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Copper(II) Diamino Acid Complexes: Quantum Chemical Computations Regarding Diastereomeric Effects on the Energy of Complexation

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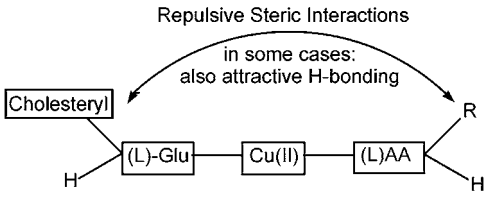
ABSTRACT



Quantum chemical calculations were used to rationalize the observed enantiodifferentiation in the complexation of α-amino acids to chiral Cu(II) complexes. Apart from Cu(II)–π interactions and steric repulsions between the anchoring cholesteryl-Glu moiety and an aromatic amino acid R group, hydrogen bonding also plays a role. In fact, in the case of tryptophan, C═O···H–N hydrogen bonding between the glutamate moiety and the tryptophan N–H group compensates for the loss of intramolecular hydrogen-bonding and diminished Cu(II)–π interactions.

The large-scale separation of chiral compounds remains a topic of considerable interest given the relative ease of many reactions that yield racemic mixtures.[1] One approach to this problem regarding the separation of α-amino acids makes use of ultrafiltration, which allows the process to be set up in a continuous rather than a batchwise fashion.[2] This approach is based on the selective complexation of one of the enantiomers to a chiral Cu(II) complex based on cholesteryl-(L)-glutamate. This compound is embedded in a micelle, which is of a size that is too large to pass through the pores of an ultrafiltration membrane. Selective complexation of one of the enantiomers thus leads to preferential passing of the other enantiomer through the pores and thus to enantiomeric enrichment. This process leads to operational selectivities, α_{op}, as high as 14.5 and 8.2 for phenylglycine (PheGly) and Phe, respectively.[3] These values were, at a basic level, rationalized using steric arguments depicted in Figure 1, since the highest values for α_{op} were found for relatively large substituents. A most surprising result, however, was obtained for Trp, for which $\alpha_{op} = 1.0 \pm 0.1$ was measured.

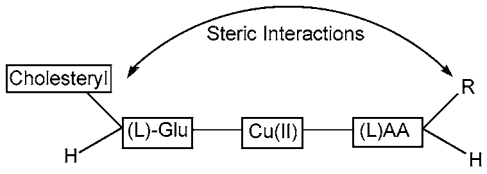


Figure 1. Enantiodifferentiation of amino acid AA based on steric interactions with cholesteryl anchor.

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Thermodynamic data on the enantiodifferentiation obtained by isothermal titration calorimetry showed that the complexation of the amino acid to the cholesteryl-(L)-glutamate−Cu(II) complex is driven by entropic contributions (the reaction is endothermic) and that differences in complexation of enantiomeric amino acids are solely caused by differences in the enthalpy of complexation.[4] This allows for a quantitative study of the complexation by quantum chemical methods, as these are very well suited for obtaining small differences in complexation enthalpies. The present paper aims to present a rational approach to clarification of the remarkable lack of enantioselectivity for Trp via detailed quantum chemical studies.

Despite the importance of blue copper proteins, studies of copper(II) diamino acid complexes have been surprisingly sparse.[5] The paucity of molecular mechanics studies[6] is certainly partially due to the lack of suitable analogues of the highly constrained and unusual metal environments commonly found in metalloproteins.[7] In addition, quantum chemical studies of De Bruin et al. have shown that copper(II) diamino acid complexes display a wide variation of ESP charges in highly similar geometries,[8] which hampers accurate molecular mechanics studies.[9] A systematic density functional study of Gly−Cu(II)−Gly showed that the trans orientation (NH_2 group of one amino acid close to the carboxylate of the other rather than close to the other NH_2 group) is much more stable than the cis orientation and the only configuration that needs consideration.[8] The present investigation studies the other interactions (sterics, Cu(II)$\cdots\pi$ interactions and hydrogen bonding) that determine the relative stabilities of diamino acid Cu(II) complexes. All studies were performed with Gaussian 03.[10] Optimizations were performed with the B3LYP functional with the basis sets 6-31G(d,p) for all atoms except Cu, for which 6-311G(d) was used [which we call 6-31G(d,p)(Cu1)], and followed by single-point B3LYP/6-311+G(d,p) computations on the entire system.

