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Computational Comparison of Cation Coordination to Human Prion Peptide Models

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The coordination of the cations Cu(II), Co(II), Rh(III), Ir(III), Ni(II), Pd(II), Pt(II), and Zn(II) to the copper-binding octapeptide region in the human prion protein has been compared through structural optimization. The initial coordination mode used in the calculations is a five-coordinated mode obtained from previously published crystallographic data for Cu(II). The computational results show that, among these cations, the coordinations of Co(II) and Rh(III) are the most similar to that of Cu(II). The cations Ni(II), Pd(II), and Pt(II) prefer a four-coordinate square-planar coordination by the peptide ligand. The paramagnetic Co(II) ion with its large quadrupole moment is not a good substitute for Cu(II) to be used in NMR spectroscopic studies of the coordinated peptide region. Rh(III) has more attractive NMR spectroscopic characteristics than Cu(II) and Co(II) and may represent a suitable substitute for Cu(II) in these types of studies. Some preliminary experimental studies using NMR spectroscopic methods indicate that Rh(III) coordinates the copper-binding octapeptide region of the human prion protein, although further studies are required to determine the mode of interaction in detail.

Introduction

Copper has an important role in the body as a trace element, and it functions as a cofactor in many enzymes. The delicate copper balance in the body is governed by a complicated system of proteins. The cytoplasmic copper ion concentration is below 10^{-18} M.[1] Copper is a cofactor in many oxygen-processing enzymes, such as cytochrome oxidase and superoxide dismutase. Several proteins are needed as chaperones in copper transport and storage. Two proteins that are connected to neurodegenerative diseases have the ability to bind copper.[2] The amyloid precursor protein has been reported to bind copper and is related to Alzheimer's disease. In addition, the prion protein is associated with various prion diseases, such as Creutzfeldt−Jakob disease, BSE, and scrapie.[3−6]

Prion diseases are connected to the conversion of the naturally occurring prion proteins, PrP^C, into misfolded conformers, PrP^{Sc}. During the conversion process, the prion changes from a mainly α-helical structure to one more dominated by *β*-sheets. The exact conversion mechanism remains unknown, but it has been shown that PrP^C has the ability to bind copper, whereas PrP^{Sc} does this to a lesser degree or not at all. The binding of copper takes place in the unstructured N-terminal region of the prion protein, where also the octapeptide sequence PHGGGWGQ is repeated four times consecutively between the amino acids 60 and 91. This fragment has been shown to coordinate up to four Cu(II) ions in the PrP^C form. Cu(II) ions also bind to a region between the residues 90 and 115.[7] The ability to bind copper ions could be related to the function of the prion protein. It is possible that the protein either participates in copper transportation or displays antioxidant activity. A deeper insight into the coordination of the prion protein to copper ions can provide a better understanding about prion-related diseases.

The binding modes of copper in the N-terminal region remain unknown. It has been established that the presence of copper leads to a more ordered structure of the N-terminal

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region. According to an X-ray study,[8] HGGGW is the fundamental binding unit in the octapeptide region. In the HGGGW−Cu^{2+} complex, the His imidazole and its neighboring Gly residues are identified as ligands. The role of the subsequent Trp residue in the crystal structure is more indirect; it hydrogen bonds a water molecule, which, in turn, is axially coordinated to the copper ion. A square-pyramidal complex is thus formed with three nitrogen and one oxygen equatorial ligands and an axial water molecule. The proximity of the Trp residue to the metal ion was also indicated in an NMR spectroscopic study, but the interaction was not fully characterized.[9] Although some spectroscopic studies support the crystallographic data, there are also contradictory results and it is not clear if the interaction with the Trp residue is as significant in solution as in the crystal structure.[8−13] Ongoing molecular dynamics simulations in this group are focused on the interaction of Cu(II) with this structurally more flexible region of the peptide.[14] Electron paramagnetic resonance (EPR) studies of the solution structure indicate that there are three nitrogen ligands, and these are the N_δ in the His imidazole and the deprotonated amides of the two subsequent Gly residues.[8] A study of the role of the Gly residues in the octapeptide region shows that replacing the Gly residues by other amino acids destabilizes the Cu^{2+} complex.[15]

The prion protein appears to be highly specific for Cu^{2+}.[16] Somewhat opposing results on the binding ability of Ni^{2+}, Zn^{2+}, and Mn^{2+} can be found in the literature.[17,18] One study states that Mn^{2+} does not bind to the octapeptide region,[17] whereas another study reports that these cations can be coordinated by the octapeptide region, although with lesser affinity than Cu^{2+}.[18] Viles and coauthors[19] performed a survey of diamagnetic probes for Cu^{2+} binding to the prion protein to be used in ^1H NMR spectroscopic studies. According to their work, Pd^{2+} was able to form diamagnetic complexes with models of the octapeptide region, but the resulting structure is different from the crystal structure[8] known for HGGGW−Cu^{2+}. The other diamagnetic probes Ni^{2+}, Pt^{2+}, and Au^{3+} did not form square-planar complexes with the octapeptides. Viles and coauthors[20] also used ^1H NMR spectroscopy for investigating the binding of Cu^{2+} to the prion protein by using Ni^{2+} as a probe. However, this study focused on the region of the prion protein between the residues 90 and 126 and not the octapeptide region.

