Cis-trans isomerization of bisglycinato copper: new insights from studies with quantum chemistry and COSMOtherm

David A. Gallagher*, AIChE, Nov 2007

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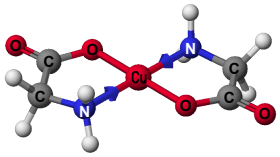

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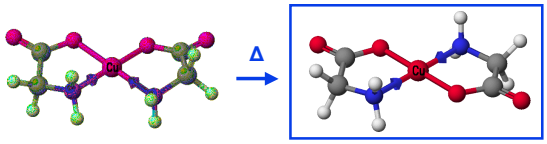
Copper: catecholoxidases, tyrosinases

Abstract:

Transition metals such as iron, cobalt, copper, zinc and manganese play an important role as active centers of metalloproteins in many biological processes. Their functions range from hydrolysis processes and isomerizations, to redox reactions, oxygen activation, electron transfer and transport and storage functions.

Copper is an essential part of enzymes such as catecholoxidases and tyrosinases. Hence, there is considerable interest in the chemistry of copper with proteins and amino acids. Bisglycinato Copper (II) provides a conveniently simple model for the demanding computational requirements of theoretical quantum chemistry studies. Bisglycinato Copper exists as both cis and trans isomers. Although, the trans isomer can be synthesized in aqueous solution, it is easily converted to the cis form on heating in the solid state. To gain a better understanding of the thermodynamics and kinetics of the cis-trans isomerization mechanism and, the conditions that favor the formation of each isomer, a quantum mechanics study was undertaken to model potential reaction pathways from simple intramolecular isomerization to water-catalyzed isomerization in solution. The theoretical results are compared with experimental observations and offer new insights into the chemistry of copper.

Bisglycinato copper exists as two stable isomers



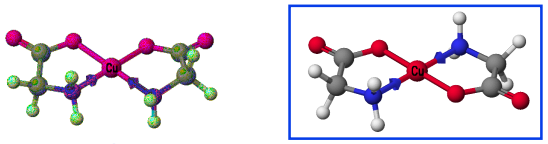
Cis bisglycinato copper (II) — *trans* bisglycinato copper (II)

cis undergoes novel solid state rearrangement to *trans* on heating*

suggesting *trans* is more thermodynamically stable

*Delf, B.W. *et al*, 1979, J.C.S. Dalton, p.1302

Calculations agree, *trans* is most stable



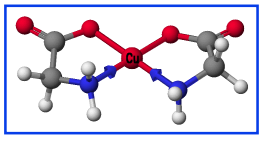
cis — *trans*

calculated free energies @ 298 K for single molecule

Gas phase:			
(kcal/mol)	Cis	Trans	Most stable
*BP_TZVP	-1386030.2	-1386042.0	Trans, -12

*total free energies, Turbomole (gas-phase)

However, *cis* is the product in water! (not *trans*)



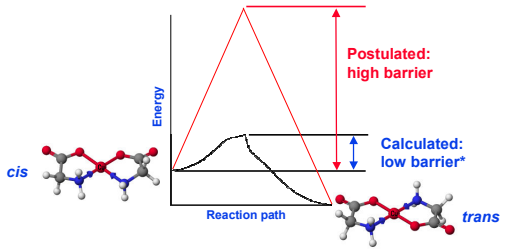
synthesis —H_2O→ *cis* (product in water)

Literature* claims that *cis* is the kinetic product

which implies a high barrier to interconversion

*Pike, R.M. et al, Microscale Inorganic Chemistry, John Wiley & Sons, 1991, Chap. 10, p.341
*O'Brien, P. J. Chem. Ed., Dec 1982, V.59, No.12, p.1052

Kinetic control requires high barrier to interconversion



Calculated low kinetic barrier (E_A ~ 6 kcal/mol) suggests "interconversion should occur spontaneously above 100 K" so, *cis* should NOT be kinetically stable in gas or solution phase.*

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

The Apparent Paradox

Crystals of *cis* decompose on heating to *trans*
but *cis* is synthesized and is stable in water !

Literature claims *cis* is the kinetic product in water. This requires a high barrier to interconversion !

