

# On the CH⋯Cu agostic interaction: chiral copper(II) compounds with ephedrine and pseudoephedrine derivatives

Miguel Castro,<sup>\*a</sup> Julián Cruz,<sup>a</sup> Horacio López-Sandoval<sup>b</sup> and Norah Barba-Behrens<sup>\*b</sup>

Received (in Berkeley, CA, USA) 21st April 2005, Accepted 2nd June 2005

First published as an Advance Article on the web 24th June 2005

DOI: 10.1039/b505554g

The ephedrine derivative, (H<sub>2</sub>ceph), yields [Cu(Hceph)<sub>2</sub>], showing a CH⋯Cu(II) agostic interaction; while in the analogous compound [Cu(Hcpse)<sub>2</sub>], with pseudoephedrine (H<sub>2</sub>cpse), that interaction is absent, despite the fact that these two diastereomers differ only in the orientation of the methyl and phenyl groups: *erythro* in H<sub>2</sub>ceph and *threo* in H<sub>2</sub>cpse. The X-ray crystal structure of [Cu(Hceph)<sub>2</sub>], indicates a Cu⋯HC length of 2.454 Å and the theoretical study reveals the formation of a Cu⋯HC bond since the associated electronic density shows both a bond critical point and a bond ring critical point.

The stereospecific binding of metal ions towards biological relevant ligands may control the conformation of the molecules and so affect their chemical and biological properties. In this context, we have been interested in the coordination behavior of chiral ephedrine and pseudoephedrine derivatives towards metal ions, specially on the effect of the stereogenic nitrogen in the stereoselective reactions. In previous work we reported new chiral coordination compounds, [Cu(Hcpse)<sub>2</sub>] **I** and [Cu(Hceph)<sub>2</sub>] **II**.<sup>1,2</sup>

In this paper we investigated the possibility of an agostic type interaction in compound **II**. When a C–H bond of transition metal ligands is oriented towards the metal ion, indicating some weak interaction between the metal and the H atom, this has been considered as an agostic interaction.<sup>3</sup> The existence of the CH⋯M bond can be deduced from five criteria, crystallographic data, spectroscopic (NMR chemical shifts to high field and coupling constants; IR) and the AIM theory, which requires an accurate charge density.<sup>4</sup> In our case, the CH⋯Cu(II) interaction is discussed in terms of X-ray crystal structures and a theoretical study.

Compounds *N*-[2-hydroxy-1(*S*)-methyl-2(*S*)-phenylethyl]-*N*-methylglycine (H<sub>2</sub>cpse) and *N*-[2-hydroxy-1(*S*)-methyl-2(*R*)-phenylethyl]-*N*-methylglycine (H<sub>2</sub>ceph) are diastereomers, differing in the orientation of the methyl and phenyl groups: *threo* in H<sub>2</sub>cpse and *erythro* in H<sub>2</sub>ceph (Fig. 1).<sup>5</sup> It has been observed that they give place to stereoselective coordination compounds.<sup>6</sup> This is clearly exemplified by the obtained copper(II) coordination compounds [Cu(Hcpse)<sub>2</sub>] **I** and [Cu(Hceph)<sub>2</sub>] **II**, which are optically pure, as shown by their optical rotation in solution: [α]<sub>D</sub> = −67.72° (MeOH, *b* = 1 dm) for **I** and [α]<sub>D</sub> = −204.40° (MeOH, *b* = 1 dm)

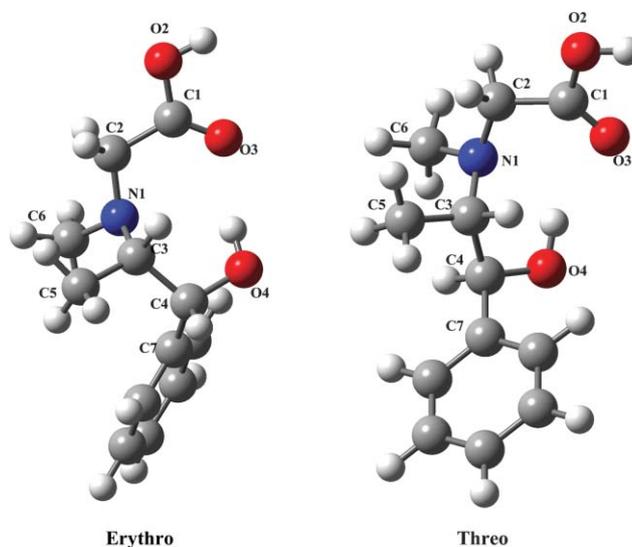


Fig. 1 Theoretical B3LYP/6-31G\*\* optimized structures for the *erythro* (H<sub>2</sub>ceph) and *threo* (H<sub>2</sub>cpse) ligands. See text.