NMR spectroscopy is a powerful tool for the determination of biomolecular structures.[21] Detailed information about the structure is essential for elucidating the function of a biomolecule. The potential of NMR spectroscopy in the investigation of copper-binding biomolecules is limited by some disadvantages of Cu(II). Cu(II), a d^9 ion, is paramagnetic, and the unpaired electron affects both the chemical shift and relaxation rates irrespective of the nucleus under study. On the other hand, Cu(I) is diamagnetic and more suitable for NMR spectroscopic studies. Another disadvantage of copper is the relatively large quadrupolar moment of the ^{63}Cu nucleus, which in most chemical environments leads to very broad signals in direct copper NMR spectroscopic experiments. The observation of multiple couplings or small changes in the chemical shift is therefore unlikely.[22,23]

Because of the various difficulties encountered when using Cu(II) in NMR spectroscopy, it is of interest to identify a substitute for experimental model studies. This task is complicated by the prion protein showing selectivity for Cu(II).[16] A good substitute should be coordinated in a fashion similar to that of Cu(II) ions but should be more suitable for NMR spectroscopic studies. Of particular interest is the suitability for ^1H and ^{13}C NMR spectroscopy, as well as multinuclear spectroscopy. Diamagnetic nuclei are therefore appropriate substitutes, thus avoiding the paramagnetic effects of shifts and line broadening. The peptides HGGG and HGGGW are used as models when comparing the coordination of different substitute cations. Because the structural role of the Trp residue may be indirect and also differ in solution in relation to the known crystal structure, the shorter peptide, HGGG, may represent a sufficient model of the copper-binding region. The initial structures were taken from crystallographic data for the HGGGW−Cu^{2+}−$3H_2O$ complex.[8] The atomic coordinates were gratefully obtained directly from the authors. The segment HGGG was also used in an earlier computational study of Cu(II) coordination,[24] where different coordination modes of Cu(II) to the HG and HGGG peptides were compared. It was recognized that the most stable neutral configuration corresponded to the coordination mode observed in the crystallographic work and EPR spectroscopic studies.

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The scope of this study on a more fundamental level is to study the differences in the coordination of several cations, e.g., Co(II), Rh(III), Ir(III), Ni(II), Pd(II), Pt(II), and Zn(II), to the copper-binding octapeptide region in the human prion protein. All cations were included for the sake of completeness in the comparison, regardless of their NMR spectroscopic properties. Interestingly, Co(II) also exists in the literature as a substitute for Cu(II) in other kinds of systems, despite its poor NMR spectroscopic properties.[25,26] The trivalent Ir(III) and Rh(III) were chosen instead of their divalent counterparts because the trivalent oxidation state is a more stable oxidation state in an aqueous solution. The results are then used when considering the suitability of these cations as possible substitutes for Cu(II) in NMR spectroscopic studies of the copper-binding octapeptide.

A preliminary and exploratory NMR spectroscopic study was also made in order to investigate the binding of the best Cu(II) replacement ion to the copper-binding octapeptide region of the human prion protein.

Computational Methods

The calculations were made using *Gaussian 03*.[27] The geometries were optimized at the B3LYP level of theory using the basis set 6-31G(d). The Stuttgart-group effective core potentials (ECPs) MDF and MWB were used for the metal atoms.[28,29] The ECPs were used to replace 10 core electrons in the atoms. The pseudopotentials used are relativistic or quasi-relativistic. The MDF ECPs were available for cobalt, copper, nickel, and zinc, whereas for iridium, platinum, palladium, and rhodium the MWB ones were used. The relative energies of the optimized structures were not analyzed because of the complexity of the potential energy surface (PES) for these complicated many-atom, low-symmetry systems, where a large number of local minima are expected to exist. The main goal has been to compare representative coordination geometries. An investigation of the PES of the HGGG−Cu^{2+} system by geometrically optimizing 25 different initial structures gave rise to nine different local minima on the PES, whose total energies are all within 0.9 kcal/mol in total energy. While the geometries of these nine structures show some variation, mainly in the peptide chain, they are, nevertheless, rather invariant in the cation coordination.

