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Dynamic topomerization of Cu(I)-complexed pseudorotaxanes

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Dynamic molecular motions resulting from the folding of a flexible macrocyclic component in a Cu(I)-complexed pseudorotaxane have been evidenced by variable temperature NMR experiments. The proposed conformational changes are also supported by the X-ray crystal structures of the compounds and computational studies.

Molecular motions and conformational changes of proteins play a major role in biological systems. Heterotopic allosterism in which the binding of a specific substrate induces conformational changes in the peptidic backbone of a protein to regulate its biological activity is a classical example.[1] The rotary mechanism evidenced for ATP synthase[2] and the motion of the myosin-actin complex in muscles[3] are other fascinating examples in which conformational changes generate mechanical movements. Large amplitude molecular motions are also involved in the folding of biomolecules and intensive research efforts have been carried out to understand the mechanism and the dynamics of protein folding.[4] Over the two last decades, chemists have prepared a large variety of molecular and supramolecular systems capable of mimicking the molecular motions and conformational changes observed for biomolecules.[5-7] In this particular field, threaded or interlocking molecules are particularly interesting as they offer the possibility of large-amplitude molecular motions.[7] Numerous examples of molecular shuttles in which a macrocyclic component threaded onto a molecular rod can undergo a more or less controlled translation movement have been reported.[7] Dynamic studies of catenanes in which a macrocycle can glide and spin within another one have been also described.[7] There are however only a few systems for which large amplitude folding motions are observed.[8] In this paper, we now report Cu(I)-complexed pseudorotaxanes[9] prepared from a macrocyclic phenanthroline derivative and bisphosphine ligands (Fig. 1). X-ray crystal structural analysis, variable temperature NMR studies and computational calculations allowed us to evidence particularly original dynamic molecular motions resulting from the folding of the flexible macrocyclic component.

Macrocycle **m30** was obtained in 3 steps from 2,9-dimethyl-1,10-phenanthroline (see ESI). The preparation of the Cu(I) complexed pseudorotaxanes was achieved by adding successively $Cu(CH_3CN)_4BF_4$ (1 equiv.) and the appropriate bisphosphine ligand (PP, 1 equiv.) to a solution of **m30** (1 equiv.) in CH_2Cl_2/CH_3CN. The resulting [Cu(**m30**)(PP)]BF_4 complexes were then isolated in a pure form by recrystallization (Et_2O/CH_2Cl_2). Pseudorotaxanes [Cu(**m30**)(dppe)]BF_4 and [Cu(**m30**)(POP)]BF_4 were characterized by NMR spectroscopy and electrospray mass spectrometry. Crystals suitable for X-ray crystal analysis were also obtained for both compounds.‡ As shown in Fig. 2, the X-ray crystal structural analysis of [Cu(**m30**)(dppe)]BF_4 reveals a perfect threading of the dppe moiety through the macrocyclic phenanthroline ligand. The two diphenylphosphino subunits are effectively located at opposite sides of the mean plane of the **m30** macrocycle as suggested by the C_{2v} symmetry deduced from the NMR data of [Cu(**m30**)(dppe)]BF_4. It is noted that due to some rotational freedom, one of the phenyl groups of the dppe ligand is disordered. However, only one of the two possible orientations in the crystal lattice is shown in Figure 1 for the sake of clarity. As typically seen for $[Cu(phen)(PP)]^+$ complexes, packing induced distortions from an idealized pseudotetrahedral geometry are observed.[10,11] Close inspection of the crystal packing reveals that interactions involving a phenyl unit of the dppe ligand and the phenanthroline belonging to an adjacent molecule induce a slight rocking (*ca*. 10°) of the dppe ligand (Fig. S1).

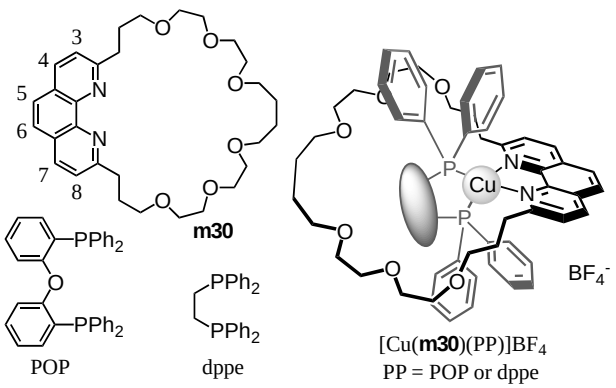

Fig. 1. Cu(I)-complexed pseudorotaxanes prepared from **m30** and PP ligands (dppe and POP).

