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FULL PAPER

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How to identify promising metal scavengers? D-penicillamine with copper as a study case

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Abstract

Therapeutic chelating agents are used to prevent the effects of the metal accumulation. These are molecules that form complexes with transition metals and they are referred here as *metal scavengers*. The main idea of this investigation is to recognize the most relevant chemical features to identify potential *metal scavengers*. D-penicillamine with copper (DPEN-Cu) is used for this purpose. The first requirement that must be fulfilled by a good *metal scavenger* is the exergonicity of the chelating reaction. In the DPEN-Cu case the most likely complexation pathway was found to have ΔG equal to −24.3 kcal/mol. It is desirable that the chelating molecule could also be a free radical scavenger. D-penicillamine is a good free radical scavenger following the hydrogen atom transfer reaction. An additional advantage is that the DPEN-Cu may act as ·OH-inactivating ligand. It is proposed that chelating agents fulfilling these requirements may be a promising candidate to be used in metal chelation therapies as *metal scavengers*.

KEYWORDS
antioxidant, antiradical, chelating therapy, scavenger

1 | INTRODUCTION

Metalloproteins contain metal ions that carry out catalytic, structural, and regulatory roles.[1] In particular copper ions are cofactors of several enzymes that are involved in electron transfer processes and detoxification of oxygen radicals. For this reason, it is considered an essential element for human body.[2] Naturally the liver is the organ that controls the amount of copper in the organism; when the mechanisms to excrete copper are deficient it accumulates to toxic levels. It is well known that an accumulation of Cu in the human body is dangerous, since it is related to oxidative damage of proteins, lipids, and nucleic acids.[3–8] The major genetic disorder of copper metabolism in humans is known as the Wilson's disease.[9–16] In this disease, Cu accumulates in the liver cells and participates in Haber–Weiss reactions producing toxic hydroxyl free radicals that increase the oxidative stress, as shown in the following[17]:

$$Cu(II) + O_2{}^{\cdot -} \rightarrow Cu(I) + O_2$$

$$Cu(I) + H_2O_2 \rightarrow Cu(II) + OH^- + \cdot OH$$

To prevent the effects of the copper accumulation, therapeutic chelating agents are frequently used.[18–24] These are organic or inorganic molecules, which—as their name indicates—form chelates with transition metals. Since the important fact is to remove metals, here such molecules are referred as *metal scavengers* to distinguish them from chelating agents with other purposes.[25] Logically, a good *metal scavenger* must form stable complexes. It is also desirable that such complexes contain more than one metal atom per chelating molecule.

Several *metal scavengers* had been used to treat Wilson's disease.[13–16,26–29] In particular with copper, D-penicillamine (DPEN, Figure 1) is the most widely used for treating this disease around the world.[26–29] It is likely that the DPEN scaffolds could provide efficient Cu(I) and Cu(II)

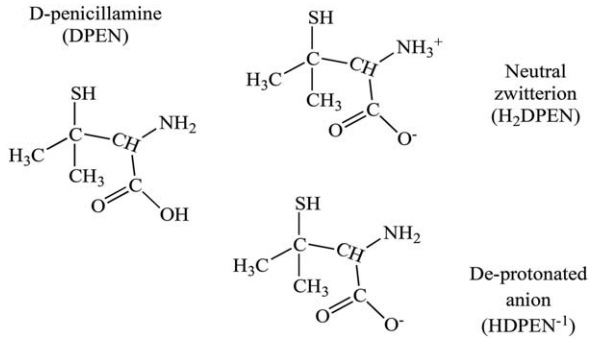


FIGURE 1 Schematic representation of D-penicillamine (DPEN). At physiological conditions (pH = 7.4) two species coexists: neutral zwitterion (H_2DPEN; 76.8%) and de-protonated anion ($HDPEN^{-1}$; 23.2%)

chelators in vivo. It was introduced in 1956[26] but now it is known that it presents some side effects.[30,31] More precisely, DPEN could contribute to increase the neurologic deterioration, which may be due to a lack of its specificity. This motivates investigations to obtain new chelating agents.

