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## Energies, Geometries, and Charge Distributions of Zn Molecules, Clusters, and Biocenters from Coupled Cluster, Density Functional, and Neglect of Diatomic Differential Overlap Models

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**Abstract:** We present benchmark databases of Zn–ligand bond distances, bond angles, dipole moments, and bond dissociation energies for Zn-containing small molecules and Zn coordination compounds with H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, NH<sub>3</sub>, O, OH, H<sub>2</sub>O, F, Cl, S, and SCH<sub>3</sub> ligands. The test set also includes clusters with Zn–Zn bonds. In addition, we calculated dipole moments and binding energies for Zn centers in coordination environments taken from zinc metalloenzyme X-ray structures, representing both structural and catalytic zinc centers. The benchmark values are based on relativistic-core coupled cluster calculations. These benchmark calculations are used to test the predictions of four density functionals, namely B3LYP and the more recently developed M05-2X, M06, and M06-2X levels of theory, and six semiempirical methods, including neglect of diatomic differential overlap (NDDO) calculations incorporating the new PM3 parameter set for Zn called ZnB, developed by Brothers and co-workers, and the recent PM6 parametrization of Stewart. We found that the best DFT method to reproduce dipole moments and dissociation energies of our Zn compound database is M05-2X, which is consistent with a previous study employing a much smaller and less diverse database and a much larger set of density functionals. Here we show that M05-2X geometries and single-point coupled cluster calculations with M05-2X geometries can also be used as benchmarks for larger compounds, where coupled cluster optimization is impractical, and in particular we use this strategy to extend the geometry, binding energy, and dipole moment databases to additional molecules, and we extend the tests involving crystal-site coordination compounds to two additional proteins. We find that the most predictive NDDO methods for our training set are PM3 and MNDO/d. Notably, we also find large errors in B3LYP for the coordination compounds based on experimental X-ray geometries.

### 1. Introduction

Zn compounds attract considerable interest in the fields of petroleum chemistry,<sup>1–10</sup> sensing,<sup>5–14</sup> nanotechnology,<sup>9–11,15–34</sup> and bioinorganic chemistry,<sup>35–76</sup> zinc metalloproteins in particular play crucial roles in various bio-

chemical processes and are important drug targets. The reliability of density functional theory (DFT) and neglect of diatomic differential overlap (NDDO) semiempirical molecular orbital calculations for modeling and predicting geometric, electronic, and energetic features of zinc compounds is not well established, although several attempts to evaluate the accuracy of these methods have been published.<sup>77–91</sup> Benchmark databases containing Zn–ligand bond distances, dipole moments, and dissociation energies in Zn

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**Table 1.** CCSD(T) Best Estimates of Zn–Ligand Bond Distances (in Å) for 26 Zn Model Compounds (from database D1), with Corresponding DFT and CCSD Values and Mean Unsigned Errors (MUEs)