for **II**. As well as by their X-ray crystal structures. This is a fundamental difference, which may give rise to stereospecific synthesis of new coordination compounds with novel chemical properties. In fact, this is the case of **I** and **II**, where **I** may further react to give a stable trinuclear Cu(II) compound,<sup>2</sup> [Cu<sub>3</sub>(cpse)<sub>3</sub>(H<sub>2</sub>O)<sub>3</sub>]·8.5H<sub>2</sub>O. Changing the configuration of the ligand, from *threo* to *erythro*, prevents the formation of the analogous trinuclear compound from complex **II**.

X-ray diffraction studies of the copper(II) coordination compounds (Fig. 2), showed that H<sub>2</sub>cpse and H<sub>2</sub>ceph behave as tridentate ligands, coordinating *via* the stereogenic nitrogen, and the oxygen atoms from the deprotonated carboxylate and the OH groups.

In compound [Cu(Hcpse)<sub>2</sub>]·H<sub>2</sub>O **I**, the Cu(II) atom is in a distorted octahedral geometry. The Hcpse ligands coordinate to the Cu(II) in a tridentate mode (*fac*-isomer), giving a bicyclic chelate with two five-membered rings, where the nitrogen atoms became chiral centers sharing opposite conformations, N(1) is *S* while N(2) is *R* (Fig. 2). Two oxygen atoms from the carboxylate and OH groups complete the coordination sphere. The Cu–N(2) and Cu–N(1) bond lengths are 2.027(6) and 2.048(6) Å, respectively, and the lengths for the carbonyl oxygens, Cu–O(3) and Cu–O(6) are 1.974(5) and 1.944(5) Å. Apical positions are occupied by the oxygens from the OH groups, Cu–O(7) 2.379(5) and Cu–O(4) 2.475(5) Å.<sup>1</sup>

<sup>a</sup>Departamento de Física y Química Teórica, DEPg. Facultad de Química, Universidad Nacional Autónoma de México, México D.F., C.P. 04510, México. E-mail: castro@quetzal.pquim.unam.mx

<sup>b</sup>Departamento de Química Inorgánica, DEPg. Facultad de Química, Universidad Nacional Autónoma de México, México D.F., C.P. 04510, México

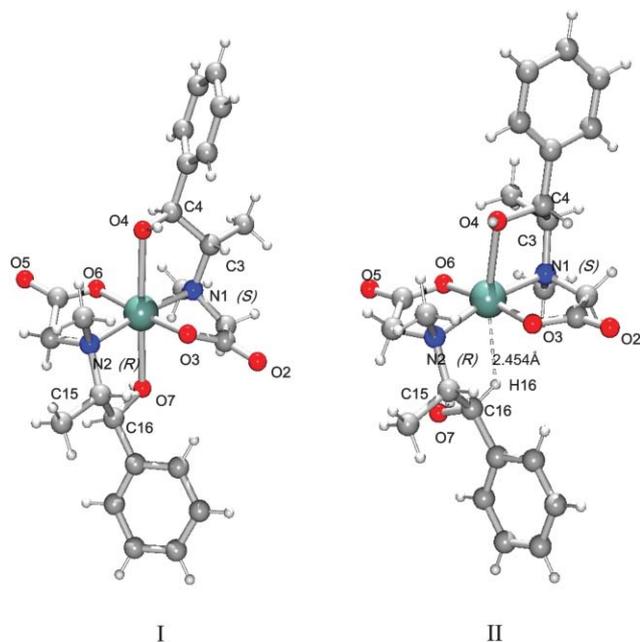


Fig. 2 X-ray crystal structures of octahedral complexes **I** and **II**.