Previous theoretical investigation reports the binding analysis of Cu(I) and three different artificial aminoacids (being DPEN one of these amino-acids).[32] Authors' prime interest was to reveal the detailed process of complexation of these molecules with Cu(II). Fundamental and extensive understanding of the binding properties and the energetic of the copper-artificial amino acid complexes were reported, and apparently, there is no doubt about the conformations that authors proposed in that theoretical study as the most likely ones. However, it was not considered the most abundant species of DPEN at physiological conditions; planar structures were not investigated neither mono-dentate compounds; and only the direct chelation mechanism (DCM) was considered, although there are experiments indicating that the coupled-deprotonation-chelation mechanism (CDCM) is a more likely route, that is, the pK_as of ligands lower when bound to the metal.[33,34] In the particular case of DPEN it has been reported that its second and third pK_as decrease as a consequence of the interaction with metals.[35]

In this investigation, DPEN was studied considering all the still unexplored aspects of its copper scavenging activity, aforementioned. They need to be answered to have a good characterization of DPEN, and probably to lead the research for new *metal scavengers*. Since DPEN is widely used to scavenge copper, it has been chosen to identify features that a good *metal scavengers* should have. The idea is to propose key steps to investigate potential *metal scavengers*. Moreover, molecules used in chelating therapy should be also useful as free radical scavengers since free radical scavengers have been recommended as adjutant to the chelator therapy.[18] In this report, the antioxidant properties of DPEN-Cu complexes were also investigated. Moreover, the capacity of DPEN-Cu to act as ·OH- inactivating ligand (OIL)[36] was also explored. OIL species are expected to prevent the damage caused by ·OH by sequestering metal ions from reductants in Haber–Weiss reactions (OIL-1) or by deactivating ·OH immediately as they are formed through Fenton-like reactions (OIL-2). The chelation concept is based on simple coordination chemistry, but the development of *metal scavengers* for chelation therapy involves an interesting process of drug design. The results reported here would be very useful for that purpose.

2 | METHODS

Gaussian 09 code[37] was employed to optimize geometries and analyzed the electronic properties. Initial geometries were fully optimized at M06/LANL2DZ level of theory.[38–45] To verify optimized minima, harmonic analysis was performed and local minima were identified by the absence of imaginary frequencies. The dielectric constant of water was included to simulate a polar environment by the SMD continuum model.[46] Optimization was performed using SMD continuum model. To verify that there is not basis set sensitivity, some geometry optimizations were repeated with 6–311++G(d,p) basis set. We also repeated the calculations with different exchange correlation functionals. Results are reported as Supporting Information, Table 1SI and Table 2SI. As can be seen there are numerical differences in the results, but the trend is independent from the methods and basis sets used.

The acid-base equilibrium of DPEN can be represented as follows:

$$H_3DPEN^{+} \leftrightarrows H_2DPEN \leftrightarrows HDPEN^{-} \leftrightarrows DPEN^{-2}$$

Under physiological conditions (pH = 7.4) two species coexists: neutral zwitterion (H_2DPEN; 76.8%) and deprotonated anion ($HDPEN^{-1}$; 23.2%). Therefore, the potential role of both species as chelating agents was considered in the present study. Cu(II) complexes were modeled in an almost square-planar four-coordinated geometry, which was previously reported to be the most likely configuration in the aqueous phase.[47,48] Conversely, $Cu(I)^{+}$ complexes were modeled in a linear two-coordinated structure that is consistent with previous experimental evidences.[49–51]

Two different chelating mechanisms were considered that have been reported before[52–57]: direct-chelation mechanism (DCM) and coupled-deprotonation-chelation mechanism (CDCM). In addition, the possible roles of DPEN as both monodentate and bidentate ligand have been taken

into account. The general formulas of the corresponding complexes are $[DPEN\text{-}Cu(H_2O)_3]^{2+}$ and $[DPEN\text{-}Cu(H_2O)_2]^{2+}$, respectively. DPEN is either H_2DPEN or $HDPEN^{-1}$. The Gibbs free energies are calculated as follows:

2.1 | DCM

$$DPEN + \left[Cu(H_2O)_4\right]^{+2} \rightarrow \left[DPEN{-}Cu(H_2O)_3\right]^{q} + H_2O$$

$$\Delta G = \left[G\left(\left[DPEN{-}Cu(H_2O)_3\right]^{q}\right) + G(H_2O)\right] - \left[G(DPEN) + G\left(\left[Cu(H_2O)_4\right]^{+2}\right)\right]$$

$$DPEN + \left[Cu(H_2O)_4\right]^{+2} \rightarrow \left[DPEN{-}Cu(H_2O)_2\right]^{q} + 2H_2O$$

$$\Delta G = \left[G\left(\left[(DPEN{-}Cu)(H_2O)_2\right]^{q}\right) + 2G(H_2O)\right] - \left[G(DPEN) + G\left(\left[Cu(H_2O)_4\right]^{+2}\right)\right]$$