Whereas the C_{2v} symmetrical pseudorotaxane structure deduced from the NMR data was confirmed by the X-ray crystal structure analysis of [Cu(**m30**)(dppe)]BF_4, the structure of the Cu(I) complex prepared from POP revealed only a partial threading of the PP ligand through **m30** (Fig. 2). Actually, one phenyl group of the POP ligand is located within the cavity of the macrocyclic ligand, whereas all the others are located on the same side of **m30**. This peculiar conformation results from the

complete folding of macrocycle **m30**. It does, however, not induce significant distortions of the coordination geometry around the Cu(I) center in [Cu(**m30**)(POP)]BF_4. Indeed, the Cu-P and Cu-N distances as well as the P-Cu-P, P-Cu-N and N-Cu-N bond angles are within the normal range when compared to known structures of $[Cu(phen)(POP)]^+$ complexes.[10]

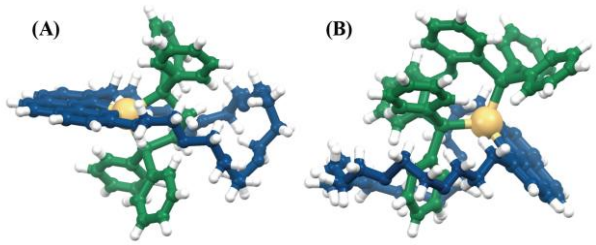

Fig. 2. X-ray crystal structures of (A) [Cu(**m30**)(dppe)]BF_4 and (B) [Cu(**m30**)(POP)]BF_4 (**m30**: blue, dppe and POP: green, Cu: yellow, the counteranion is omitted).

The ^{31}P NMR spectrum of [Cu(**m30**)(POP)]BF_4 recorded at room temperature shows a single resonance at δ = -13.57 ppm and suggests that the two P atoms of the POP moiety are equivalent. The latter observation is apparently in contradiction with the solid state structure of [Cu(**m30**)(POP)]BF_4 for which the two P atoms are different. Indeed, the four phenyl groups of the POP ligand may exchange their position inside and outside the cavity of **m30** in solution. In other words, the chain of the **m30** ligand is flexible enough to allow a fast dynamic exchange between different conformers on the NMR timescale. As a result, the two P atoms appear as equivalent in the ^{31}P NMR spectrum recorded at room temperature. In order to confirm this hypothesis, ^{31}P NMR spectra were recorded at different temperatures. As shown in Fig. 3, by cooling the solution, the exchange between different conformers becomes slow on the NMR timescale, as attested by the two sets of doublets (^2J = 115 Hz) observed for the P atoms of the POP ligand. This is in perfect agreement with the partially threaded conformation observed in the X-ray crystal structure. From the coalescence temperature (T_c = 278 K) and the separation between the two signals in the absence of exchange (Δν = 1017 Hz), the rate constant for the dynamic exchange (k_C) and the free enthalpy of activation ($\Delta G^{\ddagger}$) were estimated to be 2350 s^{-1} and 12 $kcal.mol^{-1}$, respectively.[12] Interestingly, a singlet is also observed at δ = -20.4 ppm. The latter is attributed to a C_{2v} symmetrical conformer (**B**) in which the POP ligand is fully threaded through the macrocycle. The minor population of this particular conformer suggests that it might be destabilized by steric congestion when the large phenyloxyphenyl bridging unit of the POP ligand is located within the cavity of **m30**. Indeed, the flexible **m30** macrocycle preferentially adopts a folded conformation in order to minimize steric congestion, the partially threaded conformer is thus energetically favored and its population largely major in solution. This view was fully supported by computational studies. The molecular geometry was optimized at the PM6 semi-empirical level for both conformers **A** and **B** (Fig. 3). The calculated energy difference between these two conformers is significant (5.2 $kcal.mol^{-1}$) and explains the preferential population of the **A** conformers in good agreement with the low temperature ^{31}P NMR spectrum. The energy barrier for exchange between the **A** and **B** conformers is low thus allowing a fast dynamic exchange at room temperature. In this way, each of the four phenyl rings of the POP ligand is alternatively located inside or outside the cavity of the **m30** macrocycle, the exchange taking place through the less energetically favoured conformer (**B**).