The importance of Cu(II)$-\pi$ interactions can best be seen from the evaluation of energies of conformations that either have or do not have such interactions. A clear example is provided by the complex Gly−Cu(II)−Trp, as displayed in Figure 2. In the top conformer, several atoms of the five-membered Trp ring are 3.0−3.1 Å from the copper atom, and its energy is 1.49 kcal/mol lower than that of the bottom conformer in which the aromatic group is not in close proximity to the Cu(II). This indicates significant Cu(II)$-\pi$ interactions. An even stronger interaction (5.50 kcal/mol) is obtained for stacking of a benzyl group (as in Phe).[11]

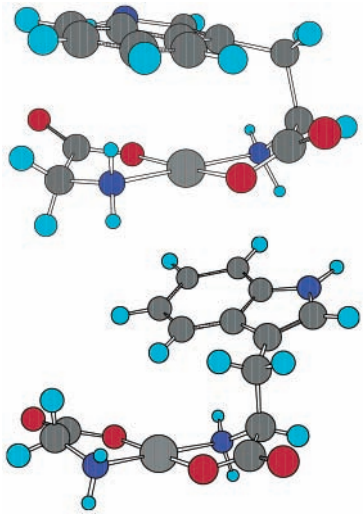

Figure 2. Gly−Cu(II)−Trp complexes with (top) and without (bottom) stabilizing Cu(II)$-\pi$ interactions.

Cholesteryl-(L)-glutamate Cu(II) complexes also display intramolecular interactions of the side chain C═O group of glutamate. The strongest involves hydrogen bonding. If there is no steric hindrance from the side-chain of the other amino acid, near-linear intramolecular C═O$\cdots$H−N hydrogen bonds can be formed, which are relatively short (r(O−N) ∼

(3) (a) α_{op} is defined as: $(\{C^o - C^p\}/C^p)^D \times (C^p/\{C^o - C^p\})^L$ in which C^o is the initial concentration of the D- or L-enantiomer and C^p is the concentration of the enantiomer in the permeate. If $\alpha_{op} = 1$, there is no enantioselectivity; if $0 < \alpha_{op} < 1$, there is a preference for binding the L-enantiomers to the selector; and if $\alpha_{op} > 1$, more D-enantiomers are bound. (b) De Bruin, T. J. M.; Marcelis, A. T. M.; Zuilhof, H., Rodenburg, L. M., Niederländer, H. A. G.; Koudijs, A.; Overdevest, P. E. M.; Van Der Padt, A.; Sudhölter, E. J. R. *Chirality* **2000**, *12*, 627.

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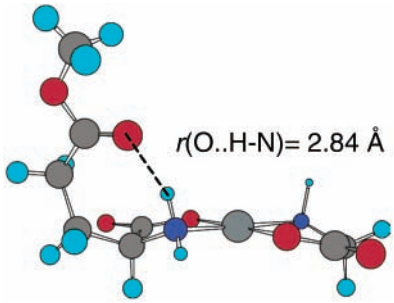

Figure 3. Intramolecular C═O···H−N hydrogen bonding in the glutamate moiety of a Glu−Cu(II)−Gly complex.

2.9 Å) and amount to ∼5−6 kcal/mol stabilization (see Figure 3). Alternatively, and somewhat less stabilizing (stabilization ∼3 kcal/mol), a C═O···Cu interaction can be observed if the glutamate side chain "bends over" a little further, in which *r*(O···Cu) is usually <3 Å.

Given the strength of this hydrogen bonding, it is clear that the steric hindrance provided by the glutamate chain or by the cholesteryl moiety that is attached to the glutamate will hamper any stabilizing Cu(II)−π interactions.

The effect of the cholesteryl moiety was investigated by ONIOM calculations[12] on cholesteryl−(L)-Glu−Cu(II)−Trp and cholesteryl−(L)-Glu−Cu(II)−Phe complexes. In these calculations, the important part of the system (called "the model") is treated at the high level required to give a proper account of all electronic effects of the copper coordination, while the rest of the system is treated in an integrated fashion at a lower level to take into account its effects on the properties of the system.[12] We used the Cu diamino acid complex with the methyl ester of the glutamate as the model that was treated at the "high level" B3LYP/6-31G(d)(Cu1), while HF/3-21G(d) calculations were used as the "low level". From these calculations, it appears that only the first six-membered ring (A-ring) of the cholesteryl moiety can have steric interactions with the side chain of the other amino acid. However, as a result of the rotational freedom of the ester, such interactions will be minimized via rotation of the ester C−O bond. This leads to a more extended overall geometry of the complex with a stronger dipolar character, which would be favorable for embedding in the micelles. As a result, the steric interactions of the cholesteryl complex can be mimicked by the glutamate methyl ester, as displayed in Figure 3.

