

## Mechanism of the Cis–Trans Isomerization of Bis(glycinato)copper(II)

Christofer S. Tautermann,<sup>†</sup> Jasmina Sabolović,<sup>‡</sup> Andreas F. Voegelé,<sup>§</sup> and Klaus R. Liedl<sup>\*,§</sup>

*Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria, Institute of Computer Science, University of Innsbruck, Technikerstrasse 27, A-6020 Innsbruck, Austria, and Institute for Medical Research and Occupational Health, Ksaverska cesta 2, P.O. Box 291, 10001 Zagreb, Croatia*

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The cis to trans isomerization reaction of bis(glycinato)copper(II) was investigated by quantum chemical methods. An electronic reaction barrier (cis  $\rightarrow$  trans) of about 7.9 kcal/mol was determined for a ring-twisting mechanism, where both glycine residues stay bidentally attached to the central copper ion throughout the reaction. Ring-opening mechanisms could be ruled out for being energetically too demanding. Isomerization rates suggest the kinetic stability of the cis isomer in the gas phase only at very low temperatures (100 K). At ambient temperatures the isomerization to trans occurs spontaneously. Therefore the experimentally proved stability of the cis isomer in the solid state may be exclusively attributed to crystal packing effects.

### Introduction

Copper is an essential transition metal ubiquitously occurring in biological systems, especially in enzymes, where it is part of the catalytically most important active site. Copper containing enzymes are cytochrome *c* oxidase, lysil oxidase, and ascorbat oxidase, to mention a few.<sup>1</sup> Recently, the prion protein, whose abnormal isoforms cause neurodegenerative diseases in humans and other mammals, was suggested to be a copper-binding protein playing an important role in the normal brain copper metabolism.<sup>2–4</sup> In vivo, copper is selectively bonded to the prion protein in the region of a structure defined by four sequential copies of highly conserved octarepeat amino acid sequences.<sup>2,3</sup> The crystal and solution<sup>5</sup> structure of an octarepeat unit in a complex with copper(II) revealed that the metal was equatorially coordinated with histidine imidazole, two glycine amides, and one glycine carbonyl. This coordination pattern is very similar to bis(glycinato)copper(II) systems; it is a 4-fold equatorial coordination by nitrogen and oxygen atoms acting as donor atoms.

The physicochemical properties of bis(glycinato)copper(II), as a prototype for studying the chelate bonding of two amino acids to copper(II), has been investigated thoroughly for more than one century. A summary of early literature has been compiled by Delf et al.<sup>6</sup> Using different experimental techniques, Delf et al. studied solid-state reactions and interconvertibility between four modifications of bis(glycinato)copper(II) identified in the solid state: namely, anhydrous *cis*-bis(glycinato)copper(II), anhydrous *trans*-bis(glycinato)copper(II), *cis*-monohydrate, and *trans*-monohydrate.<sup>6</sup> The crystal structures of these four modifications have recently been resolved by powder diffraction techniques.<sup>7</sup> On the basis of the isothermal kinetic studies of the *cis*-monohydrate complex's dehydration, Delf et al.<sup>6</sup> proposed two different pathways for the cis to trans isomerization reaction. One possibility consists of a concerted dehydration–isomerization mechanism. The second possible pathway is a

two-step procedure with prior dehydration and subsequent isomerization of the anhydrous complex. Both mechanisms occur at a temperature higher than 100 °C and require a considerable activation energy. The activation energies were determined to be in the range 23–46 kcal/mol depending on the mechanism of isomerization. In vacuo theoretical studies on the structural and electronic properties of anhydrous<sup>8,9</sup> and hydrated bis(glycinato)copper(II)<sup>9,10</sup> confirmed that the trans isomers were more stable also for isolated systems. However, these studies addressed the energetic minima of the complexes only, but no activation energy for the isomerization has been determined. Thus, although the isomerization reaction from *cis*- to *trans*-bis(glycinato)copper(II) has been known for many years, the mechanism on molecular level is still elusive.

In this study we propose an intramolecular mechanism for the cis to trans isomerization reaction of anhydrous bis(glycinato)copper(II) and report the activation energy for the reaction calculated by high level quantum chemical methods. Our study is the first step in understanding the intramolecular reaction mechanism, where both glycinate stay bidentally bound (by their carboxyl-O and amino-N atoms) to the copper(II) throughout the reaction. The mechanism may also be feasible in the solid state, as the calculated transition structure is very compact and a chelate-ring opening seems unnecessary for the geometrical transformation.