2.2 | CDCM

$$DPEN + \left[Cu(H_2O)_4\right]^{+2} \rightarrow \left[DPEN_{(-H+)}{-}Cu(H_2O)_3\right]^{q} + H_2O + H^+$$

$$\Delta G = \left[G\left[DPEN_{(-H+)}{-}Cu(H_2O)_3\right]^{q} + G(H_2O) + G(H^+)\right] - \left[G(DPEN) + G\left(\left[Cu(H_2O)_4\right]^{+2}\right)\right]$$

$$DPEN + \left[Cu(H_2O)_4\right]^{+2} \rightarrow \left[DPEN_{(-H+)}{-}Cu(H_2O)_2\right]^{q} + 2H_2O + H^+$$

$$\Delta G = \left[G\left[DPEN_{(-H+)}{-}Cu(H_2O)_2\right]^{q} + 2G(H_2O) + G(H^+)\right] - \left[G(DPEN) + G\left(\left[Cu(H_2O)_4\right]^{+2}\right)\right]$$

q is equal to 0, +1, or +2, depending if DPEN is H_2DPEN or $HDPEN^{-1}$; $DPEN_{(-H+)}$ is the de-protonated form of DPEN. The Gibbs energies of reaction were calculated considering $\Delta G_{gas}(H^+) = -4.39$ kcal/mol and $\Delta G_{solvation}(H^+) = -265.89$ kcal/mol based on the recommendation of Camaioni and Schwerdtfeger.[58] These values lead to $\Delta G\ (H^+) = -270.28$ kcal/mol in aqueous solution. For CDCM mechanism the proton is removed from the chelation site in each case.

3 | RESULTS AND DISCUSSION

3.1 | Is metal chelation viable?

The most likely chelation sites were identified considering two different chelating mechanisms: DCM and CDCM. To that purpose the Gibbs energies of the complexation reactions were calculated, considering all possible chelation sites in DPEN, that is, the S, N, and O atoms. Figures 2 and 3 show schematic representation of all possible bonding arrangements that were considered for Cu(II) compounds.

Figures 4 and 5 show the optimized structures of all the located Cu(II) complexes. As can be seen in Figure 4, monodentate compounds form Cu—S bond with $HDPEN^{-1}$ while H_2DPEN is bonded through any of the two oxygen atoms. Bidentate structures of Figure 5 show that the most stable structure of $HDPEN^{-1}$ has the copper atom forming a chelate with N and O. H_2DPEN forms two compounds with similar stability, bonded to S,O and O,O.

Table 1 reports the Gibbs free energies for DCM and CDCM considering the most stable structures of Figures 4 and 5. The most exergonic reactions are for bidentate compounds bonding according to both mechanisms (DCM and CDCM). The formation of bidentate compounds is exergonic for $HDPEN^{-1}$ and H_2DPEN (ΔG is equal to −22.9, −24.3, and −15.8 kcal/mol) The reaction with H_2DPEN forming monodentate compounds is exergonic (ΔG equal to −7.1 and −10.3 kcal/mol, DCM and CDCM respectively) but not as much as with $HDPEN^{-1}$ ($\Delta G = -20.4$ kcal/mol, DCM). Up to this point, it can be said that H_2DPEN and $HDPEN^{-1}$ are good *metal scavengers* for copper considering that the formation reactions are exergonic. All systems that present exergonic reactions (with ΔG larger than 10 kcal/mol) will be considered in what follows

As explained in the introduction, it is considered an advantage that metal chelators could also be antioxidants or free radical scavengers. In the following section the capacity of $HDPEN^{-1}$ and H_2DPEN to scavenge free radicals is analyzed and compared with the competing activity as *metal scavenger*.

3.2 | Metal chelator versus free radical scavenger

To analyze the free radical scavenger capacity of $HDPEN^{-1}$ and H_2DPEN, the formal hydrogen atom transfer (HAT) mechanism was considered, which corresponds to the following reaction:

$$*HDPEN + R\cdot \rightarrow DPEN(-H)\cdot + HR$$

DPEN can be $HDPEN^{-1}$ or H_2DPEN; R· represents the free radical; DPEN(-H)· is the dehydrogenated form of DPEN; and HR is the molecule formed with the free radical and H atom. This reaction considers the molecule as a primary antioxidant that reacts directly with the free radical.

