ЖУРНАЛ СТРУКТУРНОЙ ХИМИИ

2011. Том 52, № 5 *Сентябрь – октябрь* *С. 906 – 916*

UDC 541.6:546.56:541.49

MODELING OF THE BIS(GLYCINATO)COPPER(II) *CIS—TRANS* ISOMERIZATION PROCESS: THEORETICAL ANALYSIS

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Received August, 5, 2010

In a number of theoretical works, the *cis—trans* isomerization of bis(glycinato)copper(II) and its interaction with water molecules is investigated. The interactions with the water medium modeled either by adding water molecules explicitly or through the Polarized Continuum Model (PCM) are investigated by the density functional (B3LYP) method in order to question the reliability of theoretical results. The crucial dependence of theoretical energies on the accuracy of PCM corrections is established. It is shown that for bis(glycinato)copper(II) the differences of isomer energies are of the order of the upper limit of the reliability of PCM corrections. Based on the calculation results, two possible mechanisms for the *cis—trans* isomerization are proposed. It is shown that only the inclusion of two explicit water molecules enables the modeling of the isomerization mechanism involving the interchange of glycine and water oxygen atoms in copper coordination.

Keywords: copper(II), glycine, isomerization, DFT calculation, PCM.

INTRODUCTION

In biological systems, essential transition metals have a special role as the catalytic centers in many enzyme reactions [1—3]. Also, the redox activity of transition metals has been found to be important for their effect as mediators of oxidative stress in neurodegenerative diseases [4]. Blue copper proteins, plastocyanin, or cytochrome-c oxidase are just few examples of such, in which a copper atom is the reactive transition metal center [5]. In the investigations of model systems, it has been shown that copper(II) radical species can arise in the structures formed by a copper atom interacting with the DNA or proteins. In many studies, model systems are formed so that the copper center is bridging two identical subunits, DNA bases, or amino acids [6, 7]. Despite the extensive experimental [8—10] as well as theoretical works [11—16], the properties and interactions of even simple copper(II) complexes with the environment (e.g. solute-solvent interactions) are still not completely understood. Part of the problem may be attributed to the fact that the calculation methods (density functional, basis set, or the force field) still have not been optimized to describe all the complexities of the copper atom interactions [17, 18]. Another contribution to the problem of a complete description of copper complexes comes from the computational limitations on the system size to be theoretically investigated [11].

To improve the theoretical capabilities, in earlier works [12, 13] the new force field for molecular modeling has been developed by the comparison with DFT calculations and experimental data for the description of copper complexes in the gas phase and water environment. By a comparison of the results of DFT theoretical calculations with the available experimental data and similar investigations of the gas-phase $Cu(Gly)_2$ complex and the same complex in water solution performed previously [19—21], the properties of the *cis—trans* isomerization process have been further examined. Rates of

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conversion obtained from the DFT calculated energies of the two isomers and the transition state (TS) between these were estimated for different models of the interaction with the water medium. In the previous theoretical work considering this process, a significant lowering of the difference between the energies of *cis* and *trans* isomers in water has been found [13, 19]. In this work, an additional analysis was made in order to establish the relation of changes in the molecular properties for the isolated $Cu(Gly)_2$ complex and the same complex in water environment and in that way to deepen the understanding of the underlying mechanisms having major effect on the modeling of this process. Special emphasis has been made to address the influence of the modeling of (non)electrostatic interactions of water environment on the theoretical predictions of the isomerization mechanism.

METHODS

Geometries and single-point energies of the stationary points of $Cu(Gly)_2$ (i.e., *trans* and *cis* minima as well as the transition-state (TS) structure) in the gas phase (GP) and aqueous solution have been investigated by the UB3LYP hybrid density functional method [22—24] using the LanL2DZ basis set alone (LanL2DZ basis) and the basis sets composed of the LanL2DZ basis for Cu and H and the D95v [25] basis for C, N O atoms to which an additional set of polarization (LanL2DZ(d) basis) and diffuse and polarization functions (LanL2DZ+(d) basis) has been added. (The calculations using the latter basis set have been performed in the course of the previous work [13] and have been included here for completeness.) By the use of the aforementioned basis sets, the effective core potentials (ECPs) of Hay and Wadt [26] are used to describe the shielding effects of the electrons in copper inner shells. All the calculations have been performed using the Gaussian 03 program package [27]. The choice of the B3LYP method and the basis set was initially based on the previous studies, in which they yielded the energies and geometries of bis(amino acidato)Cu(II) systems with the values very close to those obtained by high-level methods and thus indicated that the low-level method may approximate well the higher calculation level [13, 20].