### Methods

**Quantum Chemical Methods.** To analyze the cis–trans isomerization reaction of bis(glycinato)copper(II) in vacuo, we investigated extensively and systematically the conformational space of bis(glycinato)copper(II) to obtain the minima and the transition state of the complex.

For the determination of the stationary points, we used a somewhat altered Gaussian-3 method.<sup>11–13</sup> The Gaussian-3 method using reduced Møller–Plesset order basing on hybrid density functional (B3LYP<sup>14–16</sup>) optimized geometries (i.e., the G3(MP2)-B3 method)<sup>17</sup> was slightly modified to be capable of dealing with effective core potentials (ECP) for the copper atom in our model system. Thus we applied the Los Alamos

<sup>†</sup> Institute of Computer Science, University of Innsbruck.

<sup>‡</sup> Institute for Medical Research and Occupational Health.

<sup>§</sup> Institute of General, Inorganic and Theoretical Chemistry, University of Innsbruck.

**TABLE 1: Potential Energy Barriers (kcal/mol) for the Isomerization Reaction of Bis(glycinato)copper(II)<sup>a</sup>**

	B3LYP/{D95,LanL2DZ}	G3(MP2)-B3 <sub>LanL2DZ</sub>
cis isomer →	5.06	7.92
transition state		
trans isomer →	21.66	21.48
transition state		

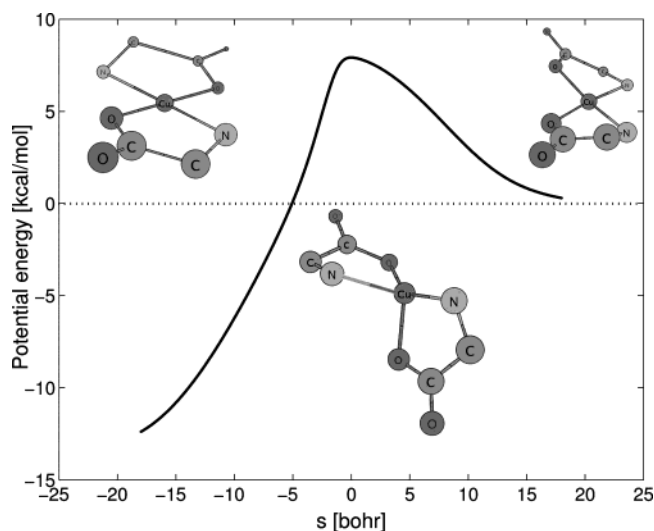
<sup>a</sup> The methods and basis sets are described in the text in detail.

LanL2DZ basis set<sup>18–21</sup> with ECPs to the copper atom through all stages of the computation. The modified method is now termed G3(MP2)-B3<sub>LanL2DZ</sub>. All stationary points were verified by normal-mode analysis, the minima revealing only positive eigenvalues of the Hessian and the transition state with exactly one negative eigenvalue leading to an imaginary frequency of 160i cm<sup>-1</sup>.

The potential-energy-surface (PES) between the stationary points was calculated at a lower level of theory by employing the hybrid density functional method B3LYP, using the D95 basis set<sup>18</sup> for all atoms except copper, where again the LanL2DZ basis set with the corresponding ECPs was applied (denoted as B3LYP/{D95,LanL2DZ} in the following). As density functional theory (DFT) is known to reproduce results of high level methods quite well for similar systems,<sup>22–25</sup> the points yield a qualitative correct description of the reaction swath (i.e., the conformational space enclosed by the stationary points of the reaction<sup>26</sup>). Table 1 shows the good correspondence of the DFT energy values to the high level methods and thus indicate the qualitative correct behavior of the low level-method.

**Variational Transition State Theory.** We applied the variational approach to transition state theory<sup>26–33</sup> including quantum chemical effects such as tunneling and corner cutting to calculate the reaction rates for the isomerization reaction at different temperatures. The minimum energy path (MEP), which is the path of least energy connecting products and reactants (i.e., cis and trans configurations in our case), in internal mass weighted coordinates is determined using the Page–McIver method.<sup>34,35</sup> The step size in mass scaled coordinates (scaled to 1 amu) had to be taken very small, as the PES is very shallow in some sections as the energy gradient turned out to be close to zero in an unusual large region close to the transition state. A step size of 0.01 au was used for the first 118 steps from the transition state to the minima and afterward a step size of 0.05 au was chosen. Second derivatives of the potential energy with respect to the coordinates were calculated every step, again due to the sensitivity of the hypersurface. Thus the calculation included more than 900 evaluations of the second derivative matrix. The PES was interpolated to the three high level stationary points (i.e., the reactants, the transition state and the products at the G3(MP2)-B3<sub>LanL2DZ</sub> level of theory) according to an interpolation scheme, which also maps the moments of inertia and normal frequencies onto the high-level data.<sup>36</sup> Tunneling was taken into account by various approaches (large-curvature<sup>30,37</sup> and small-curvature<sup>32,38,39</sup> tunneling) in the framework of the semiclassical theory,<sup>40</sup> leading to the microcanonical optimized multidimensional tunneling method ( $\mu$ OMT),<sup>41</sup> which is an excellent approach for including tunneling corrections over a large temperature range.