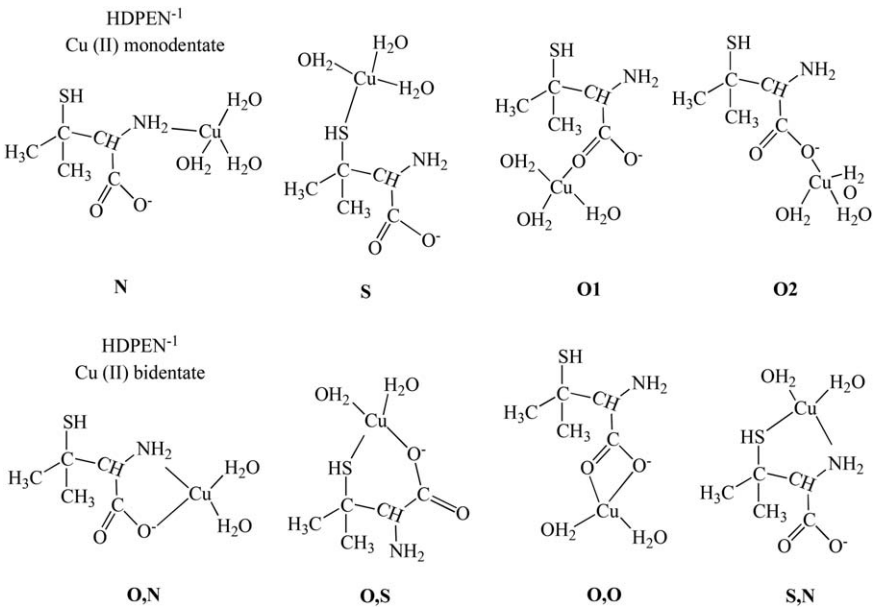


FIGURE 2 Schematic representation of the initial geometries for all possible positions that were considered for Cu(II) compounds, monodentate and bidentate, with DPEN deprotonated anionic molecule ($HDPEN^{-1}$). Levels are for identification purposes and indicate the atoms of $HDPEN^{-1}$ where the copper is bound

Table 2 presents the ΔG values for this reaction, when different free radicals are involved. These values are compared with those reported in Table 1 to evaluate if this molecule is better as *metal scavenger* or as a primary antioxidant.

As expected, the most exergonic reaction is with ·OH. This free radical is very reactive and it will be interacting with every molecule. In fact, the concentration of this free radical in the human body is not very large since as soon as it is produced, it reacts with any other molecule. For this reason it is difficult to analyze the primary antioxidant capacity considering only this free radical. However, it is important to notice that in the presence of Cu(II) and OH·, the reaction with OH· will be thermodynamically preferred.

There are other reactions with free radicals that present similar Gibbs free energies than the chelation reaction with Cu(II). This means that $HDPEN^{-1}$ and H_2DPEN might be also good free radical scavengers or primary antioxidant. Based on these results it can be concluded that this molecule is both, a good *metal scavenger* for copper and also a good primary antioxidant for some free radicals.

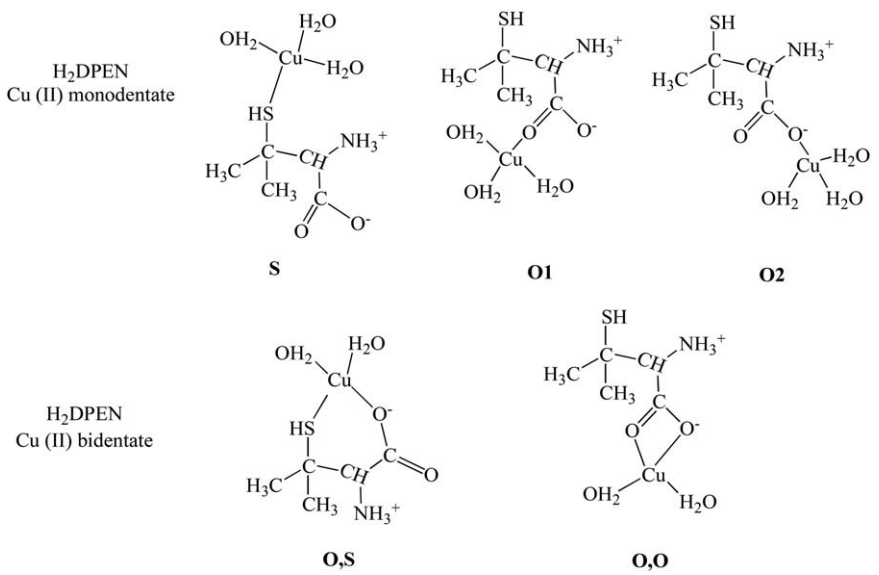


FIGURE 3 Schematic representation of the initial geometries for all possible positions that were considered for Cu(II) compounds, monodentate and bidentate, with DPEN zwitterion neutral (H_2DPEN). Levels are for identification purposes and indicate the atoms of H_2DPEN where the copper is bound

