The First Observation and Full Characterization of All Atropisomers and Their Allowed Interconversions in an Octahedral Bis(bipyridine)ruthenium(II) Complex with Two Lopsided Bicyclic Ligands, as Studied by 2D NMR Techniques at Variable Temperature

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The binding of the well-known antitumor drug *cis*-[$PtCl_2(NH_3)_2$] to two neighboring guanines of DNA is generally accepted to be the main interaction responsible for its antitumor activity.[1] Whereas the orientational behavior and the fluxional behavior of cis bifunctional coordinated square-planar complexes with lopsided N-heterocycles have been studied extensively and are in an advanced stage of understanding,[2] all factors influencing the orientation and dynamic behavior of lopsided ligands on cis-coordinated octahedral complexes are poorly understood. Such knowledge is important to understand the coordinative binding of biologically available N-heterocycles to six-coordinated complexes,[3] like ruthenium compounds, which are currently under investigation for their antitumor properties.[4] The antitumor-active *cis*-[$Ru(dmso)_4Cl_2$] has been proven to be a suitable compound for the investigation of the fluxional behavior of heterocyclic ligands,[5] and its bifunctional adduct with a benzimidazole derivative is the first example of a mononuclear octahedral complex with lopsided bicyclic ligands of which two (of the four possible) different atropisomers have been identified in solution.[6]

In this Communication we report the first observation of all possible atropisomers of the bifunctional coordinated ruthenium(II) complex *cis*-[$Ru(bpy)_2(MeBim)_2](PF_6)_2$ (**1**), in which bpy is 2,2′-bipyridine and MeBim stands for the bicyclic ligand 1-methylbenzimidazole. For two cis-coordinated lopsided ligands on a metal ion, the corresponding atoms can be on the same side (head-to-head, HH) or on opposite sides (head-to-tail, HT) of the ligand−metal−ligand plane. The two benzimidazoles in **1** can both orient in two different ways (vide infra) resulting in three different atropisomers: two HT conformers (which both have a two-fold symmetry axis) and two identical HH conformers (which lack a two-fold symmetry axis). Using 2D NMR techniques such as COSY, NOESY, TOCSY, and ROESY, the complete structural characterization of the conformers was done and their interconversion as a function of temperature studied.[7]

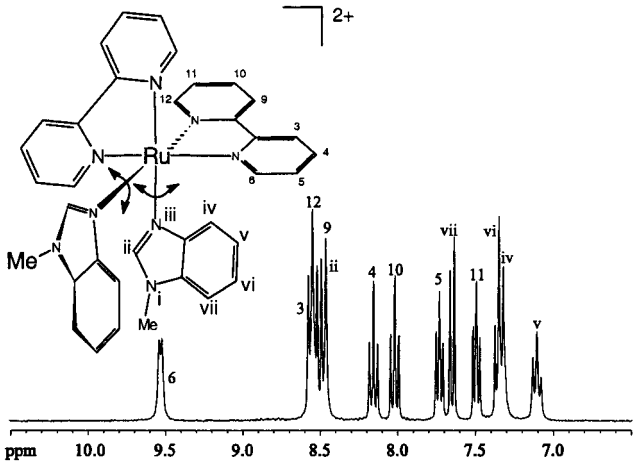

Figure 1. Structural representation and proton numbering scheme of the Λ-enantiomer of *cis*-$[Ru(bpy)_2(MeBim)_2]^{2+}$ and the aromatic region of the ^1H NMR spectrum of **1** at 50 °C.

Complex **1** appears to be a highly fluxional system on the NMR time scale and is in fast exchange at 50 °C, showing 13 sharp signals in the aromatic region (Figure 1). Upon lowering of the temperature, all peaks of **1** first start broadening, finally resulting in two sets of 13 peaks (**A** and **C**) and one set of 26 peaks (**B**) at −95 °C (Figure 2). From characteristic interligand NOE cross peaks between the benzimidazole Hii and Hiv, and the bpy H6 and H12 resonances, the three sets of signals could be unambiguously assigned to all three possible rotamers of **1** as depicted in Figure 2.[8] The relative abundance of the three rotamers at −95 °C was calculated from the integration values of the H6 peaks: **A**, 74%; **B**, 16%; and **C**, 10%.