The vibrational frequencies were evaluated in order to characterize the stationary points obtained. Some of the calculations were made in a vacuum. Solvent effects were taken into account by including explicit water molecules as well as modeling the surrounding solvent using the polarizable continuum model (PCM)[30] with United Atom Topological Model UAHF.[31] A dielectric constant of 78.39 was used to characterize the aqueous solvent. Explicit water molecules were included in some structures in order to study the effects of water coordination.

Results and Discussion

Several factors are of importance when considering other cations coordinating to the octapeptide region instead of Cu(II). Co(II) has previously been used as a substitute for Cu(II) in other systems[25,26] and is thus suspected to exhibit structural features similar to those of Cu(II) also in this case. Viles and coauthors claim, through their ^{1}H NMR and CD spectroscopy studies, that Ni(II) can be used as a probe for Cu(II) binding to the prion protein.[20] However, another copper-binding region of the human prion protein, the residues between 90 and 126, has been studied in that case. Subsequently, the use of Ni(II) as a probe is more justified because Cu(II) forms a square-planar complex in this region, which is also the geometry of choice for Ni(II).

The structural preferences of the cations arise from the differences in electronic structure, number of d electrons, and d-orbital ligand-field splitting. For example, the four-coordinate complexes can have strong preferences toward either a square-planar or tetrahedral configuration. However, the fact that some coordination types are more preferred by no means excludes other possibilities. They should rather be regarded as the ones that in many cases will result in the lowest energy, but other factors, such as the shape or conformational restrictions imposed by the ligand, may influence coordination as well.

The chemical differences of the cations must also be taken into account. For example, in this case it must be noted that all cations are not able to deprotonate the amide group, which is an unavoidable step on the way to obtaining the desired coordination structure. All of the cations Co(II), Cu(II), Ni(II), Pd(II), Pt(II), and Zn(II) have been shown to be capable of deprotonating the amide group.[32,33] The strength of this ability descends in the order Pd(II) (2) > Cu(II) (4) > Ni(II) (8) > Co(II) (10) for some of the cations, where the pK_a values are given in parentheses.[32] There are some disagreements on the deprotonating ability of Zn(II); some studies claim that Zn(II) cannot deprotonate the amide group, whereas others confirm its deprotonating ability.[32] Because of the lack of experimental data, the cations Rh(III) and Ir(III) can only be presumed to behave similarly as their neighbors in this aspect.

The models HGGG and HGGGW and a longer HGGGW model were used to represent the Cu(II)-binding region, and

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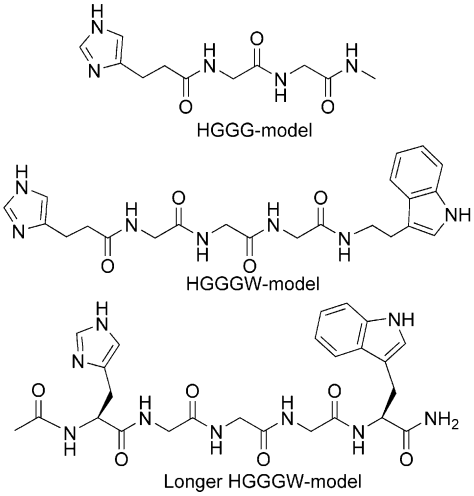

Figure 1. HGGG, HGGGW, and longer HGGGW models.

they are shown in Figure 1. Between the pH values of 6.0 and 9.2, the protonation state of His is ϵ.[34] The coordination mode and the initial configuration were chosen according to previously published crystallographic data.[8] The coordination mode is characteristic of Cu(II) ions because Cu(II) ions show a strong preference for nitrogen ligands, especially the His imidazole.

Structural Comparison in a Vacuum. The crystal structure of HGGGW−Cu^{2+} with three water molecules was used for the starting configuration.[8] The same starting configuration resulted in markedly different optimized geometries for the eight cations. The optimized structures are displayed in Figure 2. The bond lengths and angles are also tabulated in Table 1 in order to facilitate the comparison. The frequency calculations show that these structures have no imaginary frequencies; i.e., they are local minima on the complicated PESs. However, they are unlikely to be global minima. Only Cu(II), Co(II), Zn(II), Ir(III), and Rh(III) maintain the coordinated water molecule in their optimized structures. When the angles and bond lengths around the cations are compared, the structures of Co(II) and Rh(III) are those most similar to that of Cu(II). The coordination geometry around Zn(II) is tetrahedral, which is typical for Zn(II). One of the ligand−cation−ligand angles marked in the figure is relatively close to 180°. The other ligand−cation−ligand angle also marked in the figure is significantly smaller. The water molecule is positioned in such way that a nearly perpendicular angle is formed between the water oxygen atom, the cation, and the carbonyl oxygen atom. The coordination geometry can be interpreted as trigonal-bipyramidal. The other two water molecules have reoriented themselves so that they are stabilized by hydrogen bonding to other parts of the peptide. The structure with Ir(III) is somewhat similar but more square-pyramidal in its geometry. The other cations prefer a coordination mode that only includes the peptide as a tetradentate ligand. In the structure with Zn(II), the coordination number is also 4 because the carbonyl oxygen atom no longer participates in coordination. The structures with Ni(II), Pd(II), and Pt(II) display very similar characteristics. The water molecules have moved to interact with the backbone carbonyl oxygen atoms through hydrogen bonding. The coordination geometry around the cation is close to square-planar. A trend may be observed in increasing bond lengths to the cation as the size of the cation grows.