The X-ray crystal structure of  $[\text{Cu}(\text{Hcpeph})_2]\cdot\text{H}_2\text{O}$  **II** is quite different from that of  $[\text{Cu}(\text{Hcpse})_2]\cdot\text{H}_2\text{O}$  **I**, due to the fact that one of the alcohol groups is not coordinated to the metallic center and, the geometry around copper(II), initially thought to be square pyramidal, is in fact octahedral, Fig. 2. The bond lengths in the equatorial plane are  $\text{Cu}-\text{O}(6) = 1.928(3)$  Å,  $\text{Cu}-\text{O}(3) = 1.934(4)$  Å,  $\text{Cu}-\text{N}(1) = 2.064(4)$  Å, and  $\text{Cu}-\text{N}(2) = 2.045(4)$  Å. A longer value,  $2.357(3)$  Å, was found for the  $\text{Cu}-\text{O}(4)$  bond length, lying on the apical position. On the other hand, EPR solid state spectra of  $[\text{Cu}(\text{Hcpeph})_2]\cdot\text{H}_2\text{O}$ , at room and low temperatures, have an isotropic pattern, with a  $g$  of 2.11. This value is very similar to those of the octahedral compounds,  $\text{K}_2\text{Pb}[\text{Cu}(\text{NO}_2)_6]$  ( $g_i = 2.10$ ) and  $[\text{Cu}(\text{en})_3](\text{SO}_4)$  ( $g_i = 2.13$ ).<sup>7</sup> These findings suggest the existence of a sixth Cu–ligand bond in complex **II**. The X-ray

results reveal that the hydrogen, H(16), atom lies in an appropriate position to form a Cu–H bond. This is consistent with the value of the Cu···H distance,  $2.454$  Å, determined in the X-ray crystal structure, that is slightly smaller than the sum of the van der Waals radii of the hydrogen ( $1.20$  Å) and copper ( $1.40$  Å) atoms. Then, the question is, which would be the origin of this weak bonding interaction. One possibility may be a hydride character of the hydrogen atom. Another possibility is the formation of an agostic bond, which has been observed in some metal···HC systems.<sup>3</sup> If this is so, another interesting question is, why the oxygen atom of the alcohol group, O(7), is not coordinated to  $\text{Cu}^{2+}$ , instead of H.

In an attempt to understand the bonding properties of the *threo* and *erythro* ligands in **I** and **II**, we have performed a Density Functional Theory study for these complexes and for the bare ligands.<sup>8</sup> All-electron calculations were done, using the Gaussian-98 program,<sup>9</sup> at the B3LYP/6-31G\*\* level of theory.<sup>10,11</sup> In Fig. 1 the optimized structures for the bare moieties are reported. The population analysis of neutral *erythro* yields a charge of  $+0.234$  electrons (e) for the H(16) atom. Furthermore, the electronic structures of **I** and **II** were determined at their corresponding experimental geometries. Even in **II**, the charge of H(16) is  $+0.089$  e, which also excludes a hydride behavior. Then, the Bader theory “atoms in molecules” (AIM) was used for to characterize the bonding interactions in complex **II**.<sup>12</sup> In this way, the behavior of the electronic density along the Cu···H internuclear region, indicates the formation of a Cu···H bond, since the associated electronic density shows a bond critical point ( $\rho = 0.012$  e au<sup>-3</sup>,  $\nabla^2\rho = -0.012$  e au<sup>-5</sup>). This Cu···H bond implies the formation of the Cu–H–C–N cycle; see Fig. 3. The results also show a ring critical point ( $\rho = 0.011$  e au<sup>-3</sup>,  $\nabla^2\rho = -0.011$  e au<sup>-5</sup>), confirming that the electronic density is closed along this cycle. Moreover, the molecular orbital analysis shows that the highest occupied molecular orbital (HOMO) significantly contributes to the Cu···H bonding. In fact, as shown in Fig. 4, the contour plot of HOMO clearly reveals this feature. Note that in **II**, see Fig. 3, also appear bond critical points along  $\text{O}7\cdots\text{H}14\text{a}$ ,  $\text{H}15\cdots\text{O}3$ , and  $\text{H}20\cdots\text{O}3$  implying the formation of the corresponding hydrogen bonds, with bond lengths of  $2.30$ ,  $2.55$ , and  $2.68$  Å, respectively. It