The Polarized Continuum Model (PCM) of Tomasi and coworkers [28], modified by Barone and coworkers [29, 30] has been used to describe the effects of the aqueous medium in the self-consistent reaction field (SCRF) calculations. The environment temperature has been set to 300 K. The water solvent was specified by the dielectric constant of 78.39. The default (UA0) as well as the United Atom Topological Model applied on solvent radii optimized for the PBE0/6-31G(*d*) level of theory (UAKS) have been used to describe the effects of the dielectric medium [31—33]. Additionally, the effect of water bonding to Cu(II) in the axial octahedral positions was presumed and modeled by adding explicitly one or two water molecules to the $Cu(Gly)_2$ isomer and then applying PCM for such defined structure. The calculations performed are thus defined by: 1. *the type of the structure* (*cis*, *trans* isomer or TS), 2. *the number of explicitly added water molecules* (1 or 2), 3. *the continuum model* (GP calculation, PCM using UA0 radii (PCM), PCM using UAKS radii (PCM/UAKS)), and 4. *the basis set used* (LanL2DZ, LanL2DZ(d), LanL2DZ+(d)). Therefore, for example, *trans* $Cu(Gly)_2\cdot 2H2O$ (PCM/UAKS) LanL2DZ in the following stands for: the UB3LYP/LanL2DZ//UB3LYP/LanL2DZ calculation of *trans* $Cu(Gly)_2$ with two explicit water molecules surrounded by the medium modeled by PCM using UAKS radii for solvent description.

The initial atom positions for the geometry optimizations of the *cis* and *trans* minima of $Cu(Gly)_2$ were taken from D′Angelo et al. [14]. The positions of axial water molecules are taken from the respective crystal data where applicable [14], or in other cases, from de Bruin et al. [19]. The transition state of $Cu(Gly)_2$ in the aqueous solution at room temperature was successfully calculated only upon using good enough initial guess for the transition structure and by applying the Synchronous Transit-Guided Quasi-Newton (STQN) method implemented in the program invocated by the QST3 keyword [34, 35]. This initial guess was the gas-phase transition-state structure obtained by Tautermann et al. [20]. Conversely, the use of more simple transition-state search protocols implemented in TS or QST2 methods did not generate the transition-state structure of the expected geometry characteristics between the *cis* and *trans* minima as the structure converged to a local energy maximum close to the *trans* $Cu(Gly)_2$ isomer. The optimized geometries of the stationary points have been checked by frequency calculations to be those of the required optimization state (transition-state or energy minimum). On such optimized structures the Natural Population Analysis part of the full Natural Bond Orbital analysis has been performed [40—42]. The energies and electronic properties have been calculated using the same level of the theory and the basis set as ones used for optimizations.

The obtained Gibbs free energy values have been used in the expressions

$$k_{cis\to trans} = \frac{k_B T}{h} e^{-\Delta G_{cis—TS}/RT} \tag{1}$$

$$k_{trans\to cis} = \frac{k_B T}{h} e^{-\Delta G_{trans—TS}/RT} \tag{2}$$

from standard transition-state theory to calculate *cis*—*trans* rate constants, as explained previously [13, 16].

RESULTS AND DISCUSSION

Water-complex interactions: modeling and accuracy. The optimized structures for the LanL2DZ gas-phase and PCM(UAKS) Cu(Gly)$_2$ calculations are shown in Fig. 1. From a comparison of differences in the total complex energies, Gibbs free energies (Table 1), geometries (Table 2) and the distribution of natural charges at Cu and four ligand atoms (Glycine O1 and N) (Table 3) obtained for LanL2DZ with those obtained by the largest considered basis set LanL2DZ+(d), it may be observed that these are very close for the respective (*cis*, *trans*, TS) structures. From a comparison of PCM correction energies it is also seen that a change in the TS barrier as well as the lowering of the difference in *cis* and *trans* state energies is dependent on large differences in the PCM corrections for the *cis* and *trans* isomers in water (Table 1). This change in turn is what makes the very basis of the conclusions about the energetics of the isomerization process made in previous investigations [13, 19]. Understanding that the quality of calculations of the (relative) energies for bis(glycinato)copper(II) isomers in water is thus mainly dependent on the good modeling of water interactions mostly introduced by PCM, additional investigations have been made using the standard (UA0) and PBE0-optimized (UAKS) choices of atomic radii. In these, the LanL2DZ basis set was used. Apart from the speed of calculations, the choice is also based on the observation that the use of this basis has yielded results in good agreement with the experiment, comparable or even surpassing those obtained by the use of larger basis sets (to be shown below).

Consistent with the general expectations of the effects of enlarging the basis set on the other hand, the energies of the each isomer of the complex both in water environment and in the gas phase are predicted lower (more negative) when using more complete basis set (both polarization and diffuse functions included). From a comparison of the calculations performed using only additional polarization functions, LanL2DZ(d) with the LanL2DZ+(*d*) and LanL2DZ results (Table 1), individual contributions of each type of additional basis set functions may be estimated. It is thus seen that the effect of the inclusion of polarization functions is approximately by the order of magnitude greater than the effect of the inclusion of diffuse functions. This is to be expected since copper ligand bonding is established by the major contribution of Cu *d* and N and O *sp*^{3}-hybridized orbitals, which are of defined directionality. It is nevertheless interesting to note that the relative energies for both included polarization and diffuse functions are closer to the LanL2DZ result than to LanL2DZ(d). This may mean that the effects of the use of additional diffuse and polarization functions are of opposite signs, and the use of polarization only could bias the results.

