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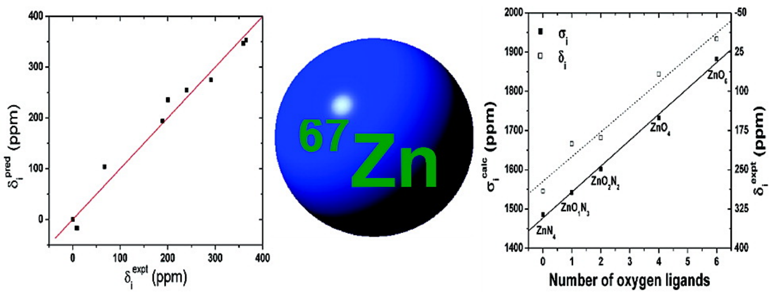

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^{67}Zn NMR Chemical Shifts and Electric Field Gradients in Zinc Complexes: A Quantum Chemical Investigation

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Zinc is an essential cofactor[1] in each of the fundamental enzyme classes: oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases.[2] However, there are few spectroscopic probes available since the d^{10} Zn^{2+} ion is not amenable to UV−visible or EPR spectroscopic investigations (e.g., as with Cu^{2+} and $Fe^{2+/3+}$) and ^{67}Zn Mössbauer spectroscopy is rather challenging.[3] A potentially more attractive probe of Zn electronic structure and bonding is ^{67}Zn NMR. In previous work, we reported[4] the first natural abundance ^{67}Zn NMR spectrum of a model complex, $Zn(OAc)_2$·$2H_2O$, in which both the isotropic NMR chemical shift (δ_i) and the electric field gradient at the ^{67}Zn nucleus, or the quadrupole coupling constant, could be determined. The ^{67}Zn NMR quadrupole coupling constant (C_Q) is given by:

$$C_Q = e^2 Q q_{zz}/h \qquad (1)$$

where e is the electron charge, Q the zinc nuclear quadrupole moment, q_{zz} the largest component of the electric field gradient at the zinc nucleus, and h is Plank's constant. Since $I = {}^5/_2$ for ^{67}Zn, the second-order broadening effect is relatively small, and by using a combination of high field, low temperature, spin−echo, cross-polarization, and other techniques, the shifts and C_Q values of a variety of zinc complexes and zinc proteins have now been reported.[5−12] However, there have been no reports of the calculation of ^{67}Zn NMR chemical shifts, a surprising fact given that there have been several reports of C_Q calculations in these same systems.[11−13] Indeed, experimental C_Q results and theoretical calculations have recently been used to help elucidate the mechanism of action of carbonic anhydrase.[12]

In this paper, we present the results of quantum chemical calculations of both ^{67}Zn NMR isotropic chemical shifts as well as the C_Q values in a series of biomimetic zinc complexes having various coordination environments and discuss the relationship between the zinc chemical shift and the zinc coordination environment. These results should open up the use of ^{67}Zn NMR chemical shifts (and C_Q values) in protein structure investigations.

In zinc enzymes, the common ligands are His (N), Asp (O), Glu (O), Cys (S), and H_2O/OH (O), which provide nitrogen, oxygen, and sulfur donor atoms.[2] We chose to investigate first the following zinc complexes: (**1**) Zn(acetate)$_2$·$2H_2O$; (**2**) Zn(acetate)$_2$; (**3**) Zn(imidazole)$_2$(acetate)$_2$; (**4**) tris(3-*tert*-butyl-5-methylpyrazolyl)-hydroborato zinc; (**5**) Zn(imidazole)$_4$(ClO_4)$_2$; and (**6**) Zn(thiourea)$_4$-(NO_3)$_2$, which contain most of the structural features seen in zinc proteins. Their X-ray structures show ZnO_6,[14] ZnO_4,[15] ZnO_2N_2,[16] ZnO_1N_3,[17] ZnN_4,[18] and ZnS_4[19] coordination motifs, and all are molecular complexes, except for **2**, which has a 2D polymeric structure.[15] We also investigated several zinc complexes having 3D polymeric structures: (Zn(formate)$_2$·$2H_2O$), which has both an anhydrous site (**7**) and a hydrous site (**8**) (both of ZnO_6 coordination),[10] together with, by way of reference, two purely inorganic solids (hexagonal ZnO (**9**) and hexagonal ZnS (**10**)), which have ZnO_4 and ZnS_4 coordination, respectively.[20] The ^{67}Zn δ_i and C_Q values in these systems cover a range of 365 ppm and 38.75 MHz, respectively (Table 1).