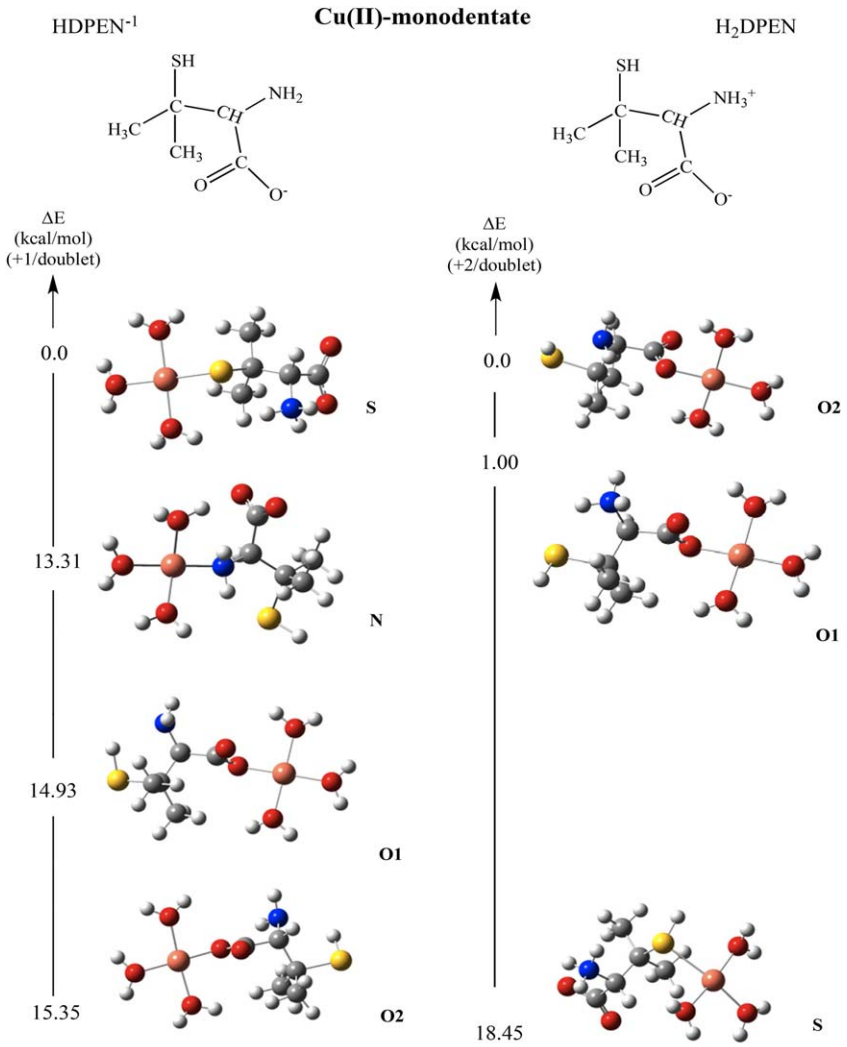


FIGURE 4 Optimized structures of D-penicillamine interacting with Cu(II) forming monodentate products. D-penicillamine as deprotonated anionic ($HDPEN^{-1}$) and neutral zwitterion (H_2DPEN) are included since both are stable at physiological conditions. Energy difference (ΔE) with respect to the most stable structure, global charge and multiplicity are also reported. Levels indicate the atoms where the copper is bound according to Figures 2 and 3

3.3 | ·OH inhibiting ligands (OIL-1 and OIL-2)

To analyze if chelation inhibits metal reduction and, therefore, ·OH production via Haber–Weiss reaction, the structures that present exergonic chelating reactions (five of the structures in Table 1) were considered. For these five structures, the corresponding reduction to Cu(I) was analyzed by calculating the Gibbs free energies with the following equations:

Monodentate complex, Equation 1:

$$DPEN{-}Cu(II)(H_2O)_3 + O_2\cdot^{-1} \rightarrow DPEN{-}Cu(I)(H_2O) + {}^3O_2 + 2H_2O$$

Bidentate complex, Equation 2:

$$DPEN{-}Cu(II)(H_2O)_2 + O_2\cdot^{-1} \rightarrow DPEN{-}Cu(I)(H_2O) + {}^3O_2 + H_2O$$

These results are reported in Table 3. Optimized structures of compounds with Cu(I) are incorporated. The Gibbs free energies for the chelating reactions reported in Table 1 were also included in Table 3 to facilitate quick comparisons. All the reactions were found to be exergonic, which means that the chelation does not inhibit the metal reduction to Cu(I), when the radical anion superoxide ($O_2\cdot^-$) is acting as the reducing agent. Therefore, Cu(II) chelation by DPEN does not prevent the ·OH production via this reaction. In the presence of $O_2\cdot^{-1}$, Cu(II) is reduced to Cu(I) and, therefore, these compounds do not behave as OIL-1 species for copper.