With the larger peptide models HGGGW and longer HGGGW, it is possible to model the orientation of the Trp residue. The optimized structures are displayed in Figure 3. This figure does not contain bond lengths and angles in order to maintain a reasonable degree of clarity. Such data can instead be found in Table 1. The axially coordinated water molecule hydrogen bonds to the indole NH hydrogen in these models. The hydrogen bonding of the remaining water molecules differs in the two structures of the shorter and longer peptide models. There are many possibilities for the orientation of the water molecules, and the located structures are only one local minimum on each PES. It is clear that the two structures with the shorter and longer peptide models have slightly different coordination geometries around Cu(II) because the differently placed water molecules cause the peptide to fold somewhat differently.

When the Cu(II) ion interacts with the Trp residue through a hydrogen-bonding water molecule, the binding site is likely to be more specific than that in the case of the peptide interacting with cation only through the His and Gly residues. The role of the Trp residue at the binding site for Cu(II) still remains unclear in solution structures of the complex. The high specificity of the binding site for Cu(II) ions[16] could easily be explained by the necessity of being able fit in this five-coordinated pocket. However, it is possible that the tetradentate coordination to the protein, through electrostatic and electronic prerequisites, also creates sufficiently specific coordination of the binding site.

The interaction energies between the cations and the peptide model showed, as expected, significant differences between the divalent and trivalent cations. The divalent cations had interaction energies around 800 kcal/mol, whereas those of the trivalent cations were approximately 1400 kcal/mol. The supplementary data section can be consulted for further details on these results.

Structural Comparison Using PCM. In this series of calculations, slightly modified versions of the optimized structure from the previous vacuum calculation were used as starting structures. All three water molecules were no longer included in these calculations. The criterion of selection was as follows: If the oxygen atom in a water molecule was coordinated to the cation, then this water molecule was included in the PCM calculations. Application of this criterion upon modification of the structures resulted in Cu(II), Co(II), Ir(III), Rh(III), and Zn(II) models with one water molecule, whereas the models with the other cations included no explicit water. The results are displayed in Figure 4 as well as Table 1. The PCM calculations were performed in addition to the vacuum calculations in order to model the effects of the surrounding bulk. The use of PCM including the dielectric constant of water results in a damping of