Although the experimental data that could be used as a criterion for the quality of theoretical results to the best of the author's knowledge is scarce for this system in the water medium [14, 21], several issues are raised in its theoretical research, which warrant for our additional attention. From a more careful inspection of Table 1, it is observed that the differences in the predicted isomer energies are of about 10 kJ/mol. For the results for these energies to be considered relevant, the quality of the PCM correction energies should thus be about 1 % or about 0.7 kcal/mol (see $\Delta E_{s\text{-}s}$ values in Table 1). This value is at the very limit of the best B3LYP/6-31G(*d*)/CPCM-UAKS predictions, and below the overall CPCM/UAKS results of 2.6 kcal/mol found in the recent work by Takano and Houk

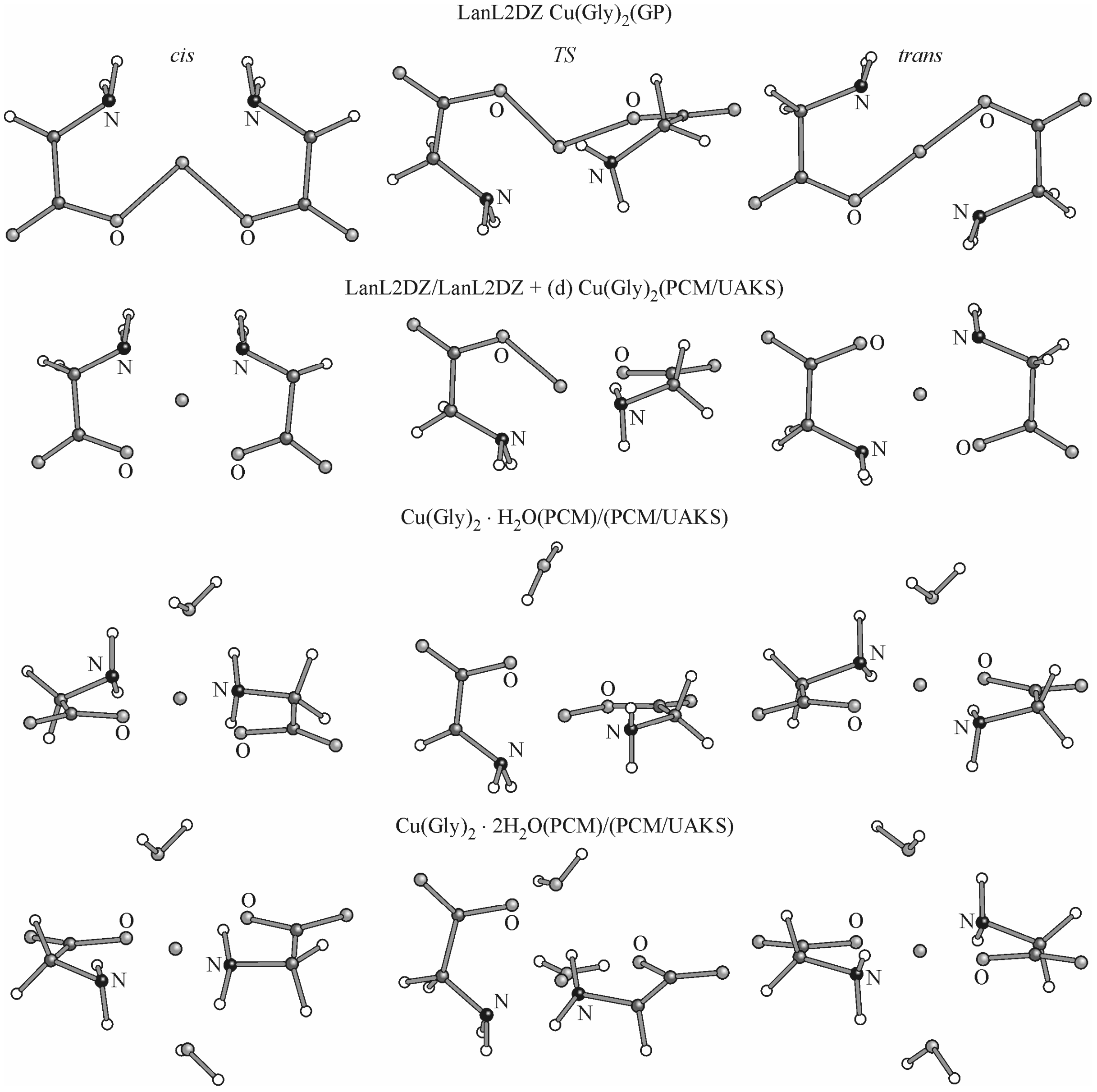

Fig. 1. Optimized geometries of all the structures considered. Because of the similarities in the geometries of the structures for LanL2DZ and LanL2DZ+(d) $Cu(Gly)_2$ (PCM/UAKS), LanL2DZ $Cu(Gly)_2 \cdot nH_2O$ (PCM) and (PCM/UAKS) calculations they have respectively been represented by the same structures. Nitrogen and oxygen glycine atoms in structures are indicated