Table 1. ^{67}Zn NMR Chemical Shifts and Quadrupole Couplings[a]

complex	δ_i^{expt} (ppm)	C_Q^{expt} (MHz)[b]	δ_i^{pred} (ppm)[d]	C_Q^{calcd} (MHz)
1 ZnO_6[14]	0[7]	(+)5.20[7]	0.2	4.13
2 ZnO_4[15]	67[c]	(+)8.25[c]	104.1	8.36
3 ZnO_2N_2[16]	189[8]	(+)8.2[8]	194.0	9.13
4 ZnO_1N_3[17]	200.5[11]	(−)30.5[11]	235.6	−32.17
5 ZnN_4[18]	291[6]	(+)2.80[6]	274.8	4.39
6 ZnS_4[19]	359[6]	(−)3.15[6]	346.6	−2.70
7 ZnO_6[10]	10[10]	(−)6.34[10]	−16.9	−7.97
8 ZnO_6[10]	8[10]	(−)9.63[10]	−16.6	−7.88
9 ZnO_4[20]	240[5]	(+)2.4[5]	254.9	1.70
10 ZnS_4[20]	365[5]	<0.4[5]	353.0	0.18

[a] References to structures and NMR measurements are shown in brackets. δ_i^{expt} is referenced to 1.0 M $Zn(NO_3)_2$ aqueous solution. [b] Signs are not known from NMR, so they are included in parentheses.[13] [c] From this work. [d] Values δ_i^{pred} are the predicted chemical shifts from eq 2.

To calculate the ^{67}Zn NMR δ_i and C_Q values, we chose to use the hybrid HF-DFT method B3LYP[21] in our calculations, together with a large basis set: 6-311G* for Zn, 6-311+G(2d) for atoms directly bonded to Zn, 6-311G* for other heavy atoms, and 6-31G* for hydrogen atoms.[22] This is basically the approach used previously to evaluate ^{57}Fe shifts and EFG properties.[23] We used crystal structure geometries from X-ray or neutron diffraction[10,14−20] and when there were several structures reported (**1**−**3**, **7**−**8**), the geometry with the lowest R_1 factor was selected. Counterions (in compounds **5** and **6**) were not included due to the expected negligible effect,[24] while polymeric structures were treated by using the self-consistent charge field perturbation (SC-CFP) approach[25] (see also Supporting Information).

In an initial set of calculations, we found only modest correlations between theory and experiment, with the results for **2** ($Zn(OAc)_2$) being particularly problematic. Since the reported C_Q and δ_i values (2.42 MHz, 245 ppm)[6] were virtually identical to those of **9** (hexagonal ZnO: 2.41 MHz, 240 ppm;[5] the C_Q value for h-ZnO is also known[3] from ^{67}Zn Mössbauer to be 2.40 MHz), it appeared that a re-examination of the C_Q and δ_i values of $Zn(OAc)_2$ might be warranted. We therefore prepared a crystalline sample of $^{67}Zn(OAc)_2$ from ethanol, using the same protocol used to prepare $Zn(OAc)_2$ for X-ray diffraction,[15] and used the quadrupole spin−echo method to obtain the experimental result shown in Figure 1A, in which we find by computer simulation that C_Q = 8.25 MHz and δ_i = 67 ppm (from a 1.0 M $Zn(NO_3)_2$ aqueous solution).

This new result, together with our computational results for the ^{67}Zn isotropic chemical shieldings (σ_i) and quadrupole coupling constants for **1**−**10**, are shown in Table 1. The C_Q values were calculated according to eq 1 with the recommended Q value[26] of 0.15×10^{-24} cm^2, used in other recent ^{67}Zn C_Q calculations.[10,12] As shown in Figure 1B, there is an excellent correlation (R^2 = 0.975) between the calculated isotropic chemical shieldings and

