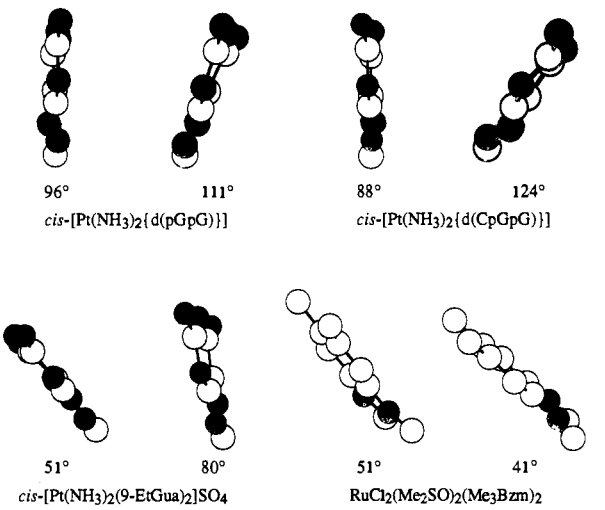

Figure 4. Depiction of B′/M (left) and B/M (right) dihedral angles (see supplementary material for additional depictions of such angles).

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Supplementary Material Available: Crystallographic data and positional and isotropic thermal parameters for **1** and **2**; figure showing B/M and B′/M dihedral angles of HH *cis*-bis(B_{5-6}) complexes (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) Crystallographic data (Mo Kα radiation). **1**·$2CH_3COCH_3$: monoclinic, $C2/c$; a = 35.020(12) Å, b = 16.308(5) Å, c = 25.507(7) Å, β = 132.870(0)°, V = 10676(8) Å^3, Z = 8; −100 °C; R = 0.056, R_w = 0.064 for 4607 unique reflections with $F > 4\sigma(F)$ and 534 variables. **2**: monoclinic, $P2_1/n$; a = 15.935(3) Å, b = 11.348(1) Å, c = 17.265(4) Å, β = 111.80(1)°, V = 2899(1) Å^3, Z = 4; 25 °C; R = 0.032, R_w = 0.047 for 5417 unique reflections with $I > 3\sigma(I)$ and 316 variables.

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