[32]. This has strong implications to the conclusions made on the energies of the examined structures. Although the *trans* structure is systematically predicted to be more stable in the water medium, because of a small energy difference between the *cis* and *trans* isomers and a large variability of the results, the original assumption of D′Angelo et al. [14] of the predominance of the *cis* isomer in water may not be rejected on the theoretical basis unless we put the additional assumption of cancellation of errors in PCM corrections when calculating the energy differences.

The calculations of the structures having one or two water molecules added explicitly yield larger PCM corrections. This is obviously the result of a larger area and stronger interaction of these water molecules with the polarized medium modeled through PCM. If the assumption is made that these additional water-PCM interactions do not introduce significant additional errors, the effect of non-

Table 1

Total complex energies (U), *Gibbs free energies* (G) (*in* a.u.) *and correction energies of the solute-solvent interaction* ($\Delta E_{s\text{–}s}$) (*in* kJ/mol) *for the structures considered. Differences in energies between cis and TS* ($E_{cis\text{—}TS}$) *and cis and trans* ($E_{cis\text{—}trans}$) *structures are given in* kJ/mol, *rate constants for cis-to-trans* ($k1$) *and trans-to-cis* ($k2$) *processes in* s^{-1}, *while K is a dimensionless reaction constant*

Calculation/structure		E opt + H_2O			$E_{cis\text{—}TS}$	$E_{cis\text{—}trans}$	$k1$	$k2$	K
		cis	*trans*	*TS*					
LanL2DZ+(d)	U	–764.06346	–764.06535	–764.03676	69.11	7.06	5.78	0.34	16.98
Cu(Gly)$_2$	G	–763.96553	–763.96774	–763.94128	63.67	5.81	51.32	5.01	10.25
(PCM/UAKS)[a]	$\Delta E_{s\text{–}s}$	–312.92	–216.06	–249.53					
LanL2DZ(d)	U	–764.04150	–764.04324	–764.01536	68.63	4.57	7.01	1.12	6.24
Cu(Gly)$_2$	G	–763.94344	–763.94551	–763.91989	61.83	5.43	107.08	12.12	8.84
(PCM/UAKS)	$\Delta E_{s\text{–}s}$	–291.28	–203.35	–234.51					
LanL2DZ	U	–763.88354	–763.88601	–763.85746	68.47	6.48	7.47	0.55	13.46
Cu(Gly)$_2$	G	–763.78588	–763.78895	–763.76211	62.41	8.05	84.85	3.37	25.21
(PCM/UAKS)	$\Delta E_{s\text{–}s}$	–335.07	–228.36	–269.77					
Cu(Gly)$_2$·H$_2$O	U	–840.32425	–840.32698	–840.29067	88.17	7.17	$2.77\cdot10^{-3}$	$1.57\cdot10^{-4}$	17.70
(PCM)	G	–840.20725	–840.20944	–840.17685	79.82	5.75	$7.87\cdot10^{-2}$	$7.84\cdot10^{-3}$	10.03
	$\Delta E_{s\text{–}s}$	–346.75	–245.60	–271.41608					
Cu(Gly)$_2$·2H$_2$O	U	–916.76214	–916.76418	–916.75824	10.24	5.36	$1.03\cdot10^{11}$	$1.20\cdot10^{10}$	8.56
(PCM)	G	–916.62678	–916.62917	–916.61583	28.75	6.27	$6.16\cdot10^{7}$	$4.98\cdot10^{6}$	12.38
	$\Delta E_{s\text{–}s}$	–334.18	–268.15	–290.439					
Cu(Gly)$_2$·H$_2$O	U	–840.32581	–840.32858	–840.29468	81.73	7.28	$3.67\cdot10^{-2}$	$1.99\cdot10^{-3}$	18.46
(PCM/UAKS)	G	–840.20929	–840.21238	–840.18049	75.61	8.12	0.43	$1.64\cdot10^{-2}$	25.91
	$\Delta E_{s\text{–}s}$	–346.70	–251.08	–281.70					
Cu(Gly)$_2$·2H$_2$O	U	–916.76082	–916.76380	–916.75954	3.36	7.82	$1.62\cdot10^{12}$	$7.05\cdot10^{10}$	23.03
(PCM/UAKS)	G	–916.62626	–916.63045	–916.62053	15.04	11.01	$1.51\cdot10^{10}$	$1.82\cdot10^{8}$	82.75
	$\Delta E_{s\text{–}s}$	–353.02	–269.57	–280.61					

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[a] Data from ref. [13].

electrostatic interactions on the calculation of the *cis—trans* energy difference may be estimated. It is thus seen that this effect on the difference $\Delta E_{cis\text{—}trans}$ can be close to 40 % (from the results of LanL2DZ Cu(Gly)$_2$ (PCM/UAKS) and Cu(Gly)$_2\cdot$2H$_2$O (PCM/UAKS) calculations). This also implies that the additional interactions are directed to an increase in this difference, making the *trans* isomer more stable.