Although the Hii and Hiv protons do show characteristic shifts in the HH rotamer,[5] the most informative proton resonances for discrimination between all three possible atropisomers appear to be the bpy H6 signals, which are found at low field well separated from the other signals. The H6 resonances are significantly influenced by the (presence or absence of the) shielding effect of the phenyl ring of one of the benzimidazoles and deshielding effect of the other benzimidazole.[9]

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(7) (a) *cis*-$[Ru(bpy)_2Cl_2]\cdot 2H_2O$[7b] and excess 1-methylbenzimidazole were refluxed in water for 3 h, and after addition of NH_4PF_6 complex **1** was isolated by filtration. Recrystallization from acetone−water yielded a red-orange microcrystalline powder. (b) Sullivan, B. P.; Salmon, D. J.; Meyer, T. J. *Inorg. Chem.* **1978**, *17*, 3334. (c) All NMR measurements were performed on a Bruker 300 MHz DPX spectrometer, equipped with a Bruker B-VT1000 variable temperature unit, which was calibrated on a MeOD-d_6 sample. All spectra were calibrated on the residual solvent peak, 2.06 ppm.
(8) One HT conformer (**A**) has the two MeBim's positioned with their phenyl rings wedged between the two bpy ligands, while the other HT conformer (**C**) has the two benzimidazoles rotated around their Ru−N axis by about 180° with respect to the orientations in **A**. The HH conformer (**B**) has one of the two benzimidazoles (Bii−iv) orientated with the phenyl ring positioned between the two bpy's, as in **A**, while the second one (Bii′−iv′) is orientated like in **C**.

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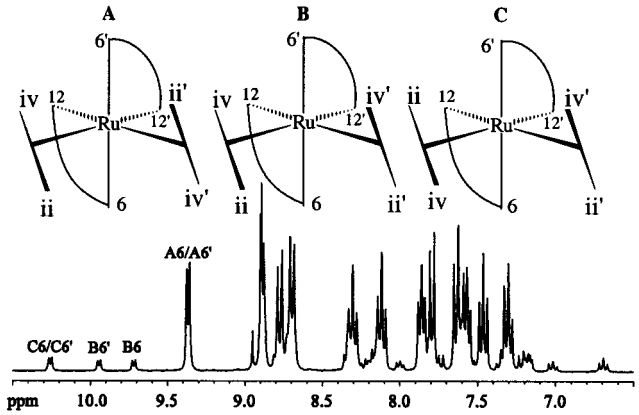

Figure 2. Schematic representation of the three different atropisomers of **1** (the arches represent the bpy ligands, and the rods represent the MeBim's) and the aromatic region of the ^{1}H NMR spectrum at −95 °C.

No exchange cross peaks between the three rotamers of **1** are found in the NOESY and ROESY spectra at −95 °C, indicating all three conformers to stand still on the NMR time scale. At −75 °C, however, **A** and **C** both show exchange peaks with **B**, which is best seen in the low-field region with the H6 resonances (Figure 3). These exchange peaks indicate that both HT conformers interconvert to the HH conformer. Apparently, **A** does not interconvert into **C** and neither does **B** give exchange peaks with itself, indicating that the atropisomerization occurs by a single step at a time, in which one benzimidazole flips around the Ru−Niii axis by approximately 180°. At −70 °C the atropisomerization is so fast that exchange cross peaks between all four H6 signals of **A**, **B**, and **C** are found.