?

Calculations suggest a low barrier to interconversion "too low for *cis* to be kinetically stable above 100ºK…"

Why is *cis* stable in aqueous solution at RT?

Does solvation affect the relative stabilities?

calculated free energies @ 298 K for single molecule

Gas phase:			
(kcal/mol)	Cis	Trans	Most stable
*BP_TZVP	-1386030.2	-1386042.0	Trans, -12

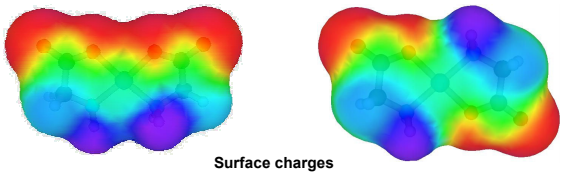
Aqueous (solution):			
(kcal/mol)	Cis	Trans	Most stable
*BP_TZVP	-1386083.0	-1386082.5	Cis, -0.5

Is this correct, does it make chemical sense?

*Turbomole, COSMOtherm

Why should *cis* become more stable in water?

Does this make chemical sense?



Surface charges

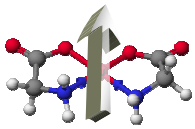
Cis *Trans*

- 0 +

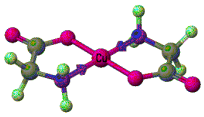
*Turbomole def-TZVP

Why should *cis* become more stable in water?

Does this make chemical sense?



Dipole moments



Cis: 14 debye*

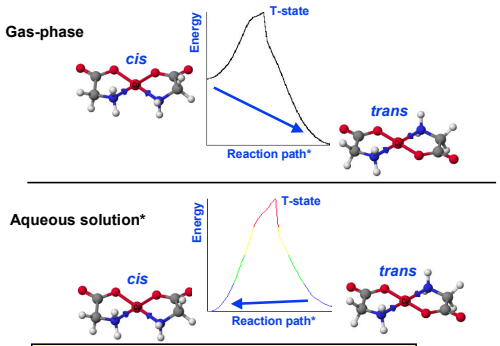
Trans: 0 debye*

cis has a large dipole moment causing strong dipole-dipole interactions with water and hence, a high energy of solvation

trans has no dipole moment to interact with water and hence, a lower energy of solvation

*Turbomole def-TZVP

Effect of water on equilibrium of isomers

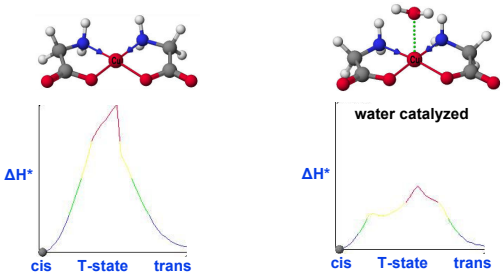


No significant difference in the activation energies

*B3LYP/6-31G(d) PCM reaction coordinates

Catalysis of Isomerization by Water

The presence of a coordinated water molecule lowers the calculated activation energy*



*B3LYP/6-31G(d) PCM reaction coordinates

*David Gallagher, CAChe Research, Email: gallagher.da@gmail.com

The Explanation

Why is *cis* stable at room temperature?

1. Calculations* show *cis* is more thermodynamically stable in water

2. In solid-phase, presumably crystal packing forces kinetically stabilize *cis* (on heating, water of crystallization is driven off and it rearranges to *trans*)

How is *cis* formed in aqueous solution?

Calculations* suggest that the barrier to inter-conversion is so low that, regardless of the kinetic product, only the thermodynamic product will prevail. Hence, *cis* is actually the thermodynamic product in water

Conclusions

1. **Solvation can have a surprisingly large effect:** Although, *trans* is more stable in gas-phase, **in aqueous solution, *cis* becomes the more stable isomer**
2. **Contrary to the literature, *cis* is the thermodynamic product in water** (not the kinetic product)
3. **Modeling* has provided breakthrough insights that better explain the experimental observations and overturn the long-standing accepted theory.**
4. **Don't trust gas-phase calculations for condensed phase chemistry** (e.g. water, biological systems).

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