| compd   | bond       | B3LYP | M05-2X | M06   | M06-2X | CCSD  | CCSD(T)              |
|---|------------|-------|--------|-------|--------|-------|----------------------|
| ZnH <sup>+</sup>                                | Zn–H       | 1.520 | 1.533  | 1.517 | 1.548  | 1.524 | 1.526                |
| ZnH   | Zn–H       | 1.624 | 1.642  | 1.640 | 1.646  | 1.605 | 1.605                |
| ZnH <sub>2</sub>                                | Zn–H       | 1.530 | 1.550  | 1.529 | 1.562  | 1.531 | 1.528 <sup>a</sup>   |
| MUE   | Zn–H       | 0.009 | 0.022  | 0.015 | 0.032  | 0.002 |                      |
| ZnMe <sup>+</sup>                               | Zn–C       | 1.990 | 1.992  | 1.957 | 2.005  | 1.972 | 1.976                |
| ZnMe  | Zn–C       | 2.056 | 2.067  | 2.066 | 2.056  | 2.014 | 2.014                |
| ZnCN <sup>+</sup>                               | Zn–C       | 1.857 | 1.866  | 1.849 | 1.880  | 1.852 | 1.852                |
| ZnCN  | Zn–C       | 1.970 | 1.985  | 1.973 | 1.998  | 1.955 | 1.951                |
| MUE   | Zn–C       | 0.020 | 0.029  | 0.024 | 0.037  | 0.002 |                      |
| Zn(NH <sub>3</sub> ) <sub>2</sub> <sup>2+</sup> | Zn–N       | 1.947 | 1.948  | 1.919 | 1.956  | 1.934 | 1.939 <sup>a</sup>   |
| Zn(NH <sub>3</sub> ) <sub>3</sub> <sup>2+</sup> | Zn–N       | 2.019 | 2.020  | 1.994 | 2.031  | 2.001 | 2.005 <sup>a,b</sup> |
| Zn(NH <sub>3</sub> ) <sub>4</sub> <sup>2+</sup> | Zn–N       | 2.082 | 2.076  | 2.054 | 2.089  | 2.058 | 2.063 <sup>a,b</sup> |
| MUE   | Zn–N       | 0.014 | 0.013  | 0.014 | 0.023  | 0.005 |                      |
| ZnO(singlet)                                    | Zn–O       | 1.704 | 1.707  | 1.694 | 1.726  | 1.715 | 1.711 <sup>a</sup>   |
| ZnO(triplet)                                    | Zn–O       | 1.885 | 1.890  | 1.885 | 1.891  | 1.852 | 1.855                |
| Zn(OH) <sup>+</sup>                             | Zn–O       | 1.762 | 1.751  | 1.740 | 1.764  | 1.748 | 1.757 <sup>a</sup>   |
| Zn(OH) <sub>2</sub>                             | Zn–O       | 1.767 | 1.771  | 1.750 | 1.781  | 1.758 | 1.767 <sup>a</sup>   |
| Zn(H <sub>2</sub> O) <sub>2</sub> <sup>2+</sup> | Zn–O       | 1.857 | 1.860  | 1.843 | 1.867  | 1.853 | 1.852 <sup>a</sup>   |
| MUE   | Zn–O       | 0.009 | 0.011  | 0.018 | 0.017  | 0.005 |                      |
| ZnS   | Zn–S       | 2.067 | 2.079  | 2.050 | 2.096  | 2.068 | 2.066 <sup>a</sup>   |
| ZnSH <sup>+</sup>                               | Zn–S       | 2.157 | 2.159  | 2.135 | 2.171  | 2.148 | 2.149                |
| Zn(SCH <sub>3</sub> ) <sup>+</sup>              | Zn–S       | 2.178 | 2.175  | 2.153 | 2.190  | 2.161 | 2.170 <sup>a</sup>   |
| MUE   | Zn–S       | 0.006 | 0.008  | 0.017 | 0.024  | 0.004 |                      |
| ZnF   | Zn–F       | 1.797 | 1.783  | 1.791 | 1.794  | 1.773 | 1.775                |
| ZnF <sub>2</sub>                                | Zn–F       | 1.730 | 1.731  | 1.717 | 1.739  | 1.722 | 1.723                |
| ZnCl <sup>+</sup>                               | Zn–Cl      | 2.060 | 2.064  | 2.034 | 2.071  | 2.050 | 2.053                |
| ZnCl  | Zn–Cl      | 2.179 | 2.181  | 2.159 | 2.185  | 2.152 | 2.151                |
| ZnCl <sub>2</sub>                               | Zn–Cl      | 2.087 | 2.098  | 2.066 | 2.106  | 2.080 | 2.078                |
| MUE   | Zn–halogen | 0.015 | 0.015  | 0.012 | 0.023  | 0.002 |                      |
| Zn <sub>2</sub>                                 | Zn–Zn      | 4.080 | 3.900  | 3.306 | 4.071  | 4.454 | 4.104                |
| Zn <sub>3</sub>                                 | Zn–Zn      | 3.550 | 3.544  | 3.132 | 4.045  | 4.220 | 3.674                |
| Zn <sub>4</sub>                                 | Zn–Zn      | 3.016 | 3.097  | 2.906 | 3.538  | 3.081 | 2.802                |
| MUE   | Zn–Zn      | 0.121 | 0.210  | 0.481 | 0.380  | 0.391 |                      |
| MUE <sup>c</sup>                                |            | 0.013 | 0.015  | 0.017 | 0.025  | 0.003 |                      |
| MUE <sup>d</sup>                                |            | 0.026 | 0.041  | 0.075 | 0.070  | 0.052 |                      |
| MUE <sup>e</sup>                                |            | 0.025 | 0.039  | 0.070 | 0.066  | 0.048 |                      |