Ruthenium polypyridyl complexes of the type *cis*-$[Ru(LL)_2Cl_2]$ (with LL a didentate diimine ligand like bpy or phenanthroline) have been under investigation for their antitumor properties,[10] as DNA-cleaving agents[11] as well as DNA probes,[12] and appear to bind well to purines. With untethered guanine derivatives, only monofunctional adducts have been found on reaction with *cis*-$[Ru(bpy)_2(H_2O)_2]^{2+}$, supporting the idea that steric hindrance prevents bifunctional coordination of this compound to two DNA guanines.[10] However, from other DNA-binding studies it has been suggested that the complex *cis*-$[Ru(bpy)_2(H_2O)_2]^{2+}$ can bind bifunctionally to two nucleobases, resulting in DNA interstrand cross linking.[11] The coordination to the Niii of MeBim is sterically less demanding than the coordination to the corresponding N7 of guanine derivatives, and the former appears to be a useful DNA-model base in the investigation of the bifunctional DNA binding of these kinds of octahedral complexes, as a bifunctional adduct is formed.

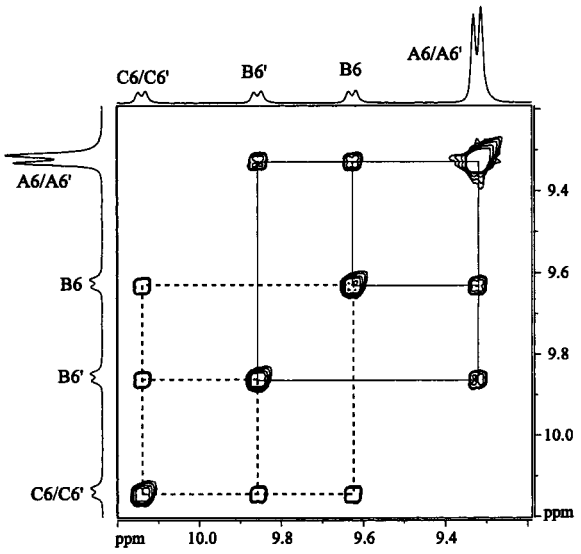

Figure 3. Low-field region of the exchange level of the ROESY spectrum of **1** in acetone-d_6 at −75 °C, recorded with a mixing time of 500 ms. Exchange between **A** and **B** is indicated by the solid lines; exchange between **C** and **B** is indicated by dotted lines.

This study clearly indicates that the complex *cis*-$[Ru(bpy)_2(H_2O)_2]^{2+}$ is sterically a borderline case in which monofunctional or bifunctional coordination of lopsided heterocycles depends on relatively small differences in the ligands. Therefore, complexes of the type *cis*-$[Ru(LL)_2(H_2O)_2]^{2+}$ are suitable compounds to investigate in detail the factors influencing the coordinative and fluxional behavior of N-heterocycles in octahedral complexes.

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Supporting Information Available: NOESY spectrum at −95 °C, ROESY spectrum at −75 °C, and the experimental details of the 2D NMR measurements of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Both methylbenzimidazoles in **1** can have two types of interactions with one H6 proton, and interestingly, in the three atropisomers all four possible combinations are present. In conformer **A** the H6 protons (9.30 ppm) are shielded by the benzimidazoles which are in the *mer* position with respect to the bpy, and not influenced by the other benzimidazole 6-ring. In conformer **B** the B6 proton (9.62 ppm) is influenced by none of the two benzimidazole 6-rings, and the B6′ proton (9.90 ppm) is shielded by one benzimidazole (Biv) but deshielded by the other (Biv′). In conformer **C**, finally, the H6 protons (10.23 ppm) are not influenced by the 6-ring of the *mer*-coordinated benzimidazole and are deshielded by the 6-ring of the *fac*-coordinated benzimidazole. Therefore, we can conclude that in **1** the deshielding of the 6-ring of the *fac*-coordinated benzimidazole is of larger influence on the H6 signal than the shielding effect of the 6-ring of a *mer*-coordinated benzimidazole.

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