PCM correction energies for the calculations using UA0 and UAKS radii are different by no more than 10 kJ/mol. This difference, nevertheless, introduces the difference in the predicted $E_{cis\text{—}TS}$ energy of the same order, resulting in a change of two orders of magnitude in the predicted rate constant for the *cis*-to-*trans* process. Furthermore, the optimization of Cu(Gly)$_2\cdot$2H$_2$O (PCM/UAKS) TS finished in a stationary state predicted by the frequency analysis to be a local minimum, and of the energy very close to the *trans* isomer and lower than the *cis* isomer energy (Table 1). As this is not the behavior of the system expected on experimental grounds; this again shows possible dominant influence of the PCM model on the conclusions from the modeling of the process having a transition barrier close to the (PCM) accuracy limit.

Table 2

Bond distances (Å) *and bond angles* (deg.) *for selected bonds in* $Cu(Gly)_2 \cdot (nH_2O)$ *cis and trans isomer complexes. Comparison of experimental and theoretical results*

Calculation/source	Cu—Ow		
	cis	*trans*	*TS*
$Cu(Gly)_2 \cdot H_2O$ (PCM)	2.24	2.25	3.97
$Cu(Gly)_2 \cdot 2H_2O$ (PCM)	2.40	2.38	3.52
	2.41		2.04
$Cu(Gly)_2 \cdot H_2O$ (PCM/UAKS)	2.26	2.25	3.95
$Cu(Gly)_2 \cdot 2H_2O$ (PCM/UAKS)	2.36	2.37	3.46
	2.44	2.40	2.04
Experimental [a]		2.4	
DFT (CPCM) [b]	[1.5] : 2.392	[2.4] : 2.459	
MM [c]	2.58	2.79	
B3LYP/6-311+G(*d,p*) $Cu(Gly)_2 \cdot 2H_2O$ [d]	2.93	3.562	
	2.881	3.562	

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[a] Data from ref. [14].

[b] Table 1 from Hattori et al. [16]. Refers to the BSII calculations which reproduce experiment somewhat better.

[c] Data from ref. [12].

[d] Data from ref. [19].

Finally, it should be noted that the $E_{cis—trans}$ value of 6.27 kJ/mol obtained for $Cu(Gly)_2 \cdot 2H_2O$ (PCM) calculation in the aqueous solution is close to the energy difference of 9.1 kJ/mol, experimentally observed by electrochemistry methods for the two isomers in their monohydrate crystal forms [36].

A tendency of the optimization process to dislocate water molecules defined in the axial positions to the equatorial plane of the $Cu(Gly)_2 \cdot nH_2O$ complex has been observed previously in DFT calculations [12, 19]. The explanation of the reason for this is not completely straightforward. In both investigations mentioned, a larger basis set has been used, which, at least in the case of de Bruin et al. [12], predicts a quite large positive charge at the Cu center. A larger positive charge on copper is also present, although in a less pronounced manner, for the calculations performed here for isomer structures with the equatorial water position (data not shown). This is in turn related to the preference of the copper-centered structure to assume tetrahedral coordination in favor of planar or distorted octahedral [44, 45]. (This issue will further be discussed below in the consideration of possible isomerization mechanisms.) Although this may help to find the tetrahedrally coordinated TS, it is not related in an obvious way to the preferred equatorial water position found in the previous investigations. It is possible that the calculations using larger basis sets are more sensitive to the fine geometry features than those using the all-LanL2DZ basis. Yet, the latter yields the geometries comparing well to the experimental findings (Table 2). Other probable reason for the above effect in de Bruin et al. might be the use of the Self-consistent Isodensity Polarized Continuum Model (SCIPCM) [46] known to have certain deficiencies [30]. In the work of Sabolović et al. [19], on the other hand no PCM has been used. This may lead to large effects, as already mentioned.