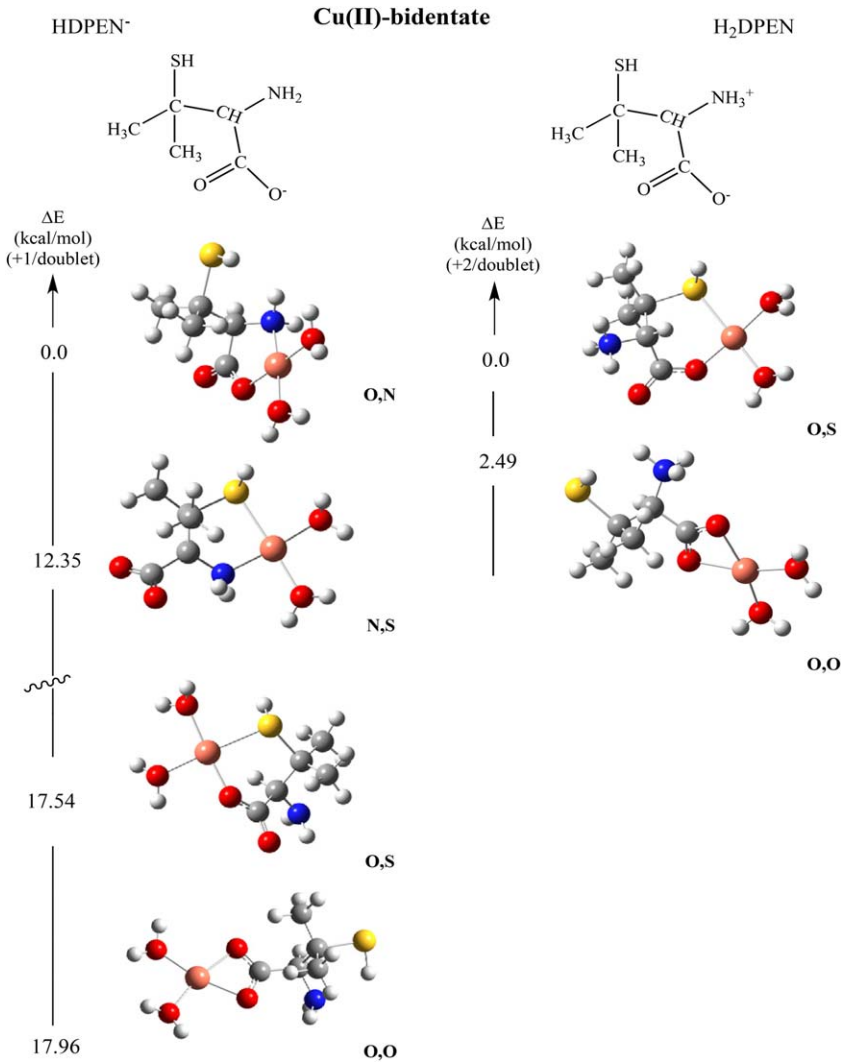


FIGURE 5 Optimized structures of D-penicillamine interacting with Cu(II) forming bidentate products. D-penicillamine as deprotonated anionic ($HDPEN^{-1}$) and neutral zwitterion (H_2DPEN) are included since both are stable at physiological conditions. Energy difference (ΔE) with respect to the most stable structure, global charge and multiplicity are also reported. Levels indicate the atoms where the copper is bound according to Figures 2 and 3

To investigate if DPEN-Cu complexes are able to act as ·OH scavengers (OIL-2) the formal HAT mechanism was considered. Every possible hydrogen atom from the ligand was taken into account and the product lowest in energy was chosen as the most likely one. The corresponding optimized geometries were used to calculate the ΔG values of the HAT process considering two free radicals: ·OH and ·OOH. The obtained results are reported in Table 4, and also de Gibbs free energies for the chelating reactions for a prompt reference. The optimized structures of dehydrogenated compounds are also included.

All the reactions reported in Table 4 are highly exergonic. In fact, the reactions are more exergonic than with free $HDPEN^{-1}$ and H_2DPEN. Based on these results it is possible to say that the presence of Cu(II) increases the antioxidant capacity of $HDPEN^{-1}$ and H_2DPEN. This is a very important result because it implies that H_2DPEN and $HDPEN^{-1}$ have two important functions: they can chelate Cu(II), reducing the health risks

TABLE 1 Gibbs free energies (ΔG(kcal/mol)) for the chelating reactions of the most stable structures

	[DPEN-Cu(II)]·3H_2O (monodentate)			[DPEN-Cu(II)]·2H_2O (bidentate)		
	Atoms bonded to Cu	DCM	CDCM	Atoms bonded to Cu	DCM	CDCM
$HDPEN^{-1}$	S	−20.4	−1.8	N,O	−22.9	−24.3
H_2DPEN	O S	−7.1	−10.3	O,S	−0.3	−15.8

DCM and CDCM are considered.