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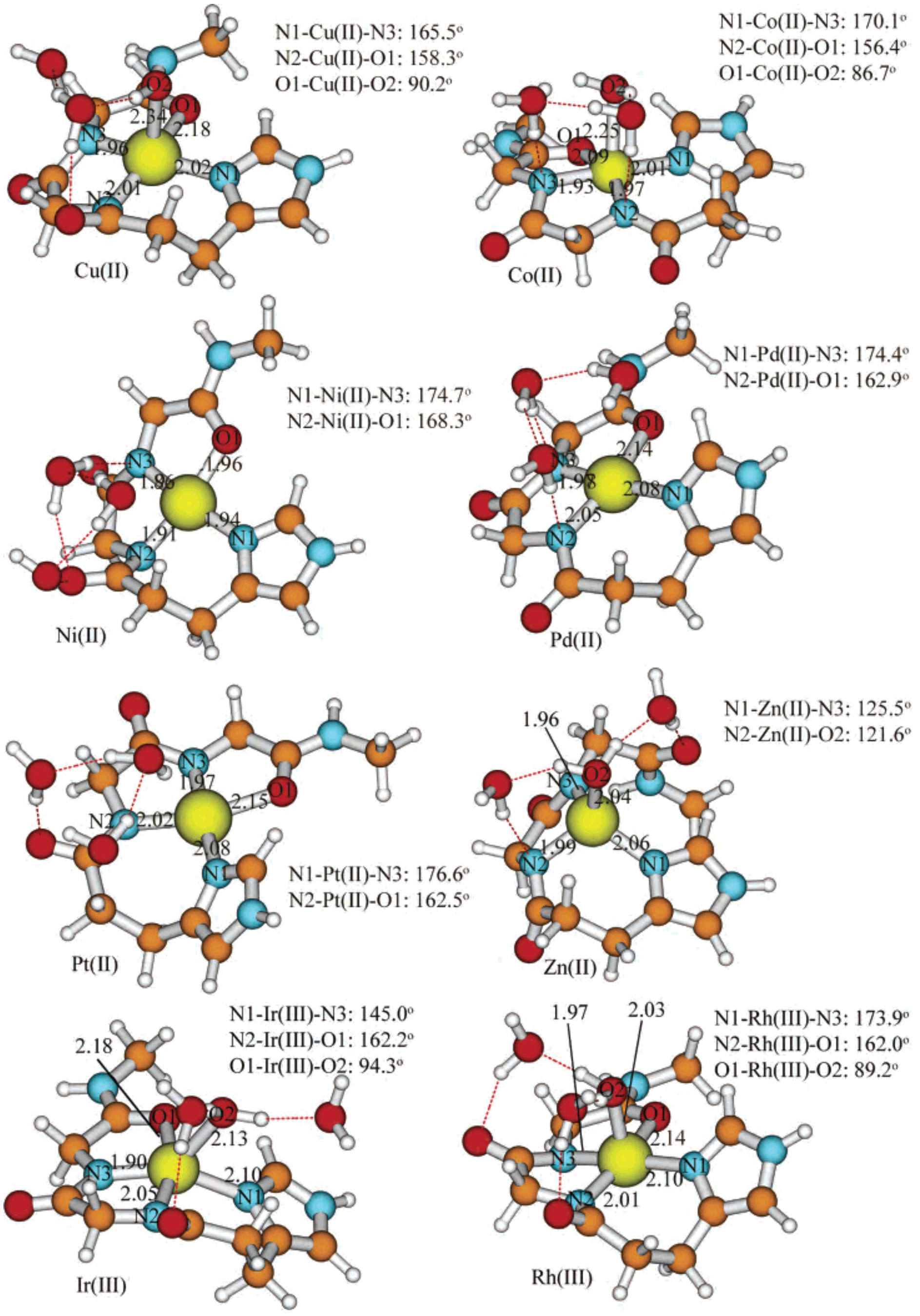

Figure 2. Optimized structures of metal ions coordinated by the HGGG model in a vacuum. The marked bond lengths are in Ångströms and the angles in degrees.

electrostatic interactions in the structural models. A direct consequence is that the PES becomes much flatter. This is also observed in the stage of frequency analysis, where most optimized structures obtained formally are transition states rather than local minima. Earlier studies have reported solvent effects on the structure of peptides.[35,36] These studies conclude that the results in PCM and the gas phase differ significantly and that PCM is a better model than gas-phase calculations. This conclusion was drawn on the basis of better coherence with experimental results.

Also in this study, the use of PCM appears to have a significant effect on the coordination geometries, most notably on the ones containing water. One difference is that, in PCM calculations, Zn(II) becomes five-coordinated. The carbonyl oxygen atom twists to coordinate to Zn(II), thereby forming a structure that more closely resembles that of Cu(II). In the structure with Cu(II), it can be noticed that the distance to the water oxygen atom is significantly longer. A comparison of the angles shows that the coordination geometry around Cu(II) now more resembles square-pyramidal rather than trigonal-pyramidal. In the Co(II) structure, the distance to the water oxygen atom is not notably affected. However, the bond angles show that the structure has changed quite

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Table 1. Bond Lengths and Angles around the Cation in the Optimized Structures[a]