All points on the PES were determined with the Gaussian98 package<sup>42</sup> and the kinetics calculations were performed with Polyrate<sup>43</sup> and Gaussrate,<sup>44</sup> being an interface between Gaussian98 and Polyrate.



**Figure 1.** Potential energy profile along the isomerization reaction of bis(glycinato)copper(II) at a G3(MP2)-B3<sub>LanL2DZ</sub>//B3LYP/{D95, LanL2DZ} level of theory. The energy zero is arbitrarily set to the energy of the cis isomer. The abscissa  $s$  corresponds to the mass weighted distance along the reaction path, where  $s = 0$  denotes the transition state. Geometries of the stationary points are displayed: (left) *trans*-bis(glycinato)copper(II); (center) transition state; (right) *cis*-bis(glycinato)copper(II).

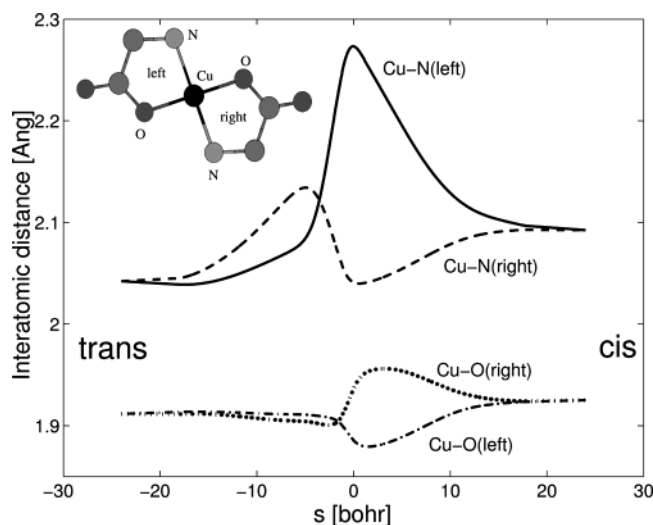
## Results and Discussion

**Energetics and Stationary Points.** The energy profile along the isomerization path is displayed in Figure 1, and the energy differences of the stationary points derived at the various levels of theory are given in Table 1.

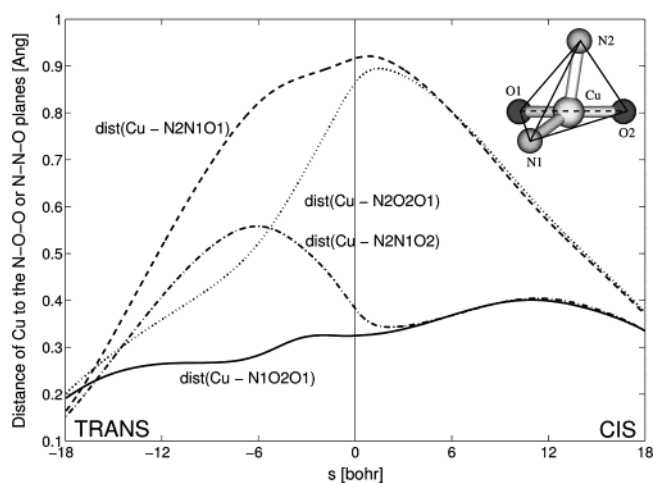
Figure 1 reveals a relatively small barrier for the isomerization from cis to trans in the gas phase, whereas the reverse reaction is energetically infeasible because of the comparatively high barrier in the back reaction. This is in accordance with the experimental results of Delf et al.,<sup>6</sup> where the isomerization was only observed in the cis → trans direction.