TABLE 2 Gibbs free energies (ΔG(kcal/mol)) for the HAT reaction considering the free radicals indicated

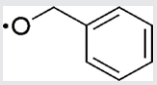
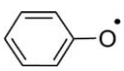
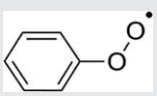
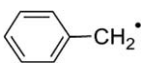
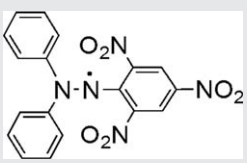
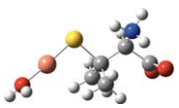
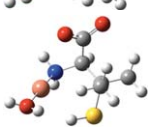
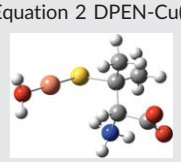
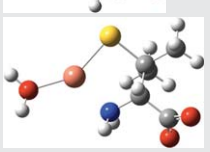
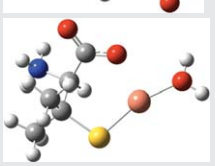
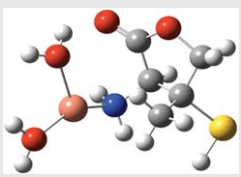
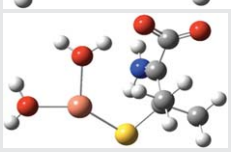
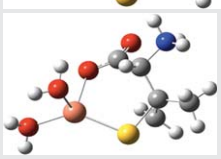
R·	$HDPEN^{-1}$	H_2DPEN
·OH	−36.0	−33.8
·OOH	−7.7	−5.6
$\cdot CH_3$	−24.7	−22.6
	−19.6	−17.5
$\cdot OOCH_3$	−5.9	−3.8
$\cdot NO_2$	−6.2	−4.0
$\cdot CCl_3$	−25.9	−23.8
$\cdot OOCCl_3$	−17.1	−15.0
	−6.1	−3.9
	−5.8	−3.7
	−10.4	−8.3
	−4.1	−2.0

TABLE 3 Optimized structures of compounds with Cu(I) and Gibbs free energies (ΔG(kcal/mol)) for the metal reduction (Equations 1 and 2)

Optimized structure DPEN-Cu(I)(H_2O)	ΔG (chelation)	ΔG [Cu(II) → Cu(I)]
Equation 1 DPEN-Cu(II)$(H_2O)_3$ (monodentate)		
	−20.4	−27.5 (1.5 → 0.2)
	−10.3	−24.7 (0.7 → 0.2)
Equation 2 DPEN-Cu(II)$(H_2O)_2$ (bidentate)		
	−22.9	−13.1 (0.9 → 0.5)
	−24.3	−4.9 (0.6 → 0.1)
	−15.8	−12.7 (0.6 → 0.1)

Gibbs free energies for the chelating reactions reported in Table 1 are included for a prompt reference. Mulliken atomic charges (in brackets) for Cu are reported for Cu(II) and Cu(I) compounds.

TABLE 4 Optimized structures of the deprotonated molecules, Gibbs free energies (ΔG(kcal/mol)) for the HAT reaction with ·OH [ΔG(·OH)] and ·OOH [ΔG(·OOH)]

Optimized structure	ΔG (chelation)	ΔG (·OH)	ΔG (·OOH)
[DPEN-Cu(II)]·$3H_2O$ (monodentate)			
	−20.4	−48.0	−19.7
	−10.3	−46.4	−18.2
[DPEN-Cu(II)]·$2H_2O$ (bidentate)			
	−22.9	−45.7	−17.4
	−24.3	−52.5	−24.2
	−15.8	−39.1	−10.8

Gibbs free energies for the chelating reactions reported in Table 1 are also included for a prompt reference.

associated with high concentrations of this ion; and can be efficient free radical scavengers both as free molecules and as DPEN-Cu. It can be concluded that DPEN-Cu complexes are good ·OH inhibiting molecules (OIL-2).

Another key factor to have a good free radical scavenger is the toxicity that should be low.