structure	N1−M^{m+}	N2−M^{m+}	N3−M^{m+}	O1−M^{m+}	O2−M^{m+}	N1−M^{m+}−N3	N2−M^{m+}−O1	O1−M^{m+}−O2
				Experimental Results				
HGGGW−Cu^{2+}	1.99	2.00	1.92	2.07	2.38	163.3	162.4	85.0
				Results with a Vacuum				
HGGG−Cu^{2+}	2.02	2.01	1.96	2.18	2.34	165.5	158.3	90.2
HGGG−Co^{2+}	2.01	1.97	1.93	2.09	2.25	170.1	156.4	86.7
HGGG−Ni^{2+}	1.94	1.91	1.86	1.96		174.7	168.3	
HGGG−Ir^{3+}	2.10	2.05	1.90	2.18	2.13	145.0	162.2	94.3
HGGG−Pd^{2+}	2.08	2.05	1.98	2.14		174.4	162.9	
HGGG−Pt^{2+}	2.08	2.02	1.97	2.15		176.6	162.5	
HGGG−Rh^{3+}	2.10	2.01	1.97	2.14	2.03	173.9	162.0	89.2
HGGG−Zn^{2+}	2.06	1.99	1.96		2.04	125.5		
HGGGW−Cu^{2+}	1.99	2.00	1.94	2.18	2.63	168.5	160.8	97.0
HGGGW−Pt^{2+}	2.08	2.02	1.98	2.15		177.0	161.9	−
longer HGGGW−Cu^{2+}	2.03	1.99	1.94	2.19	2.45	160.0	160.8	85.8
				PCM Results				
HGGG−Cu^{2+}	2.02	2.00	1.93	2.13	2.47	164.6	162.2	87.4
HGGG−Co^{2+}	2.00	1.98	1.89	2.02	2.28	169.3	163.7	89.8
HGGG−Ni^{2+}	1.96	1.89	1.84	1.94		170.7	168.0	
HGGG−Ir^{3+}	2.06	2.04	1.90	2.16	2.20	131.3	162.9	90.5
HGGG−Pd^{2+}	2.09	2.03	1.96	2.11		173.8	163.1	
HGGG−Pt^{2+}	2.09	2.04	1.98	2.12		173.8	163.2	
HGGG−Rh^{3+}	2.12	2.02	1.95	2.13	2.07	164.6	162.9	89.1
HGGG−Zn^{2+}	2.04	2.01	1.98	2.41	2.16	136.7	158.5	77.7

[a] The bond lengths are in angstroms and the angles in degrees. N1 denotes the Nδ of the His imidazole, and N2 and N3 are the deprotonated amide nitrogen atoms of the subsequent Gly residues. O1 is the carbonyl oxygen atom, whereas O2 represents the water oxygen atom. M^{m+} denotes the cation.

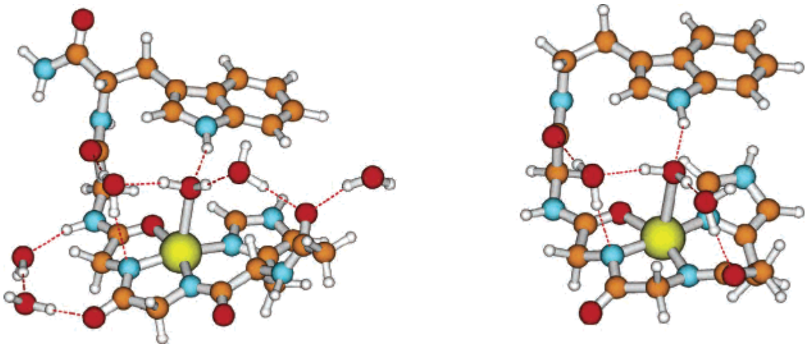

Figure 3. Optimized structures of Cu(II) coordinated by the longer (left) and shorter (right) HGGGW model in a vacuum.

significantly. The Rh(III) structure is very similar to the Cu(II) one. The most significant difference is the much shorter bond to the water oxygen atom in the case of Rh(III).

A computational study aimed at solvation effects on the alanine dipeptide[35] reported such effects on specific types of bonds. Using PCM, the exposed N−H and C═O bonds became longer, while the core HN−CO peptide bonds became shorter. Also, it was observed that the amide bridge became more planar. In the systems studied here, no general trend could be observed when comparing bond distances around the cations; some bonds are slightly longer and others slightly shorter using PCM as compared to a vacuum. However, a trend similar to that in the case of the alanine dipeptide could be noticed in N−H and C═O bonds becoming longer using PCM. The N−H and C═O bonds in the systems here can also be characterized as "exposed", when the carbonyl acting as a cation ligand is excluded. Both of these types of bonds became on average of 0.014 Å longer using PCM. The N−H and C═O bond lengths are displayed in Table S2 in the Supporting Information. When a water molecule is hydrogen bonded to a carbonyl oxygen atom, the C═O bond is significantly longer than a C═O bond not interacting with a water molecule. When this is compared with the effect of PCM on C−H bonds, it could be noticed that these were only marginally affected. The reason for N−H and C═O bonds being effected more strongly can be attributed to the more polar nature of these bonds. Because using PCM weakens electrostatic interaction, the bonds with the most polar character are affected the most upon solvation.

Platinum and Agostic Effects. The optimized structures, which contain both Pt(II) and water, display an interesting type of interaction with the water molecule. Pt(II) is not interacting with the lone pair on the water oxygen atom but rather with one of the water hydrogen atoms. This type of interaction has been encountered previously in a water layer on a platinum surface[37] and is referred to as an agostic bond. Figure 5 redisplays the structure with Pt(II) already shown in Figure 2, but here the interaction with the water hydrogen atom is highlighted. The agostic effect is evident also in the second structure in Figure 5, which contains HGGGW, Pt(II), and three water molecules. The latter structure was also optimized in a vacuum. The water molecule is oriented in

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(37) Jacob, T.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2004**, *126*, 9360−9368.

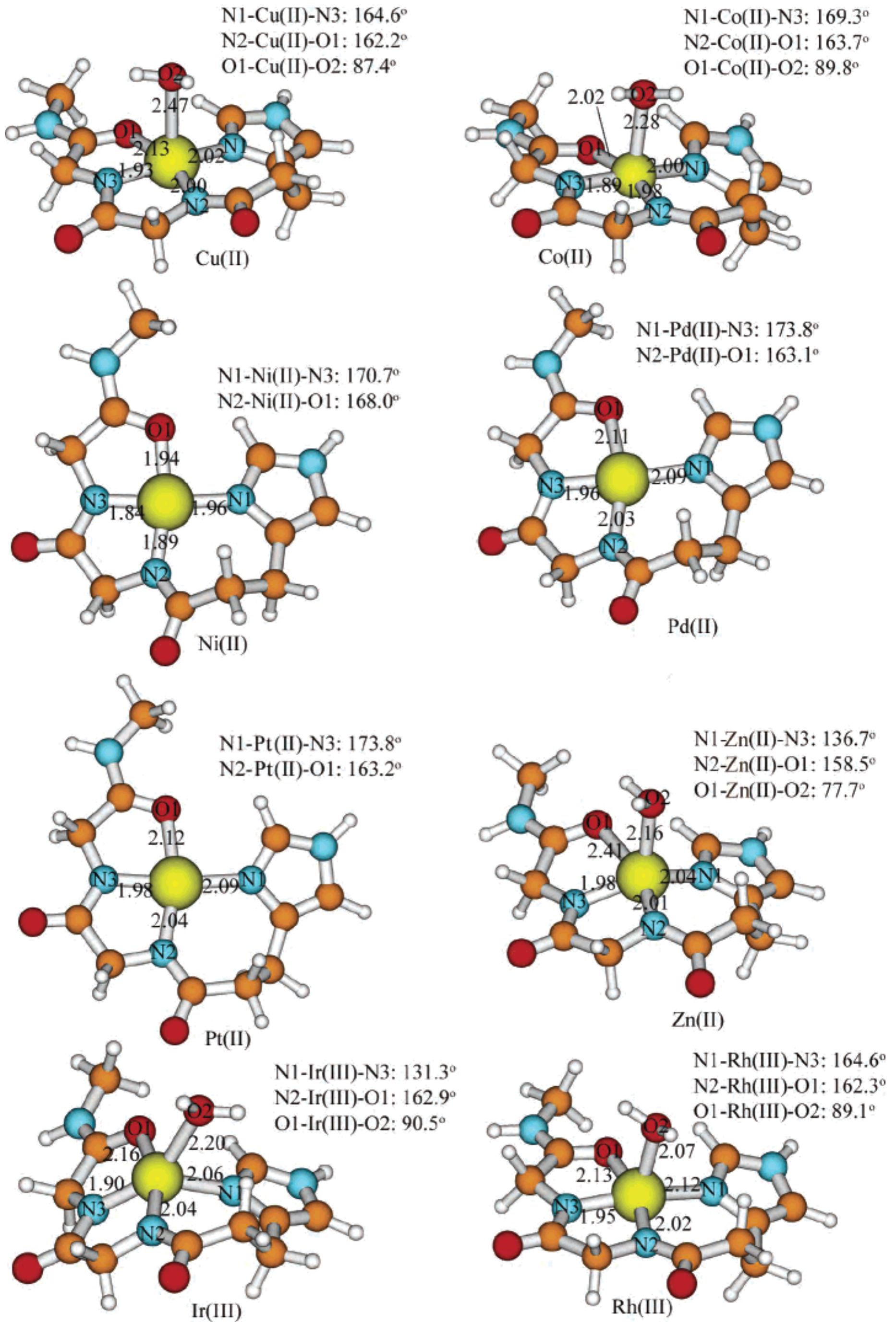

Figure 4. Optimized structures of metal ions coordinated by the HGGG model using PCM. The marked bond lengths are in Ångströms and the angles in degrees.

such fashion that the Pt(II)−H−O angle becomes nearly linear. The Pt(II)−H distance is similar in both structures, approximately 2.5 Å. This distance is somewhat longer than 2.11 Å, which is a previously reported Pt(II)−H distance.[37] The other cations that were included in this study do not show these types of agostic effects.

Substitute Candidates and NMR Spectroscopy. A structural comparison shows that Co(II) and Rh(III) result in geometries closest to those of Cu(II). Ni(II), Pd(II), and Pt(II) share such a strong preference for square-planar coordination that it is difficult for them to accommodate the axial water, despite the ability of these cations to form five-coordinate complexes in other systems.[38] The large differences in interaction structures give some coordination chemical background to why PrP shows a high selectivity for copper.

Although the structures calculated with Co(II) are quite similar to those with Cu(II), the NMR characteristics of Co(II) are no better than those of Cu(II). Co(II) is paramagnetic and has a nuclear spin $I = {}^{7}/_{2}$ and a troublesome high quadrupole moment of 0.4×10^{-28} cm^2. The NMR spectroscopic properties of Rh(III) are clearly more promising.

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(38) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, 2nd ed.; Butterworth-Heinemann: Oxford, Great Britain, 2001.

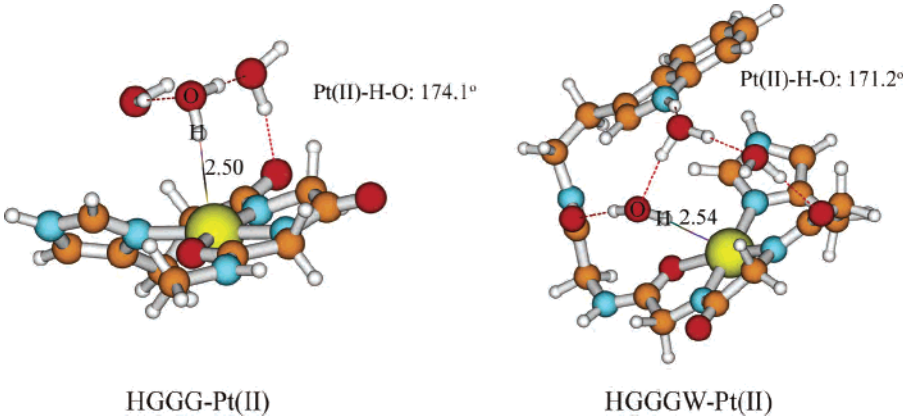

Figure 5. Optimized structures of Pt^{2+} coordinated by the HGGG and HGGGW models. The marked bond lengths are in Ångströms and the angles in degrees.

Rhodium occurs only as ^{103}Rh, which has a nuclear spin $I = {}^1/_2$. Furthermore, Rh(III) is a d^6 ion with preferred low-spin configurations, thus highly likely to show diamagnetic properties. The main setback for rhodium is its low magnetogyric ratio. Consequently, rhodium suffers from a low resonance frequency and long relaxation times in pulsed NMR experiments. Because of a great interest in rhodium in homogeneous catalysts, efforts have been made to develop special techniques to facilitate NMR spectroscopic studies of systems containing rhodium, and those should be applicable also to the peptide systems. In any case, the absence of paramagnetic nuclei allows unperturbed studies of nuclei other than ^{103}Rh.[23,39]

NMR Spectroscopic Studies. Experimental NMR spectroscopic studies focused on the coordination of HGGGW by Rh(III) complexes are in progress. Preliminary results show that the peptide ligand coordinates to Rh(III), but the exact coordination mode is strongly dependent on the choice of the Rh(III) compound used as well as the ionic medium. The kinetic lability of the Rh(III) complex formed in solution has a significant impact on the peptide coordination mode.

Conclusions

Quantum chemical calculations have been made in order to compare the coordination of several cations to human prion peptides. The peptides that were used are models of the copper-binding octapeptide region of the human prion protein, which has been represented by HGGG and two HGGGW models. The coordination of the different cations Cu(II), Co(II), Rh(III), Ir(III), Ni(II), Pd(II), Pt(II), and Zn(II) has been investigated by geometry optimization of the interaction structures.

The computational comparison was used to identify a substitute for Cu(II) ions to be used in NMR spectroscopic experiments. It is of interest to identify a better NMR nuclide than Cu(II), preferably one that is diamagnetic and has a nuclear spin $I = {}^1/_2$. The results in this study show that, out of the cations that have been considered, Co(II) and Rh(III) produce coordination structures that resemble that of Cu(II) the most. However, the NMR spectroscopic properties of Co(II) are not any better than those of Cu(II), and thus the use of Co(II) as a substitute is not of practical interest. Conversely, the characteristics of Rh(III) as an NMR nuclide are more promising, which makes it a suitable substitute. Initial NMR spectroscopic studies show that Rh(III) binds to a model peptide of the octapeptide region. However, more comprehensive studies using different Rh(III) complexes and multinuclear NMR spectroscopy are necessary in order to fully elucidate the coordination modes of Rh(III).

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Supporting Information Available: Interaction energies of the different cations and solvent effects on bond length. This material is available free of charge via the Internet at http://pubs.acs.org.

IC052079K

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(39) Ernsting, J. M.; Gaemers, S.; Elsevier, C. J. *Magn. Reson. Chem.* **2004**, *42*, 721−736.