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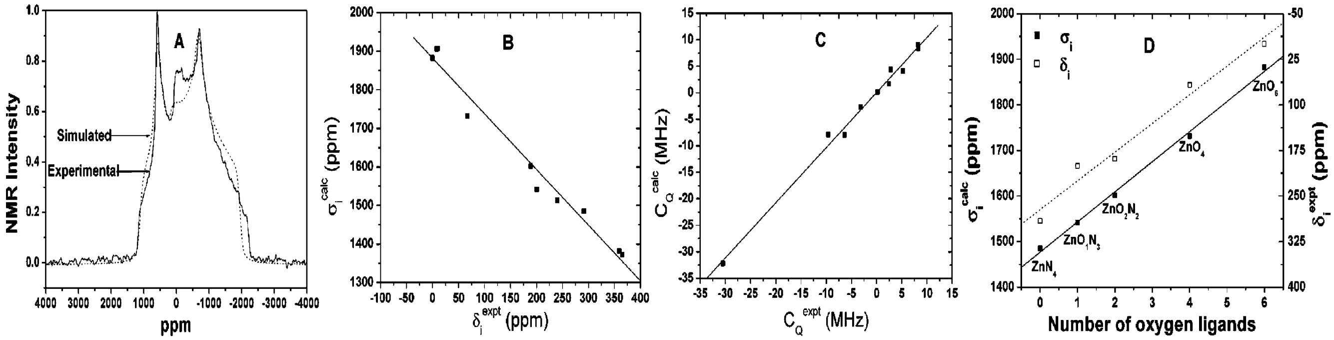

Figure 1. (A) ^{67}Zn NMR spectra of anhydrous zinc (II) acetate (**2**). (B) Calculated ^{67}Zn NMR isotropic chemical shieldings versus experimental ^{67}Zn NMR isotropic chemical shifts. (C) Calculated versus experimental ^{67}Zn NMR quadrupole coupling constants. (D) Relationships of ^{67}Zn NMR isotropic chemical shifts/shieldings and number of oxygen ligands in complexes **1**−**5**.

the experimental isotropic chemical shifts. The theoretically predicted isotropic chemical shifts (δ_i^{pred}) can then be obtained by using the regression line, and we find:

$$\delta_i^{pred} = (1882.4 - \sigma_i^{calc})/1.445 \qquad (2)$$

with the scaling factor being due primarily to basis/functional deficiencies. The rms error for the δ_i predictions is 24.3 ppm, or 6.7% of the whole experimental range. These calculations also provide excellent predictions ($R^2 = 0.991$) for the C_Q values in each system, as shown in Figure 1C, in which the slope (1.040) and intercept (0.06 MHz) are close to the ideal values of 1 and 0, respectively. The rms error is 1.17 MHz, or 3.0% of the entire experimental range. For the q_{ii} tensor elements, we obtain $R^2 = 0.972$ (Figure S1, Supporting Information), again demonstrating excellent accord between theory and experiment.

Interestingly, on further examination of the results given in Table 1, it appears for all of the biomimetic complexes (**1**−**5**) that there are linear relationships between the experimental isotropic chemical shifts (or the computed isotropic chemical shieldings) and the number of coordinated oxygen ligands. This effect can be seen in Figure 1D, where we plot δ_i^{expt} (□) and σ_i^{calc} (■) versus the number of coordinated oxygens (in ZnO_6, ZnO_4, ZnO_2N_2, ZnO_1N_3, and ZnN_4) for these O,N complexes (**1**−**5**). The R^2 values are 0.972 and 0.997 (for δ_i^{expt}, σ_i^{calc}, respectively). For the other ZnO_6 species (**7** and **8**), the differences in shifts are ≤10 ppm from **1** (which also has ZnO_6 coordination), and likewise, the shifts/shieldings for the two ZnS_4 species (**6**, $Zn(thiourea)_4(NO_3)_2$, and **10**, hexagonal ZnS) are remarkably similar (only a 6 ppm shift difference, Table 1). These relationships may, in general, give clues as to the likely coordination geometries in proteins whose structures are not yet known. Only hexagonal ZnO (**9**) is an outlier, most likely a result of its long Zn−O bond lengths (2.33−2.39 Å)[20] as compared with those of the other ZnO_4 complex, $Zn(OAc)_2$ (**2**) (1.95−1.97 Å),[15] or those of the other oxygen-containing zinc complexes studied here (1.85−2.19 Å),[10,14,16,17] which can be expected to result in substantial deshielding.

The ability to now accurately predict ^{67}Zn NMR chemical shifts as well as quadrupole coupling constants (from the same SCF results) using DFT methods should greatly facilitate the use of both of these spectroscopic properties in refining the geometric structures of Zn^{2+} binding sites in proteins, using quantum chemical geometry optimization, and in probing their electronic structures and mechanism of action.

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Supporting Information Available: Details of the SC-CFP approach, and Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Computational details are provided in the Supporting Information. This approach is associated with precisions of ≤2 ppm and ≤0.01 MHz for computed σ_i and C_Q, respectively. It introduces only ∼10 ppm and <1 MHz changes for biomimetic complexes **2**, **7**, and **8**, within the rms errors of the predictions. However, this approach leads to significant improvement in σ_i predictions for the purely inorganic solids, ZnO and ZnS, of 74 and 90 ppm, respectively.
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