Theoretical Studies of Using Amino Acids as a New Class of Antidote Drugs and their Possible Complexes with Zn^{2+}as Antidote Drugs.

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Abstract

This paper introduces a new class of bidentate ligands as antidote drugs. By semi-empirical AM1 method calculations, we showed that natural amino acids could be used as theoretically good antidote drugs. To reach this goal, we have calculated the stability energies of glycine, alanine, valine, leucine, isoleucine, serine and threonine and their complexes with Zn^{2+} as indicated.

Keywords: Antidote, Bidentate chelators, Natural amino acids.

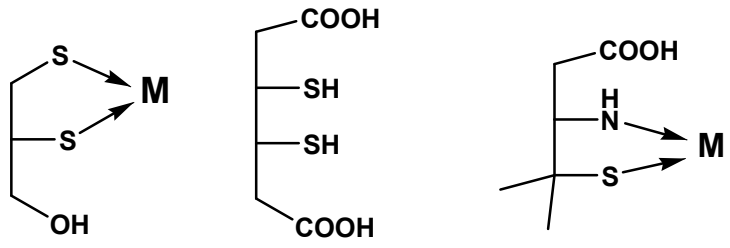
Introduction

In human metabolism complexes have an essential and vital role that control a lot of human metabolism reactios. Poisons often perturb the structure and normal reactivity of vital complexes. So there are two main groups of poisons: strong ligands and heavy metals. In medicinal approach a strong chelator ligands are applied to remove the metal poison. [1] Theoretically as much a complex is more stable; its anti-toxicity properties should be stronger. One of the most important factor in the complex stability is the conformation of chelator ligand.

Commercial antidotes against heavy metals are bidental chelators like penicilamine or succimer. They are tridental ligands which react as a bidental chelator.

In medicinal approach strong chelator ligands are applied to remove the metal poison. [1] They must provide a strong complex with heavy metal to inhibit destroying vital complexes in human metabolism.[2] Commercial antidotes against heavy metals are bidental chelators like dimercaprole (2, 3-dimercaptopropanol) (1), succimer (DMSA) (2) or penicilamine (3). They are polydental ligands which react as a bidental chelator. [3,4] (Figure 1)

Figure 1: Commercial antidote drugs; dimercaprole (2, 3-dimercaptopropanol) (1), succimer (DMSA) (2) or penicilamine (3) as bidental chelators

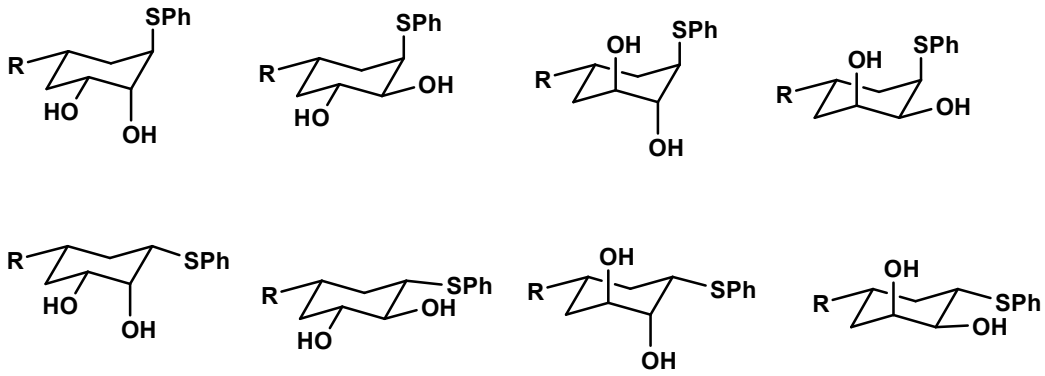


1 **2** **3**

Theoretically as much a complex is more stable; its anti-toxicity properties should be stronger. [5] One of the most important factors in the complex stability is the conformation of chelator ligand. Theoretically if a ligand is rigid, its complex will be more stable and is formed easier. Putting a cyclohexan skeleton provides this rigidity. On the other hand, the stereochemistry of coordination sites is very important.

As we had reported earlier we have synthesized and studied 2-phenylthioalcohols and 2-phenylthiocyclohexanols derivatives [7,12] and investigated some theoretical calculations about their antidote properties as bidentate chelators. [6,13] Later we extended our methodology by adding a second hydroxyl group (third position of complexation) to gives 3-phenylthio-1, 2-cyclohexandiols that provided eight different possible diastereomers and studied their use as such bidentate antidote chelators. [14] (Figure 2)