The physicochemical reasons for the energy difference in *cis* and *trans* isomers in water environment are assigned to differences in $Cu(Gly)_2$ interactions with water in several other investigations [14, 16, 19, 48]. It was assumed that the formation of hydrogen bonds is stronger than the interaction at the axial copper position [16]. From the data presented in this work, however (see a comparison with experiment in Table 2), it may be seen that the effects of water in equatorial positions can be

Table 3

Comparison of natural charges at Cu and the four ligand (Glycine O1 *and* N) *atoms for different* $Cu(Gly)_2 \cdot (nH_2O)$ *structures considered in the work*

	cis	*trans*	*TS*	*cis*	*trans*	*TS*	*cis*	*trans*	*TS*	*cis*	*trans*	*TS*
	LanL2DZ $Cu(Gly)_2$ (GP)			LanL2DZ $Cu(Gly)_2$ (PCM/UAKS)			LanL2DZ+d $Cu(Gly)_2$ (PCM/UAKS) [a]					
Cu	0.99	0.99	0.98	1.04	1.04	1.05	1.06	1.06331	1.08428			
N	–0.94	–0.93	–0.96	–0.95	–0.94	–0.99	–0.94	–0.9393	–0.98863			
O	–0.73	–0.79	–0.76	–0.79	–0.80	–0.83	–0.80	–0.80542	–0.84538			
N	–0.94	–0.93	–0.95	–0.95	–0.94	–0.93	–0.94	–0.93922	–0.91792			
O	–0.73	–0.79	–0.72	–0.79	–0.80	–0.76	–0.80	–0.80572	–0.76351			
	$Cu(Gly)_2 \cdot H_2O$ (PCM)			$Cu(Gly)_2 \cdot 2H_2O$ (PCM)			$Cu(Gly)_2 \cdot H_2O$ (PCM/UAKS)			$Cu(Gly)_2 \cdot 2H_2O$ (PCM/UAKS)		
Cu	1.01	1.01	1.08	0.98	0.99	1.02	1.00	1.00	1.06	0.98	0.99	1.01
N	–0.93	–0.93	–0.99	–0.92	–0.92	–0.93	–0.93	–0.93	–1.00	–0.93	–0.93	–0.93
O	–0.78	–0.79	–0.84	–0.78	–0.78	–0.84	–0.78	–0.79	–0.84	–0.78	–0.78	–0.84
N	–0.93	–0.93	–0.95	–0.92	–0.92	–0.93	–0.93	–0.93	–0.93	–0.92	–0.92	–0.93
O	–0.78	–0.79	–0.74	–0.78	–0.78	–0.78	–0.78	–0.79	–0.75	–0.78	–0.78	–0.79

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[a] Data from ref. [13].

modeled reasonably well by the PCM, so that no transfer of explicitly added axially-coordinated water molecules takes place in the optimizations of either of the isomer forms.

In contrast to the calculations of the energies, a theoretical reproduction of the $Cu(Gly)_2$ geometries in water shows much less variance among different calculation models and protocols (Table 2). The optimized *cis* and *trans* minima and TS structures for the gas-phase, PCM and $PCM \cdot nH_2O$ ($n = 1$, 2) calculations are shown in Fig. 1. Since the geometries of the minima for the PCM and PCM/UAKS calculations are very similar, they are represented by the same structures in Fig. 1. An additional note should be given here. Although according to [34, 35], the QST TS search should give the optimized geometries of the stationary points of the required type, for the $Cu(Gly)_2 \cdot H_2O$ (PCM/UAKS) and $Cu(Gly)_2 \cdot 2H_2O$ (PCM/UAKS) calculations a different stationary point character has been predicted by QST and the frequency analysis. In the former, the saddle point character is found (2 imaginary frequencies), while in the latter, the obtained structure has the character of the local minimum (0 imaginary frequencies). For the $Cu(Gly)_2 \cdot H_2O$ (PCM) and $Cu(Gly)_2 \cdot 2H_2O$ (PCM) calculations the stationary point character of *cis* and *trans* minima and the TS has been verified by the frequency analysis.

Isomerization mechanism: theoretical prediction. In most of the minima, the predicted structure of the copper center is the 4+2 distorted octahedral structure [47]. In most of the cases considered, the TS structure is close to the tetrahedral copper coordination structure, as expected from the previous investigation of Tautermann et al. [20]. This is supported by the larger predicted positive charge on copper obtained systematically for TS structures (Table 3). While the $Cu(Gly)_2 \cdot H_2O$ calculations yield the TS geometries in good agreement with those presumed for the tetrahedral copper coordination, the $Cu(Gly)_2 \cdot 2H_2O$ calculations show somewhat larger discrepancies (compare the results to Massa et al. [49], for example). In considering whether the copper coordination is five or six, the reproduction of experimental data is the decisive criterion. Thus, from comparisons in Table 2 it is seen that the distance of axial O_W—Cu is reproduced significantly better in six-coordinated models.