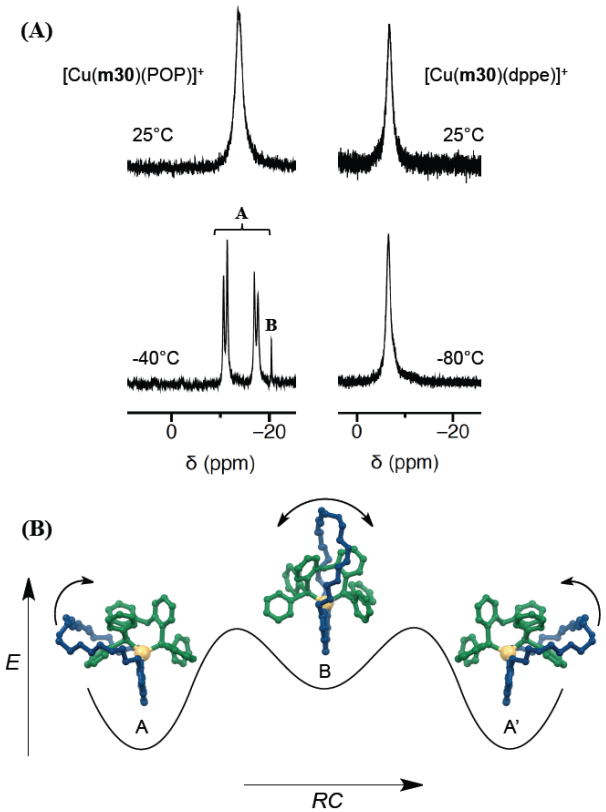

Fig. 3. (A) ^{31}P NMR spectra (CD_2Cl_2, 162 MHz) of [Cu(**m30**)(POP)]BF_4 (left) and [Cu(**m30**)(dppe)]BF_4 (right) recorded at different temperatures. (B) Calculated structures of the different topomers of $[Cu(\mathbf{m30})(POP)]^+$, a potential energy diagram is proposed to explain the dynamic exchange between topomers, *i.e.*, topomerization.

It is also worth noting that conformer **A** is chiral and the dynamic molecular motions of the flexible chain of **m30** are responsible for a dynamic racemization, *i.e.*, a fast exchange between **A** and **A'** (Fig. 3). This was clearly evidenced from the ^1H-NMR spectra recorded over a large range of temperatures (from -80°C to 100°C, see ESI and Fig. 4). At high temperatures, two doublets are seen for the phenanthroline protons H(3-8) and H(4-7). Indeed, the exchange between the different conformers is fast on the NMR timescale under these conditions and both pairs of protons [H(3)-H(8) and H(4)-H(7)] appear equivalent in the ^1H-NMR spectrum. By cooling the solution, the NMR study revealed a clear coalescence and a reversible splitting of these peaks. Indeed, the exchange of conformers becomes slow on the NMR timescale at low temperature and four sets of signals are observed for the phenanthroline protons H(3), H(4), H(7) and H(8) at -80°C. In other words, these pairs of protons are diastereotopic under these conditions due to the preferential chiral conformation

adopted by [Cu(**m30**)(POP)]$^+$. The topological constraints resulting from the macrocyclic structure of the phenanthroline ligand are responsible for this particularly original dynamic conformational exchange. By analogy to the dynamics of an ensemble of protein conformations in which a topomeric set of structures is obtainable through local backbone folding transformations that do not disrupt the covalent bonding of the peptide backbone,[13] we propose to name these particular conformers in equilibrium ***topomers***, *i.e.* conformers having different topographies.

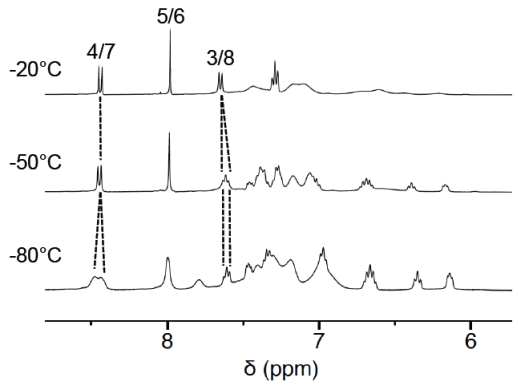

Fig. 4. ^{1}H NMR spectra (CD_2Cl_2, 400 MHz) of [Cu(**m30**)(POP)]BF_4 recorded at different temperatures.

Variable temperature NMR studies were also carried out with [Cu(**m30**)(dppe)]BF_4. In this case, no dynamic exchange between topomers could be evidenced. Whatever the temperature, a single resonance is observed in the ^{31}P NMR spectrum (Fig. 3). The C_{2v} symmetrical topomer is this time largely preferred and the partially threaded one could not be detected. These observations are in full agreement with the X-ray crystal structure of [Cu(**m30**)(dppe)]BF_4. When compared to POP, the bridging unit is smaller for dppe and does not generate particular steric congestions; thus the threaded topomer is not destabilized. Actually, computational studies revealed a significant energy difference between the fully and partially threaded topomers (6.1 kcal.mol^{-1}, see ESI). There is a clear energy penalty for the folding of the macrocycle. Indeed, in the case of POP, the fact that topomer **A** is favoured shows that the steric congestion in fully threaded **B** must be relatively important to displace the dynamic conformational equilibrium towards the partially threaded situation.

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Notes and references

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‡ [Cu(**m30**)(dppe)]BF_4: $C_{56}H_{66}CuN_2O_6P_2.BF_4$ (M = 1075.40 g.mol^{-1}); crystal system: triclinic, space group P-1; a = 11.7950(7) Å; b = 13.2034(7) Å; c = 19.7058(11) Å; α = 106.642(1)°; β = 106.201(1)° (CCDC 905751); γ = 91.402(1); V = 2805.3(3) Å^3; [Cu(**m30**)(POP)]BF_4: $C_{66}H_{70}CuN_2O_7P_2.BF_4$ (M = 1215.53 g.mol^{-1}); crystal system: triclinic, space group P-1; a = 13.6380(5) Å; b = 14.9380(5) Å; c = 15.6669(6) Å; α = 78.733(1)°; β = 72.898(1)°; γ = 83.964(1); V = 2988.29(19) Å^3 (CCDC 905746).

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