Nevertheless, the experiments were undertaken in the solid state; thus strong environmental effects may be expected. Delf et al. estimate an activation barrier of about 40 kcal/mol for the prior dehydration and the isomerization of the *cis*-bis(glycinato)-copper(II)·H<sub>2</sub>O. Powder diffraction studies of the various species of bis(glycinato)copper(II) show that changing from cis to trans isomer leads to a phase transition from orthorhombic to monoclinic systems.<sup>7</sup> In the solid state, the anhydrous molecules are linked together by the hydrogen bonds between amino hydrogens and carboxyl oxygens, and the oxygens of the adjacent unit coordinate to the copper(II) in an axial fashion.<sup>7</sup> Comparison of the calculated in vacuo minima and experimental crystal structures<sup>7</sup> yield the following rms deviations: 0.13 and 0.10 Å in all bonds, 19° and 10° in the valence angles, and 26° and 23° in torsion angles for the cis and trans isomers, respectively. The comparison reveals pronounced influence of the intermolecular interactions on the geometry of the studied isomers. The crystal surrounding hinders a ring opening or rotation of the glycine rings and a high activation barrier is to be expected.

**Isomerization Mechanism.** The isomerization reaction consists of a flipping of the glycine rings. For a better imagination of the mechanism we provide a mpeg movie and the geometries of the stationary points as Supporting Information. The bonds between the central copper and the nitrogen and oxygen atoms do not break during the isomerization process but stay always well below 2.3 and 2.0 Å, respectively, throughout the reaction.



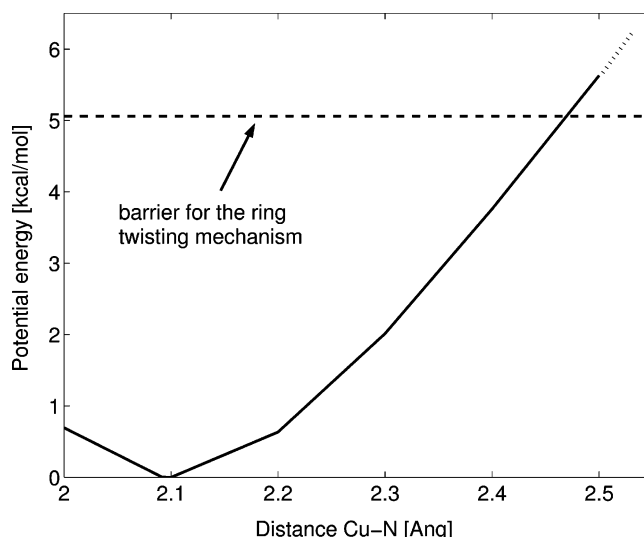
**Figure 2.** Distances between the copper and the nitrogen and oxygen atoms in the course of the isomerization reaction of bis(glycinato)-copper(II). The abscissa  $s$  corresponds to the distance along the reaction path, where  $s = 0$  denotes the transition state.



**Figure 3.** Distance of the copper atom to the four planes spanned by the two oxygen and two nitrogen ligands (the tetrahedron represents the copper(II) coordination polyhedron of the transition state) evaluated for every point on the MEP.

Nevertheless, the twisting of the rings leads to significant elongation and/or shortening of various Cu–N and Cu–O bonds, as may be seen from Figure 2. Figure 2 also shows that the Cu–N bonds in the left and right glycinato ring are same length in the beginning of the reaction. However, at some points of the reaction the difference of the two Cu–N bond lengths in the left and right ring is more than 0.2 Å. At the transition state not only the Cu–N bond lengths have a big discrepancy but also the Cu–O bond lengths differ significantly in the two rings. Interestingly, the ring with the shorter Cu–N distance (right ring) has a longer Cu–O distance and vice versa. Thus a loosening of the Cu–O bond leads to a strengthening of the Cu–N bond.

When evaluating the distance of the copper center to the various planes of the tetrahedron spanned by the four ligands of the copper atom (Figure 3), one realizes that the copper stays very close to one single plane throughout the reaction. This plane is spanned by two oxygens and one nitrogen (O1, O2, and N1; see Figure 3) and may be interpreted as the plane of the equatorial ligands. The Jahn–Teller effect<sup>45,46</sup> causes the fourth (axial) ligand N2, which is outside this plane during the reaction,



**Figure 4.** Dependence of the potential energy (B3LYP/{D95, LanL2DZ}) on the distance between the copper and one nitrogen atom in *cis*-bis(glycinato)copper(II). (The Cu–N coordinate was kept fixed at various distances while all other internal degrees of freedom were allowed to relax.) The Cu–N distance of the *cis* minimum, which is set to the energy zero, is found at 2.09 Å.

to be weaker bound to copper than the equatorial ligands. The results are in accordance with the observed diversity of Cu–O and Cu–N distances, which vary in a way that equatorial bond distances decrease whereas axial distances increase.<sup>45,46</sup> Therefore the high-level quantum chemical calculations reproduce well the (pseudo) Jahn–Teller effect expected to occur in copper(II) complexes.