Based on what is known about the orbital configurations in copper(II) coordination complexes, the distribution of populations (see the supporting information) predicting SOMO to be of d_{xy} instead

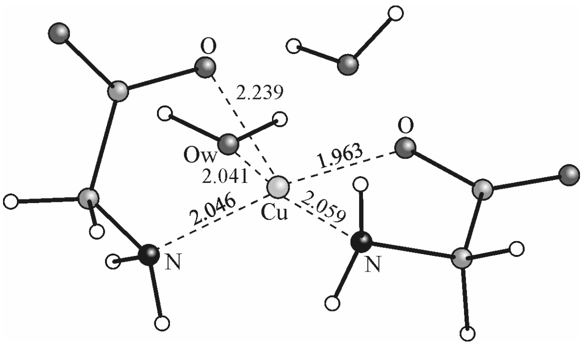

Fig. 2. Structure of TS for the LanL2DZ Cu(Gly)$_2$·2H$_2$O (PCM) calculation. Structure of the copper center is of a distorted square-pyramidal /distorted octahedral geometry, one of the in-plane ligand atoms being water oxygen (Ow) in place of the glycine oxygen now placed axially. The Cu—L distances (in Å) are presented to make this effect observable

of the $d_{x^2-y^2}$ character should not be considered reliable [16, 18b, 48, 53]. Somewhat more reasonable results of the orbital ordering (such as the inversion of d_{xy} and d_{xz} orbitals in comparison with $d_{x^2-y^2}$ in tetrahedral coordination) are obtained from the calculations using the LanL2DZ basis only, and without any explicit water molecules added. The reason for the problem may be that NBO gets into difficulty when a DFT-obtained spread molecular orbital, which is supposed to describe the copper-water interaction(s), should be related to copper atomic orbitals. It thus seems that the use of DFT with ECP does not yield results that may safely be used for the understanding of orbital changes during the transition. For this, more elaborate methods (such as Complete Active Space (CAS) methods) may have to be used. The interest in the orbital interplay in TS in comparison with the two minima is based on the relationship of copper coordination number and/or partial charges on the copper and ligand atoms with the preference for the tetrahedral in comparison to octahedral coordination. The tetrahedral copper coordination is often found in Cu(I) complexes [49, 50]. Based on this fact, one possible isomerization path may thus be assumed to be the transient reduction of a Cu(II) complex to form the tetrahedrally-coordinated Cu(I) TS complex that would help the reorganization of the structure. This mechanism is investigated in the forthcoming work and is expected to resemble the inverse of the one published by Livoreil et al. [51]. Charge distributions on Cu and its ligand atoms (Table 3) support the assumption of the larger Cu charge in tetrahedrally coordinated copper. Yet, large differences are found between the Cu(Gly)$_2$·H$_2$O and Cu(Gly)$_2$·2H$_2$O TS calculations. Namely, in the former, charges in the TS are much larger than in the *cis* and *trans* isomer forms. A small charge change on Cu for the calculations with two axial water molecules, considered together with the structures of the TS complex obtained for them, motivates us to assume yet another possible mechanism for Cu(Gly)$_2$ isomerism in water environment, which is discussed in detail here. It is based on the assumption that no change in copper coordination is really necessary in the water medium, due to the fact that water oxygen may transiently assume one of the octahedral copper ligand positions during isomerization. This may result in a much lower energy barrier for this transition in water than that previously found for the gas-phase reaction [19—21]. Furthermore, from Table 1 it is seen that non-electrostatic interactions should be important, since the *cis*-TS barrier energies are much larger in all other calculations, except those including two axially coordinated water molecules.

The TS structure for Cu(Gly)$_2$·2H$_2$O resembles closely the coordination found for either *cis* or *trans* isomers, but with one of the additional water oxygen atoms interchanged to one of the glycine ligands (Fig. 2 and Table 2). This model of the mechanism for the *cis—trans* isomerization is further supported by the energy for a change in water coordination for Cu(Gly)$_2$ found in Hattori et al. [16]. The energy for the change between 4-fold and 5-fold water coordination is found to be 7.9 kJ/mol. A part of the energy change assumed to happen in the above model comes from essentially the same type of redistribution in hydrogen bonding. The above value also is not far from 15.04 kJ/mol; the height of the *cis*-TS barrier obtained in the PCM/UAKS calculation here (Table 1), especially if differences in the applied calculation levels are taken into account. The larger energy difference for our calculation is expected since copper coordination also influences. Furthermore, the geometry of the copper coordination sphere in the [Cu(H$_2$O)$_6$]$^{2+}$ cation [52] resembles strongly those found for the *cis* and *trans* isomers. This also adds to the argument that the flexibility of the copper center in water upon the choice of the ligands may explain a possible path for isomerization.

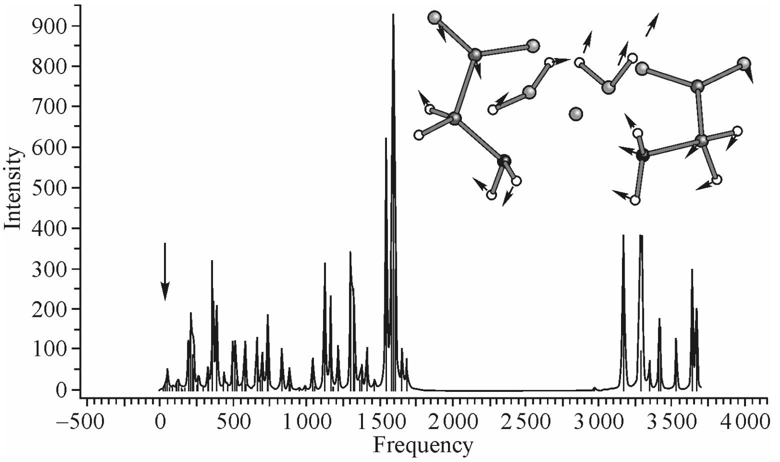

Fig. 3. Theoretical prediction of the TS $Cu(Gly)_2 \cdot 2H_2O$ IR spectrum. The vibrational mode closest to the twist of the glycine ligands, while keeping the geometries of the ligands essentially unchanged, is indicated by the arrow at the low-frequency end of spectrum. The displacements of atoms are shown in the inset