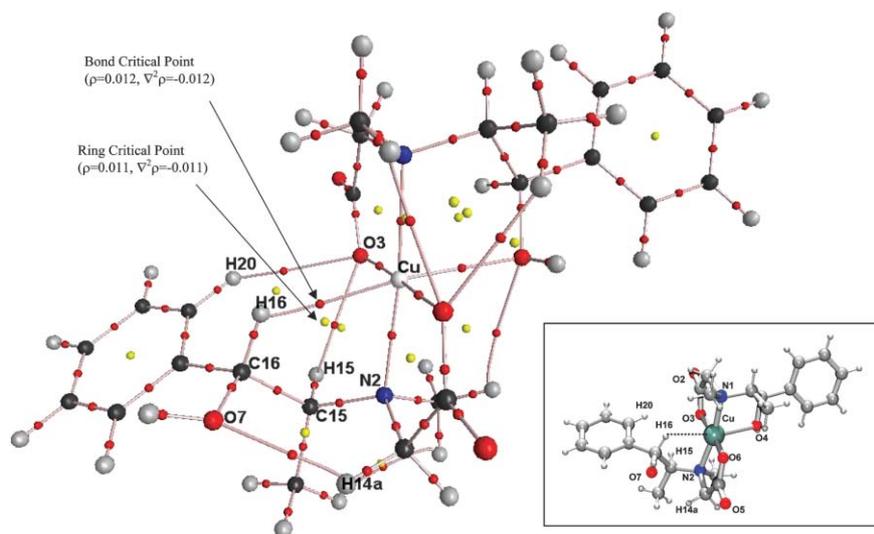
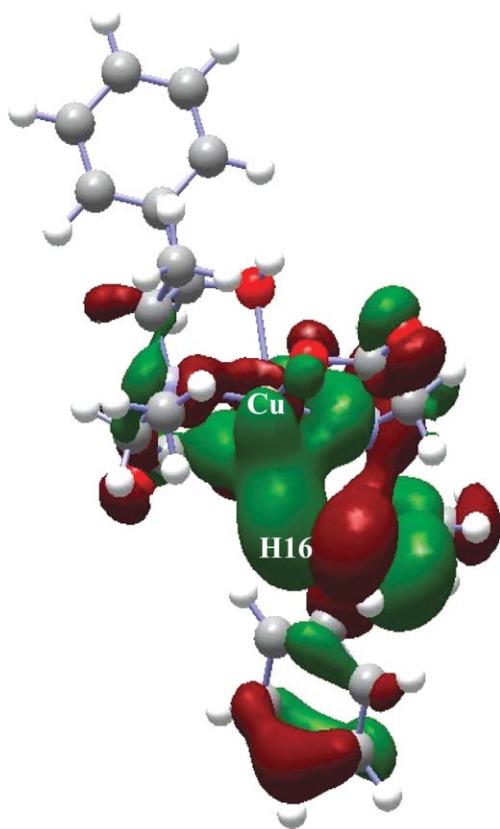


Fig. 3 Calculated bond and ring critical points based on the crystal structure of compound **II**.



**Fig. 4** Calculated contour plot of the HOMO orbital, based on the experimental octahedral geometry of complex **II**.

should be stressed that the oxygen atom of the alcohol group forms a relatively strong hydrogen bond.

To this point, the HOCH $\cdots$ Cu(II) bond has been characterized. But why is the HC(H)O–Cu(II) bond not formed? We have found that the formation of this O–Cu bond in **II**, produces a high energy structure (obtained by rotating 109 degrees around N2–C15–C16–O7), that is 20 kcal mol $^{-1}$  above the H $\cdots$ Cu agostic geometry. Even more, the geometry imposed when the Cu–O bond occurs prevents the O7 $\cdots$ H14a, O3 $\cdots$ H20, and the H15 $\cdots$ O3 hydrogen bonds formation, since the corresponding O $\cdots$ H distances are quite large. So hydrogen bond formation plays an important role in the stabilization of the Cu $\cdots$ HC agostic bond in compound **II**.

The conclusion of this work is that both, experiment and theory, indicate the existence of a Cu $\cdots$ HC bond in complex **II**, that resembles closely an agostic type bond. Due to the fact that in solution the *on-off* rates of the 6th ligand in octahedral copper(II) complexes<sup>13</sup> (Cu(MeOH)<sub>6</sub>,  $k = 5 \times 10^7$  s $^{-1}$ ) can be quite high, substitution can easily occur at the very labile axial position and, in the absence of a better ligand, a C–H hydrogen may act as a ligand to copper(II). This could have implications for stereocontrol in

some catalytic reactions driven by Cu(II) ions. To the best of our knowledge, this is the first case where a Cu(II) $\cdots$ HC agostic bond has been observed, which has been promoted by the conformation of the *erythro* ligand, by the stereogenic nature of the nitrogen atom, and by the formation of hydrogen bonds.