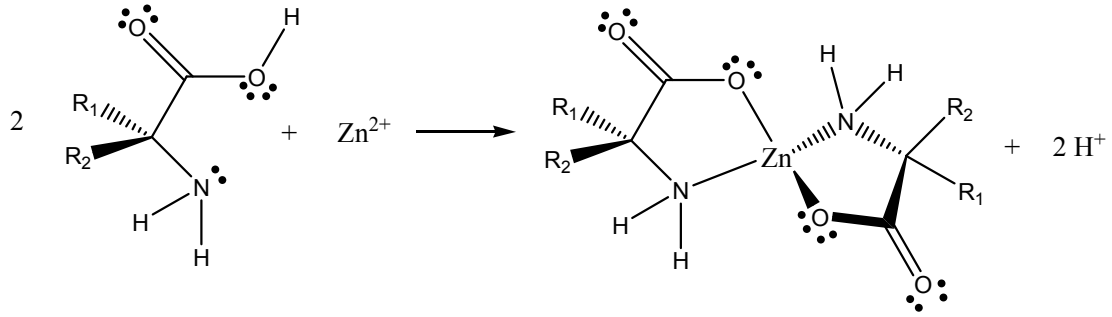
Figure 2. The eight different possible diastereomers of 3-phenylthio-1, 2-diols as bidentate antidote chelators.



We showed that for some diastereomers a competition between 1, 2 and/or 1, 3 complexations could be exist by the possibility of cyclohexane flipping. [14]

Here, with the same method of calculations, we would like to introduce natural amino acids as theoretically good antidote drugs (Figure 3).

Figure 3. The possible complex between amino acids as bidentate antidote and Zn^{2+}.



Calculations

To reach this goal in the first step we decided to calculate the stability energies of natural amino acids and then their complexes with Zn^{2+}. For theoretical calculations we used a Hyper Chem. software in AM1 method. [15]

Results and Discussions

To reach this goal, we have calculated the stability energies of glycine, alanine, valine, leucine, isoleucine, serine and threonine and their complexes with Zn^{2+} that shown in table 1.

Table 1.

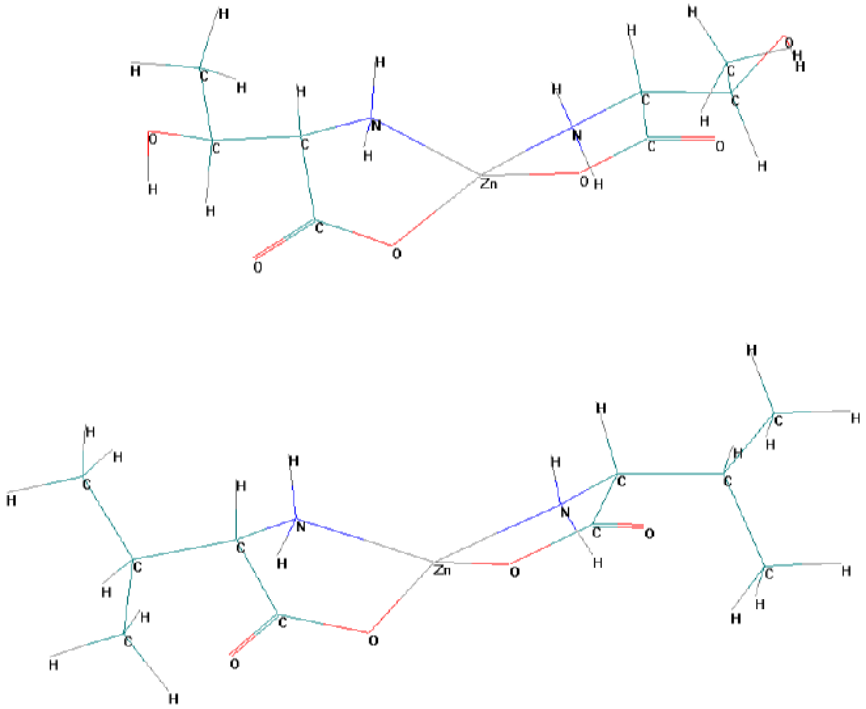
Stability Energies of Some Amino Acids and Their Complexes with Zn^{2+} (KCal./mol.)

Gly	Ala	Val	Leu	Ile	Ser	Thr
-1208.63	-1770.18	-1770.17	-2050.38	-2051.27	-1315.91	-1594.84
-1725.25	-2284.39	-3403.96	-3967.81	-3965.97	-2499.54	-3056.66
$(Gly)_2Zn$	$(Ala)_2Zn$	$(Val)_2Zn$	$(Leu)_2Zn$	$(Ile)_2Zn$	$(Ser)_2Zn$	$(Thr)_2Zn$

As indicated above, while there is not a distinguished difference between Ile and Lue, but Val might be very better than Ala. According to above data, Thr and Ser could be the best chelators.

The most stable calculated conformations of Thr and Ser with Zn^{2+} are shown in figure 4.

Figure 4. The most stable calculated conformations of Thr and Ser with Zn^{2+}.



Acknowledgements

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