The competition of stabilizing interactions is evident in the case of (L)-Glu−Cu(II)−Phe complexes (see Figure 4). If the side chains are positioned at the same side of the plane defined by the amino acid heteroatoms (L-Phe), in syn orientation, then it is not possible to have simultaneous C═O···H−N and Cu(II)···π interactions. In the anti orientation that is obtained with D-Phe, this is possible (Figure 4, top left), making complexes of D-Phe much more stable than those of L-Phe, by >5 kcal/mol (precise value dependent on conformational details). As a result, in micelle-enhanced ultrafiltration experiments D-Phe should bind more strongly

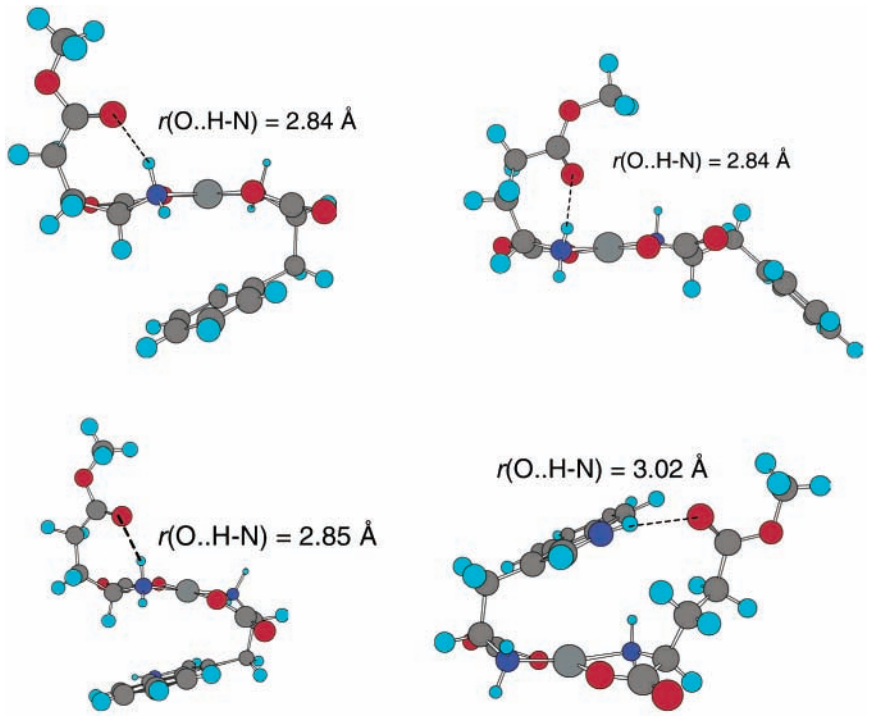

Figure 4. Anti and syn orientations of (L)-Glu−Cu(II)−(D)-Phe (top left), (L)-Glu−Cu(II)−(L)-Phe (top right), (L)-Glu−Cu(II)−(D)-Trp (bottom left), and (L)-Glu−Cu(II)−(L)-Trp (bottom right) complexes, respectively.

to the Cu-containing micelles, and a large and positive value of α_{op} is expected, as indeed observed. This situation applies to all other aromatic side chains, apart from to Trp.

For (L)-Glu−Cu(II)−Trp, a different situation arises. In the anti orientation, simultaneous C═O···H−N and Cu(II)···π interactions can occur, making this a stable complex (Figure 4, bottom left). However, in the syn orientation, Cu(II)···π interactions can be combined with hydrogen bonding if the glutamate moiety is bent slightly backward. This allows a C═O···H−N hydrogen bond [$\angle$O···H−N = 147°; r(N−H···O) = 3.02 Å] to be formed between the glutamate C═O bond and the tryptophan N−H bond (Figure 4; bottom right). Although the resulting geometry is optimal neither for Cu(II)···π bonding nor for hydrogen bond formation, this geometry does as least provide the possibility of simultaneous occurrence of both. As a result, the syn complex is calculated to be only 2.2 kcal/mol higher in energy than the anti complex, which implies that a significantly smaller enantioselectivity is expected in the ultrafiltration experiments, as indeed observed. We attribute the small difference between the experimental enantioselectivity ($\alpha = 1.0 \pm 0.1$) and computational stabilization values to the lack of hydration and micellar effects in the theoretically studied complexes and intrinsic imperfections in the theoretical methods used. The present case study thus displays the power of quantum chemistry in the rationalization of transition-metal-based (chiral) separations of organic compounds.

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