The authors acknowledge financial support from DGAPA-UNAM, grant IN-107905, and from CONACyT-México: grant 41128-Q, J. C. and H. L.-S. thank their fellowships. The access to the supercomputer SG Origin 2000/32 at DGSCA-UNAM is strongly appreciated.

## Notes and references

- H. López-Sandoval, N. Barba-Behrens, S. Bernès, N. Farfán and H. Höpf, *J. Chem. Soc., Dalton Trans.*, 1997, 3415.
- H. López-Sandoval, R. Contreras, A. Escuer, R. Vicente, S. Bernès, H. Nöth, G. Jeffery Leigh and N. Barba-Behrens, *J. Chem. Soc., Dalton Trans.*, 2002, 2648.
- (a) M. K. Van der Boom, M. A. Iron, O. Atasoylu, L. J. W. Simón, H. Rozenberg, B. D. Yehoshoa, L. Konstantinowski, J. M. L. Martin and D. Milstein, *Inorg. Chim. Acta*, 2004, **357**, 1854; (b) J. Patel, W. R. Jackson and A. K. Serelis, *Inorg. Chim. Acta*, 2004, **357**, 2374; (c) I. Corral, O. Mò and M. Yañez, *Int. J. Mass Spectrom.*, 2003, **227**, 401; (d) T. Kawamoto, I. Nagasawa, Y. Kushi and T. Konno, *Inorg. Chim. Acta*, 2003, **348**, 217; (e) J. W. Steed, K. Johnson, C. Legido and P. Junk, *Polyhedron*, 2003, **22**, 769; (f) M. G. Klimpel, H. W. Gortlitz, M. Tafipolsky, M. Spiegler, W. Scherer and R. Anwender, *J. Organomet. Chem.*, 2002, **647**, 236; (g) C. J. Siemer, F. A. Meece, W. H. Armstrong and D. M. Eichhorn, *Polyhedron*, 2001, **20**, 2637; (h) X. Fang, J. Huhmann-Vincent, B. L. Scott and G. J. Kubas, *J. Organomet. Chem.*, 2000, **609**, 95; (i) K. J. Adams, T. D. McGrath, G. M. Rosair, A. S. Weller and A. J. Welch, *J. Organomet. Chem.*, 1998, **505**, 315; (j) W. Yao, O. Eisenstein and R. H. Crabtree, *Inorg. Chim. Acta*, 1997, **254**, 105.
- P. L. A. Popelier and G. Logothetis, *J. Organomet. Chem.*, 1998, **555**, 101.
- N. Farfán, L. Cuellar, J. M. Aceves and R. Contreras, *J. Synth. Org. Chem.*, 1987, **10**, 927.
- (a) T. Mancilla and R. Contreras, *J. Organomet. Chem.*, 1987, **321**, 121; (b) N. Farfán, T. Mancilla, P. Castillo, G. Uribe, L. Carrillo, P. Joseph-Nathan and R. Contreras, *J. Organomet. Chem.*, 1990, **381**, 1.
- G. Wilkinson, J. A. McCleverty, and R. D. Gillard, Eds., *Comprehensive Coordination Chemistry, Late Transition Elements*, vol. 5, Pergamon Press, 1987, p. 663.
- K. B. Lipkowitz and D. B. Boyd, Eds., *Reviews in Computational Chemistry*, Wiley-VCH, John Wiley and Sons, Inc., New York, 2000, Vol. 15, Chapter 1, Kohn–Sham Density Functional Theory.
- M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, GAUSSIAN 98 (Revision C.3); Gaussian Inc.: Pittsburgh, PA, 1995.
- A. D. J. Becke, *Chem. Phys.*, 1993, **98**, 5648.
- C. Lee, W. Yang and R. G. Parr, *Phys. Rev.*, 1988, **B37**, 785.
- R. F. W. Bader, *Atoms in Molecules. A Quantum Theory*; Clarendon: Oxford, UK., 1990.
- R. G. Wilkins, Ed., *Kinetics and Mechanism of Reactions of Transition Metal Complexes*, VCH, Weinheim, 1991, Chapter 4.