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New Insights into the Chemistry of Amino Acid Complexes of Copper from MOPAC

An Apparent Paradox Explained

MOST THEORETICAL studies to date on copper amino acid complexes and metallo-enzymes have been limited to gas-phase calculations. Unfortunately, these calculations do not necessarily account for observed behavior in solution or *in vivo*. A recent enhancement to CAChe and MOPAC,¹ the COSMO solvent capability for transition metals, has opened up copper's condensed-phase chemistry to theoretical study. MOPAC calculations now offer new insights that contradict previous rationalizations of the properties of bisglycinato copper(II) in solution.

Background

Bisglycinato copper(II) exists as two stable isomers in the solid state at room temperature, *cis* and *trans*. When crystals of the *cis* monohydrate are heated, they first lose water of crystallization then isomerize to the *trans* isomer.² This is in agreement with both MOPAC and high-level quantum mechanics gas-phase calculations³, which indicate that the *trans* isomer is more thermodynamically stable than the *cis*, by more than 10 kcal/mol. The same high-level calculations also suggest that the gas-phase energy barrier for the *cis* to *trans* isomerization is so low that the *trans* isomer is likely to be formed spontaneously above 100 K.

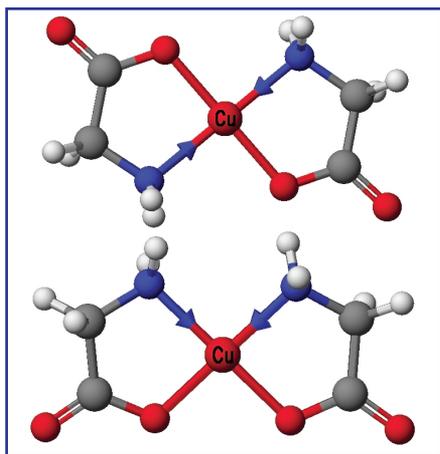


Figure 1: Structures of *trans* (upper) and *cis* (lower) isomers.

However, the fact that crystals of the *cis* isomer are stable at room temperature, has been attributed to the crystal packing forces being sufficiently strong to prevent isomerization occurring in the solid state.²

Paradoxically, the *cis* isomer is the product from synthesis in aqueous solution. It is reportedly because the *cis* isomer is the kinetic product, *i.e.* *cis* crystallizes from solution before it can isomerize to the *trans* isomer.⁴ However, as there should be no significant crystal packing forces in solution, this is inconsistent with the calculated low energy barrier that should lead to spontaneous isomerization to *trans* above 100 K.³

New Insights

MOPAC offers a different explanation. While AM1 calculations agree that the *trans* isomer is more thermodynamically stable in the gas-phase, the presence of a high-dielectric water solvent field, simulated by COSMO,⁵ appears to stabilize the *cis* isomer more than the *trans* isomer, to the degree that their relative thermodynamic stabilities are reversed in aqueous solution. The table below shows the free energies calculated by AM1 at 298 K (lower energy means more thermodynamically stable). Higher-level B3LYP/6-31G(d) calculations show similar results. This would account for the *cis* isomer being formed preferentially in aqueous solution. *Cis* would be the thermodynamic product in water, rather than the kinetic product.

Other than by heating solid crystals of *cis*-bisglycinato copper(II), it is reported the *trans* isomer can be prepared by heating a suspension of the *cis* isomer in saturated aqueous solution⁴ with the caveat that, if the suspension dissolves completely then only *cis* will recrystallize out

of solution. No explanation is offered for this apparent anomaly. However, the calculated relative thermodynamic stabilities from MOPAC clearly suggest that any *trans* isomer in solution should be converted back to *cis*, while the *cis* isomer in the lower-dielectric solid-state suspension would isomerize to *trans* on heating thus, rationalizing the observed behavior.

Conclusion

MOPAC calculations on transition metal complexes in solution lead to new insights into the mechanism of formation of *cis*-bisglycinato copper(II) in solution, *i.e.* the *cis* isomer is the thermodynamic product in water rather than the kinetic product. Further, the results suggest that even high-level gas-phase quantum mechanics calculations may not be adequate to model the chemistry of transition metals in living systems, such as copper containing enzymes, unless the solvent or environment is appropriately accounted for.

Editor's Note: MOPAC with transition metal capability is available as stand-alone, integrated with CAChe from Fujitsu, and as CS MOPAC Ultra integrated with Chem3D from CambridgeSoft. The authors used CAChe MOPAC to perform the research for this article.

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¹CAChe® WorkSystem Pro, Version 6.1.12 (2004); Fujitsu Computer Systems Corp., 15244 NW Greenbrier Parkway, Beaverton, Oregon, 97006.

²Delf, B.W. *et al*, *J.C.S.Dalton*, **1979**, 1301-1305.

³Tautermann, C.S. *et al*, *J. Phys. Chem. B* **2004**, 108, 2098-2102.

⁴Pike, R.M. *et al*, *Microscale Inorganic Chemistry*, John Wiley and Sons, **1991**, Chap. 10, Expt. 49, p.341.

⁵Klamt, A.; Schüürmann, G. *J. Chem. Soc. Perkin Trans. 2*, **1993**, 799-805.

Free Energies at 298 K (kcal/mol)	AM1 in gas phase	AM1 in water (COSMO)
<i>cis</i> -bisglycinato copper (II)	-193.5	-247.2
<i>trans</i> -bisglycinato copper (II)	-209.5	-244.2