Indications for the experimental verification of the proposed mechanism. The reaction surface for the $Cu(Gly)_2 \cdot 2H_2O$ isomerization is found to be very complex (several local minima were found close to the TS structure while scanning the structures in the TS search). Thus, the prediction of the TS vibrational spectrum and the above mechanism allow only the assumptions about the important modes contributing to the isomerization process. More conclusive results from this part of the investigation are limited by: a) the complexity of the reaction surface involving two fluctuating water molecules and b) the possible overestimation within the limitations of the model of the effects of higher modes, which include contributions of bond torsions of individual glycine ligands, on this mode. Yet even more than these, the true physical situation is inconsistent with the assumptions of the model consisting of two, and the same two, water molecules involved in the isomerization process. It is not reasonable to assume the *same* water molecules to necessarily participate in the transition. It is much more plausible that the placement of water molecules found in the TS and minima are few local stationary point configurations, yet they do not need to be connected at all by the same reaction path, since c) different water molecules can (and are expected to) participate to the bonding in each of the named states. In such a situation, a comparison with the gas-phase TS spectrum may prove fruitful because it may point to the important mode for the *cis—trans* transition in the absence of water molecules. The imaginary mode for this transition in the gas phase is located at 121 cm^{-1}, with an intensity of 42 km/mol. The same mode may or may not be important in the water solution, since the structure modeled includes two explicit water molecules introducing changes in the mode force constants. From the calculated IR spectrum of $Cu(Gly)_2 \cdot 2H_2O$ (Fig. 3) and mode displacements (Supplementary material) the mode at 125 cm^{-1} is certainly expected to contribute to isomerization. Yet, its intensity is very low (about 8 km/mol). However, the vibrational mode in the low-frequency band centered at about 40 cm^{-1} is of a much larger intensity (34 km/mol), and at the same time, of the appropriate expected structure: the largest contribution coming from a twist of two glycine ligand planes with respect to each other (Fig. 3). The mode of the same features is also present in the spectra of $Cu(Gly)_2 \cdot 2H_2O$ *trans* and *cis* isomers at essentially the same frequency. Thus, it can be assumed that it also has at least significant contribution to the *cis*-to-*trans* transition in the water solution.

The coordination of the copper(II) center in anhydrous Cu(II) amino acidate crystals is square planar or flattened tetrahedral, as observed by X-ray spectroscopy. The structure of the bis(glycinato)copper(II) monohydrate coordination is on the other hand distorted octahedral [12, 14]. This shows the important effect that water molecules have in the formation of copper(II) coordination. These observations, together with the issues raised in the considerations of orbital and charge distribution influences may be used to motivate further investigations in order to understand details of the interactions of $Cu(Gly)_2$ in water and specifically in the mechanism of the crystal formation [13, 15].

CONCLUSIONS

The reliability of the theoretical results is put in perspective: it has been shown that, although PCM-only and explicitly added water molecules yield closely similar geometries, one has to be cautious when calculating the energies of the isomerization process in the water medium because the greatest influence comes from PCM correction energies. This is especially so in the situation, in which the energies of interest are of the order of the quality of theoretical results obtained using PCM, as encountered here.

From the results of the performed calculations two alternative mechanisms for Cu(Gly)$_2$ isomerization have been proposed. Of these, in this work the emphasis has been put on the mechanism relying on the interchange of water and glycine ligand atoms, while at the same time copper coordination remaining more or less unchanged. The theoretical prediction of the mechanism of this type has become possible only upon the addition of two explicit water molecules to the Cu(Gly)$_2$ complex. The discussion of the other proposed mechanism, involving Cu(Gly)$_2$ reduction, will be given in the forthcoming paper.

To be able to investigate the orbital interplay during the isomerization, high quality population analysis should be performed, probably by the use of a more advanced calculation method (for example, using the CAS methods). Furthermore, more molecules in the Cu(Gly)$_2$ coordination sphere should be added explicitly to completely take into account the possibility of the exchange of copper ligands with water molecules. The latter investigations are presently underway.

Acknowledgments. The calculations performed in the course of this work have been made using the resources of Isabella computing cluster at SRCE, Zagreb. The work has been partially supported by the Croatian Ministry of Science, Education and Sports project 022-0222148-2822.

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