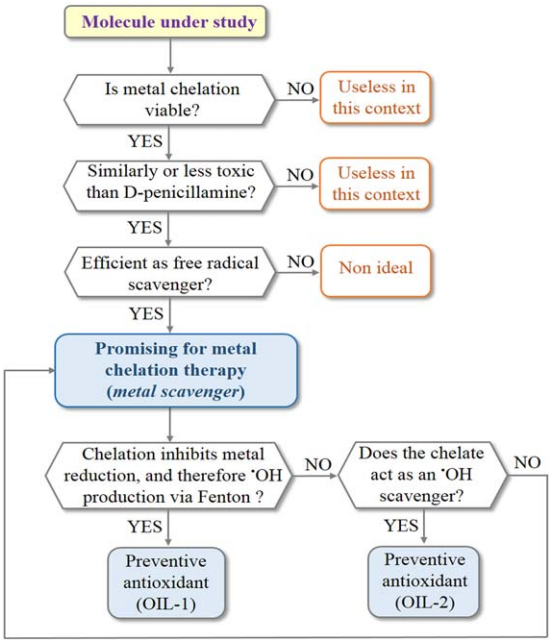
3.4 | Toxicity

Several descriptors were estimated to predict the toxicity of DPEN. To that purpose the Toxicity Estimation Software Tool (T.E.S.T.), version 4.1, was used. This program allows predicting several toxicity descriptors by means of quantitative structure activity relationships (QSAR). Those estimated here are:

- LD_{50}: amount of chemical (mg) per kg of body weight that leads to the death of the 50% of rats, after oral ingestion;
- M: this is known as the Ames mutagenicity, and is used to predict carcinogenic potential. A chemical compound is considered mutagenic if it causes growth of a colony of *Salmonella typhimurium*;
- LC_{50}^{F}: concentration in water (mg/L) that leads to the death of 50% of *fathead minnow*, after 96 h;
- LC_{50}^{D}: concentration in water (mg/L) that leads to the death of 50% of *Daphnia magna*, after 48 h;
- IGC_{50}: concentration in water (mg/L) that inhibits 50% of growth for *Tetrahymena pyriformis*, after 48 h.

To compute these descriptors there are different methods. The one used here was the consensus method. It predicts toxicity by the averaging the toxicities predicted using various QSAR methodologies, and considering their applicability domain.[59] The accuracy and coverage of this method is usually higher than those achieved with other methodologies.

The values of the toxicity descriptors for DPEN were: $LD_{50} = 3449.88$, $LC_{50}^{F} = 1561.55$, $LC_{50}^{D} = 1.76$, $IGC_{50} = 169.58$, and M = positive (0.68). The most problematic descriptor seems to be mutagenicity. Thus, ideally, better metal chelators should retain (at least) the chelating ability of this compound but they should have negative mutagenicity.



SCHEME 1 Flow chart showing the questions to be answered to recognize a good *metal scavenger*

3.5 | Chemical features of metal chelators

The main idea of this investigation is to propose some key chemical features that are relevant to identify potential *metal scavengers*. Molecules used in chelating therapy should be also useful as free radical scavengers since a free radical scavenger might be recommended as adjutant to the chelator therapy. Following these ideas, Scheme 1 presents a flow chart with the questions that needs to be answered to recognize a good *metal scavenger*. The two first questions allow distinguishing a promising molecule as *metal* scavenger.

Once this point is established, it is important to investigate the capacity to inhibit ·OH induced damage. As pointed out before in this report, $HDPEN^{-1}$ and H_2DPEN are good *metal scavengers* for copper, efficient as free radical scavengers and also useful as preventive antioxidants acting as OIL-2 species. It is proposed that this chart can be followed to investigate molecules as good chelating agents with potential use in therapies to deal with metal overload.

4 | CONCLUSIONS

D-penicillamine (DPEN) was used as a study case to explore the most relevant chemical features that are expected from molecules that are potential candidates as *metal scavengers*. This investigation was performed using copper as the target metal.

Logically, the first requirement that must be fulfilled by a good *metal scavenger* is the ability of yield metal complexes through exergonic reactions, under physiological conditions. In the DPEN case the most likely complexation pathway was found to have ΔG equal to -24.3 kcal/mol.

It would also be desirable, albeit not mandatory, that the chelating agent also behaves as a free radical scavenger. In this way there would be no need to implement a combined therapy involving more than one active molecule. DPEN is also a good free radical scavenger according with the HAT mechanism.

In addition, it would be advantageous that DPEN-Cu chelating complexes may act as ·OH inactivating ligand, thus inhibiting the oxidative damage induced by this radical. Copper complexes with DPEN are not efficient antioxidants acting as OIL-1 but they are useful as preventive antioxidants acting as OIL-2.

It is proposed that chelating agents fulfilling all the requirements shown on Scheme 1 may be a promising candidate to be used as *metal scavengers* in metal chelation therapies.

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