<sup>a</sup> Values published in ref 89. <sup>b</sup> Values estimated by extrapolation from MP2/B2. <sup>c</sup> MUE without Zn–Zn bonds (23 bond lengths). <sup>d</sup> MUE without extrapolated values (24 bond lengths). <sup>e</sup> MUE over all bond distances (26 bond lengths).

model compounds with H, O, OH, H<sub>2</sub>O, NH<sub>3</sub>, S, and SCH<sub>3</sub> were presented recently,<sup>89</sup> together with an evaluation of various density functional approximations. In that study, out of 39 density functionals and eight other molecular orbital methods that were tested, the M05-2X<sup>92</sup> density functional was recommended as the best affordable method to obtain accurate geometric parameters, dipole moments, and bond dissociation energies for the selected Zn centers.

In the present paper, we greatly enlarge the benchmark database for Zn compounds presented in ref 89 in terms of the number of compounds and the diversity of coordination motifs. Our broadened test set has two parts.

The first part represents Zn molecules and clusters and it includes compounds with Zn–H, Zn–C, Zn–N, Zn–O, Zn–S, and Zn–halogen bonds and clusters with two to four Zn atoms; this part comprises two new databases. The first (called database D1), for molecules and clusters, contains 26 bond distances, nine bond angles, 20 dipole moments, and 29 dissociation energies. As experimental values for these parameters are not currently available, benchmark geometries and bond dissociation energies in this database are obtained by relativistic-core coupled cluster theory with single and double excitations and a quasiperturbative treatment of connected triple excitations [CCSD(T)<sup>93</sup>]; dipole

moments are obtained from relativistic-core CCSD<sup>94</sup> calculations. Including relativistic-core M05-2X geometries and relativistic-core coupled cluster calculations at relativistic-core M05-2X geometries as benchmarks permits us to enlarge the database to 43 bond distances, 38 bond angles, 22 dipole moments, and 36 dissociation energies (database D2).

The geometries obtained with four density functionals (B3LYP,<sup>95–98</sup> M05-2X,<sup>92</sup> M06,<sup>99,100</sup> and M06-2X<sup>99,100</sup>) are tested against CCSD(T) benchmarks, while the geometries produced by NDDO methods [AM1,<sup>101–104</sup> PM3,<sup>105</sup> PM3-(tm),<sup>105–109</sup> MNDO/d,<sup>110,111</sup> PM6<sup>112</sup> and the new parametrization of PM3 method for Zn named ZnB recently proposed by Brothers et al.<sup>84</sup>] are evaluated against the larger D2 benchmark database incorporating the M05-2X bond distances and bond angles. Dipole moments and dissociation energies from DFT and NDDO calculations are also tested against this enlarged benchmark database.

The second part of our test set contains four zinc coordination compounds, three inorganic and one organometallic, designed to mimic zinc sites in metalloproteins. For these structures, we fix key geometric parameters at their experimental metalloenzyme X-ray structure values and use these structures to test approximate methods for dissociation energies, bond stretching energies, dipole moments, and

**Table 2.** M05-2X Benchmark Bond Distances (in Å) for 17 Additional Zn Model Compounds

| compd   | bond | M05-2X |
|---|------|--------|
| ZnMe <sub>2</sub>                                   | Zn–C | 1.962  |
| ZnEt  | Zn–C | 2.108  |
| ZnEt <sub>2</sub>                                   | Zn–C | 1.977  |
| Zn(CN) <sub>2</sub>                                 | Zn–C | 1.894  |
| Zn(NH <sub>3</sub> ) <sub>2</sub> <sup>2+</sup>     | Zn–N | 1.945  |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | Zn–N | 2.179  |
| Zn(NH <sub>3</sub> )(OH) <sup>+</sup>               | