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Characterization of Metal Centers in Bioinorganic Complexes Using Ab Initio Calculations of ^{113}Cd Chemical Shifts

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Determination of ^{113}Cd chemical shift is of significant interest in NMR characterization of metal porphyrins, metal–histidine interactions, and other metal–ligand interactions in many bioinorganic complexes and metalloproteins. In this study, we present a detailed account of a number of quantum chemical investigations aimed at relating isotropic and anisotropic ^{113}Cd chemical shifts to the structure of several biologically relevant complexes with discrete and polymeric structures. Calculated and experimentally determined chemical shift values are compared to correlate the variation of the chemical shift values with the structural changes around the metal center. Our results infer that the density functional theory using the Sadlej basis set on the cadmium atom is a suitable method for estimating cadmium shielding values to a reasonable accuracy.

Metalloporphyrins and metal−hisitidine interactions play a prominent role in the biological activity of many metalloproteins such as cytochromes, hemoglobin, metallothioneins, myoglobin, phosphotriesterase, and photosystem II.[1a−d] For example, metal porphyrins in cytochromes[1e] play an important role in an electron transport mechanism. Similarly, the metal−histidine interaction is essential for the function of phosphotriesterase, an enzyme involved in the hydrolysis of phosphotriesters. Therefore, a better understanding of the metal−ligand interaction could be of considerable value in relating the molecular structure with the function of metalloproteins.

In the last 30 years, many of these metal sites were studied using the surrogate probe strategy.[2a,b] In the applications of NMR spectroscopy, this is achieved by substituting insensitive metal centers with spectroscopy-friendly nuclei such as Cd^{2+}.[2c−g] NMR studies of cadmium proteins as well as model cadmium complexes have provided valuable structural information, such as the coordination number and geometry, about the metal center. On the other hand, for several cases, experimentally measured chemical shift values alone were inadequate.[3] This inadequacy necessitates the use of theoretical methods that could provide supplementary information for the experimentally determined cadmium chemical shifts. Nakatsuji et al.[4a] and Ellis et al.[4b] initiated cadmium chemical shift calculations using Hartree−Fock (HF) calculations, and a recent study reported nonrelativistic density functional theory (DFT) calculations on several model molecules.[5] With the use of available quantum chemical calculation methods, we inferred that calculated ^{113}Cd chemical shift values tend toward experimental values in discrete cadmium centers such as cadmium nitrate tetrahydrate and cadmium histidinate.[5] On the basis of these ab initio studies, we expect that the calculations of isotropic and anisotropic ^{113}Cd chemical shifts and a comparison with solid-state NMR experimental results would provide a unique way to understand the relationship between the chemical shift parameter and the local structure of metal complexes. These calculations on simple model cadmium complexes were performed to achieve our ultimate goal to study biological systems such as enzymes and proteins with active metal centers. As a first major step

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(1) (a) Kojima, Y.; Kagi, J. H. R. *Trends Biochem. Sci.* **1978**, *3*, 90. (b) Antonini, E.; Burnori, M. *Haemoglobin and Myoglobin in Their Reactions with ligands*; Elsevier: New York, 1971. (c) Smith, K. M. *Porphyrins and Metalloporphyrins*; Elsevier: Amsterdam, 1975. (d) Benning, M. M.; Kuo, J. M.; Raushel, F. M.; Holden, H. M. *Biochemistry* **1995**, *34*, 7973. (e) Barrett, J.; Lemberg, R. *Cytochrome*; Academic Press: New York, 1973.

(2) (a) Coleman, J. E.; Vallee, B. L. *J. Biol. Chem.* **1961**, *236*, 2244. (b) Latt, S. A.; Auld, D.; Vallee, B. L. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1383. (c) McAteer, K.; Lipton, A. S.; Ellis, P. D. Cadmium-113 NMR. A Surrogate Probe for Zn and Calcium in Proteins. In *Encyclopaedia of Nuclear Magnetic Resonance*; Grant, D. M., Harris, R. K., Eds.; John Wiley & Sons: New York, 1996; Vol. 2, pp 1085−1091 and references cited within. (d) Ellis, P. D. *J. Biol. Chem.* **1989**, *264*, 3108. (e) Rivera, E.; Kennedy, M. A.; Adams, R. D.; Ellis, P. D. *Adv. Magn. Reson.* **1987**, *13*, 257. (f) Armitage, I. M.; Pajer, R. T.; Schoot Uiterkamp, A. J. M.; Chlebowski, J. F.; Coleman, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 5710. (g) Summers, M. F. *Coord. Chem. Rev.* **1988**, *86*, 43.

(3) (a) Barrie, P. J.; Gyani, A.; Motevalli, M.; O'Brien, P. *Inorg. Chem.* **1993**, *32*, 3862 and references cited within. (b) Omburo, G. A.; Mullins, L. S.; Raushel, F. M. *Biochemistry*, **1993**, *32*, 9148.

(4) (a) Nakatsuji, H.; Nakao, T.; Kanda, K. *Chem. Phys.* **1987**, *118*, 25. (b) Ellis, P. D.; Odom, J. D.; Lipton, A. S.; Gulick, J. M. *J. Am. Chem. Soc.* **1993**, *115*, 755.

(5) (a) Srikanth, K. S.; Ramamoorthy, A. *J. Phys. Chem. A* **2002**, *106*, 10363. (b) Srikanth, K. S.; Lee, D. K.; Ramamoorthy, A. *Inorg. Chem.*, in press.

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toward this goal, in this study, we report a detailed account of ^{113}Cd chemical shift calculations on several biologically relevant complexes with discrete and polymeric structures.

Isotropic and anisotropic cadmium chemical shift values were calculated using Gaussian-98.[6] DFT with B3PW91 hybrid functionals was utilized for these calculation. Basis sets considered were Kello−Sadlej[7] for Cd and 6-311+G for other atoms. Neutron diffraction or optimized X-ray structures of cadmium complexes were used in the calculations.[3,8] Since crystal structures of porphyrin and its pyridine adduct are not available in the literature, the structures were obtained by optimizing the crystal structure of the piperidine adduct of the tetraphenyl mesoporphyrinato cadmium complex. All the hexa-, penta-, and tetracoordinated species were referenced with respect to the isotropic chemical shift value of cadmium histidinate while the octacoordinated (18-crown-6)cadmium dichloride and cadmium−annulene complexes were referenced with respect to cadmium nitrate tetrahydrate.

This work considers three different types of cadmium complexes. The first set of complexes involves discrete cadmium centers with different coordination numbers (4, 5, 6), geometry, and coordination to the ligands by N and O atoms. These complexes are cadmium histidinate (Cd−His), bis(2,2′-dipyridylamine)dinitrato cadmium (Cd−Pyr), bis(2-aminomethyl pyridine)dinitrato cadmium (Cd−Pyramin), mesoporphyrin without phenyl rings (Cd−Por), and the pyridine adduct of mesoporphyrin (Cd−Pyrpor). Coordinating atoms for these complexes are given in Table 1. The second set of complexes is connected to the neighboring molecules either through bridging coordinate bonds or by hydrogen bonds. These complexes are cadmium alaninate (Cd−Ala), cadmium glycinate (Cd−Gly), and two crystalline forms of cadmium glycylglycinate (Cd−GlyGly, Cd−GlyGlyB). The last set of complexes involves octacoordinated (18-crown-6)cadmium dichloride and its nitrogen analogue.

Table 1. Theoretical and Experimental ^{113}Cd Chemical Shifts (in ppm) for Several Cadmium Complexes with Coordination Numbers 4, 5, and 6[a]

molecule	C	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	span	ref
Cd−His	4N	286^T	414	343	102	312	
	2O	286^E	416	354	88	328	5b
Cd−Pyr	4N	240^T	525	248	−52	577	
	2O	218^E	558	224	−128	686	8a
Cd−Pyramin	4N	39^T	210	30	−122	332	
	2O	51^E	208	39	−92	300	8b
Cd−Por	4N	383^T	640	261	250	390	
		399^E	626	285	285	341	11
Cd−Pyrpor	5N	441^T	503	429	395	108	
		432^E	502	397	397	105	11
Cd−Pippor	5N	469^T	505	481	421	84	
		467^E	522	467	412	110	11b
Cd−Ala	4O	251^T	360	312	81	279	
	2N	177^E	321	266	−56	377	3a
Cd−GlyGly	4O	163^T	322	270	−102	424	
	2N	169^E					8f
Cd−GlyGlyB	4O	140^T	345	195	−121	466	
	2N	92^E					8f

[a] Span = ($\delta_{11} - \delta_{33}$); T = theoreticalvalues and E = experimental values, referenced with respect to Cd−His, the absolute shielding, σ_{iso} = 3523 ppm (equals isotropic chemical shift, δ_{iso} = 286 ppm); C = coordinating atoms.

We recently reported that the difference between the isotropic chemical shift values of Cd−Pyr and Cd−Pyramin complexes obtained using ab initio calculations matched well with the experimental values.[5] Even though both these complexes have 4N and 2O atoms surrounding the cadmium center, interestingly, the isotropic ^{113}Cd chemical shift values differ by 170 ppm. We also found that the isotropic ^{113}Cd chemical shift value of cadmium histidinate is 286 ppm, which is quite different from the values for the preceding two complexes, even though it has a N_4O_2 coordination geometry.[5b] This clearly shows the complexity involved in comparing the structure with the cadmium chemical shift values. On the other hand, this complex nature can be exploited to examine the accuracy of ab initio calculations of ^{113}Cd chemical shifts by comparing with solid-state NMR experimental results. DFT calculations on these complexes using nonrelativistic hybrid functionals and Sadlej basis set were able to predict the subtle changes in the chemical shift values as given in Table 1. Moreover, the magnitude of the chemical shift tensor values matched reasonably well with the experimental values. One common trend seen in the calculated values is that the most shielded tensor element, δ_{33}, in all the three molecules had the greatest deviation from the experimental value (see Table 1). Possible reasons for this observation are discussed here. Earlier, Ellis et al.[9] hypothesized a set of rules, and one of the rules suggests that the most shielded element orients perpendicular to the longest Cd−O bond. In the case of two nitrato molecules, Cd−Pyr and Cd−Pyramin, oxygen of the nitrates forms the longest Cd−O bond. Even though these molecules are discrete, there may be some weak intermolecular interactions between the nitrate and the neighboring molecule affecting the Cd−O bond distance. Further, errors in the experimentally determined tensor values due to the omission of the ^{113}Cd−^{14}N dipolar coupling could contribute to the difference in the experimental and theoretical values. Similarly, in cadmium histidinate, the carboxylate oxygen binding to the cadmium center, which has the longest Cd−O bond length,

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(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98,* revision A.5; Gaussian, Inc.: Pittsburgh, PA, 1998.

(7) Kello, V.; Sadlej, A. J. *Theor. Chim. Acta* **1995**, *91*, 353.

(8) (a) Griffith, E. A. H.; Hui-Ying, L.; Amma, E. L. *Inorg. Chim. Acta* **1988**, *148*, 203. (b) Rodeseiler, P. F.; Griffith, E. A. H.; Charles, N. G.; Amma, E. L. *Acta Crystallogr.* **1985**, *C41*, 673. (c) Matkovic, B.; Ribar, B.; Zelenko, B.; Peterson, S. W. *Acta Crystallogr.* **1966**, *21*, 719. (d) Huess, H.; Bartunik, H. *Acta Crystallogr.* **1976**, *B32*, 2803. (e) Kretsinger, R. H.; Cotton, F. A. *Acta Crystallogr.* **1963**, *16*, 651. (f) Takayama, T.; Ohuchida, S.; Koike, Y.; Watanabe, M.; Hashizume, D.; Ohashi, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1579. (g) Drew, M. G. B.; Cabral, J. De O.; Cabral, M. F.; Esho, F. S.; Nelson, S. M. *J. Chem. Soc., Chem. Commun.* **1979**, 1033. (h) Paige, C. R.; Richardson, M. F. *Can. J. Chem.* **1984**, *62*, 332. (i) Demaret, A.; Mercier, D. *J. Appl. Crystallogr.* **1983**, *16*, 279.

(9) (a) Honkonen, R. S.; Ellis, P. D. *J. Am. Chem. Soc.* **1984**, *106*, 5488. (b) Honkonen, R. S.; Doty, D. F.; Ellis, P. D. *J. Am. Chem. Soc.* **1983**, *105*, 4163.

may be influenced by weak hydrogen bonds with the neighboring molecules. These intermolecular interactions may in turn influence the Cd−O distances affecting the δ_{33} value. In the tetracoordinated (Cd−Por) and pentacoordinated meso-porphyrin (Cd−Pyrpor) complexes, solid-state NMR experiments for the first time showed that the shielding tensor elements could provide more information on that structure compared to the isotropic chemical shift values.[11] As given in Table 1, the experimental isotropic chemical shifts for these two complexes differ by a small value of 33 ppm, but the tensor elements differ by 124 and 112 ppm in opposite directions compensating each other. These values are compared with our calculations in Table 1. Removal of phenyl rings in our calculations reduced the computation time and was assumed to have a negligible contribution based on previous studies on zinc complexes.[12a,b] The match between calculated and experimental isotropic δ_{11} values is excellent. In addition, our calculations predicted a nonaxially symmetric tensor (δ_{33} and δ_{22} differ by 11 ppm for Cd−Por and 34 ppm for Cd−Pyrpor) unlike the experimental data. This may be attributed to irregularities in the assumed structure, which was obtained from the piperidine adduct of tetraphenyl mesoporphyrinato cadmium, used in the calculations. Nevertheless, the calculated values are close to the experimental values when compared to the ^{113}Cd chemical shift span.

In the case of cadmium−amino acid complexes, the error in the calculated values increases uniformly along all the three principal elements. Calculated tensors of cadmium alaninate deviate the most from the experimentally determined values. This is mainly because Cd−Ala forms a three-dimensional network through strong intermolecular H-bonding, which was not included in the calculation as the size of the molecule becomes too big. Similarly, large deviations were seen in Cd−Gly. Calculated chemical shifts for the two cadmium glcylglycinate complexes are given in Table 1 for which the experimental tensor values are not available.

Our last set of calculations involved octacoordinated (18-crown-6)cadmium dichloride and its analogue. The theoretically determined values were in very good agreement with the experimentally determined values (see Table 2). For example, experiments showed a large chemical shift span (1114 ppm)[12c] whereas theory led to a span of 1095 ppm. Unlike the (18-crown-6)cadmium dichloride complex, MAS experiments indicate that its nitrogen analogue has a shorter span and anisotropy,[12d] and this is in agreement with the calculated values. The mismatch in the magnitude of the principal shielding elements obtained from theory and experiment may be due to the errors in the sideband analysis as mentioned earlier and also the presence of chlorine atoms in the lattice, which were considered in the calculations.

Table 2. Theoretical and Experimental ^{113}Cd Chemical Shifts (in ppm) for Several Octacoordinated Cadmium Complexes[a]

molecule	C	δ_{iso}	δ_{11}	δ_{22}	δ_{33}	span
Cd−crown ether	8O	16^T	385	372	−710	1095
		33^E	414	384	−700	1114
Cd−annulene	6N,	-146^T	−91	−160	−188	97
	2O	-76^E	−32	−58	−138	106
Cd-crown6_1	6O[b]	-740^T	−701	−758	−760	59
$Cd(NO_3)_2 \cdot 4H_2O$ with $13H_2O$	8O	-102^T	26	−159	−173	199
		-102^E	22	−154	−174	196

[a] Span = ($\delta_{11} - \delta_{33}$); T = theoretical values and E = experimental values, referenced with respect to $Cd(NO_3)_2 \cdot 4H_2O$ with $13H_2O$, $\sigma_{iso} = 3847$ ppm (equals $\delta_{iso} = -102$ ppm). [b] Complex had a net charge of +2.

Results presented in this study clearly show that nonrelativistic calculations could provide valuable information about the structure for discrete cadmium molecules. Most recently, Krauss et al.[14] have presented a report pertaining to theoretical cadmium chemical shift calculations of model cadmium complexes mimicking Cd−PTE active centers using a method similar to the one used in this study. Their results predict a coordination number difference of 1 (Cd1, 5; Cd2, 6) between the two cadmium sites. Thus, this method seems to be a powerful tool to understand Cd structures in metalloproteins. As mentioned before, the deviations in the calculated values from the experimental values may be related to the errors in the analysis of the spinning sidebands obtained from magic-angle spinning NMR experiments. It should also be mentioned that the accuracy of the magnitude of the tensor elements is dependent on the number of spinning sidebands considered from an experimental spectrum.[13] We also noted that the agreement between theoretical and experimental values vastly improved when discrete molecules with similar coordination number were compared. The advent of higher magnetic fields and recent developments in solid-state NMR methods would also significantly improve the accuracy of experimentally measured ^{113}Cd chemical shift tensors enabling routine applications of ab initio studies on metalloproteins.

We believe that this report will aid in establishing a database of calculated cadmium chemical shifts for molecules with different coordination numbers ranging between 4 and 8 and henceforth assist in comprehending the link between geometry and nuclear shielding. For example, removal of the two chlorine-containing perchlorate molecules and water solvent bonded to the central cadmium from (18-crown-6)-cadmium dichloride (denoted as Cd-crown6_1) drastically changed the isotropic chemical shifts as well as the shielding tensor elements (see Table 2). We also suggested earlier that inclusion of relativistic calculations may enhance the results, but our preliminary results on a series of cadmium complexes show that the current relativistic methods are insufficient for improving the calculated cadmium chemical shift values.

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Supporting Information Available: Structures of all the complexes used in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Herzfeld, J.; Berger, E. *J. Chem. Phys.* **1980**, *73*, 6021.

(11) Jakobsen, H. J.; Ellis, P. D.; Inners, R. R.; Jensen, C. F. *J. Am. Chem. Soc.* **1982**, *104*, 7442.

(12) (a) Strohmeier, M.; Orendt, A.; Facelli, J. C.; Solum, M. S.; Pugmire, R. J.; Parry, R. W.; Grant, D. M. *J. Am. Chem. Soc.* **1997**, *119*, 7114. (b) Matsuzawa, N.; Ata, M.; Dixon, D. A. *J. Phys. Chem.* **1995**, *99*, 7698. (c) Kennedy, M. A.; Ellis, P. D.; Jakobsen, H. J. *Inorg. Chem.* **1990**, *29*, 550. (d) Marchetti, P. S.; Bank, S.; Bell, T. W.; Kennedy, M. A.; Ellis, P. D. *Inorg. Chem.* **1989**, *28*, 2063.

(13) Wei, Y.; Lee, D.; Mcdermott, A. E.; Ramamoorthy, A. *J. Magn. Reson.* **2002**, *158*, 23.

(14) Krauss, M.; Olsen, L.; Antony, J.; Hemmingsen, L. *J. Phys. Chem. B* **2002**, *106*, 9446.