However, in no stage of the reaction the ring opens and the maximal Cu–N distance is less than 2.3 Å. To estimate the energetical feasibility of a ring-opening mechanism, we calculated the energy, which is needed to elongate the Cu–N bond. We varied the Cu–N distance of *cis*-bis(glycinato)copper(II) from 2.0 to 2.5 Å in steps of 0.1 Å to get an energy scan. Separate optimization runs for each Cu–N distance were performed, where just the Cu–N coordinate was frozen and all other degrees of freedom were allowed to relax. Figure 4 shows that the elongation of the Cu–N bond to 2.5 Å already requires a higher energy than the barrier of the proposed ring-twisting isomerization mechanism (at the B3LYP/{D95,LanL2DZ} level of theory).

Moreover, the ring opening seems to be improbable in the solid state, as the space requirement is apparently larger than that for the ring-twisting mechanism. Thus the ring rotation mechanism might also occur in the solid state, although it is very difficult to assign in vacuo results to the solid state and transferring the gas-phase mechanism to the solid state is very speculative.

**Reaction Rates.** By means of variational transition state theory we derived reaction rate constants for the isomerization reaction in the gas phase in the temperature range from 100 to 400 K. The calculations are based on a dual level potential energy hypersurface (see Methods) and may be found in Table 2. One can realize a much higher isomerization rate for the reaction from *cis* to *trans* in the gas phase than is observed in the solid state.<sup>6</sup> This may be attributed to crystal packing effects present in the solid state. The *cis* isomer is expected to be kinetically stable in the gas phase, only at very low temperatures ( $\approx 100$  K), whereas at increasing temperatures the isomerization to the *trans* isomer occurs spontaneously.



**TABLE 2: Reaction Rates Determined by Variational Transition State Theory Including Quantum Effects ( $\mu$ OMT) for the Isomerization of Bis(glycinato)copper(II)**

temp (K)	$k_{\text{cis} \rightarrow \text{trans}} (\text{s}^{-1})$	$k_{\text{trans} \rightarrow \text{cis}} (\text{s}^{-1})$
100	5.0E-06	6.4E-36
200	2.6E+03	3.4E-12
300	2.1E+06	2.7E-04
400	5.8E+07	2.3

Reaction enhancement by tunneling was found just in the lowest temperature range and to a very small extent. At 100 K an acceleration of 3% was found; at temperatures above 200 K no significant impact of tunneling could be found. This is exactly what is to be expected as the isomerization reaction mostly includes heavy atom movement along a very long reaction path with low curvature and quite low barrier.<sup>26</sup> Comparison with, e.g., proton-transfer reactions<sup>47,48</sup> shows that proton-transfer reactions have much higher tunneling contributions due to much shorter reaction paths through higher and narrower barriers and smaller tunneling masses.

Nevertheless, the result that the transition energy barrier is much higher in the solid state than in the gas phase points out that crystal packing effects are strong enough to hinder chelate ring twisting and allow the isolation of crystalline *cis*-bis-(glycinato)copper(II) structures.

## Conclusions

By the means of *ab initio* quantum chemical methods we have found a mechanism for the isomerization reaction from *cis*- to *trans*-bis(glycinato)copper(II) in gas phase. During the reaction, four donor atoms remain attached to the central copper atom while the glycinato chelate rings twist with respect to each other (a movie of the reaction can be found as supporting material). The energy barrier for an alternative isomerization process through a ring-opening mechanism is found to be higher than the barrier for the ring twisting. Thus the ring twist mechanism may be expected to be the most probable one in the gas phase. As the twisting of the rings requires less space than a ring opening, the former mechanism may be supposed to occur also in the solid state. Determined reaction rates suggest a very quick reaction from *cis* to *trans* isomers at ambient temperatures. The kinetic stability of the *cis* isomer is only given at quite low temperatures (100 K). Much higher reaction barriers determined experimentally in the solid state may be explained by environmental effects, i.e., that crystal packing forces keep the *cis* isomer stable at ambient temperature.

**Supporting Information Available:** Cartesian coordinates of the stationary points as well as a *mpeg* movie of the whole isomerization reaction (*trans* to *cis*) are provided as supporting material. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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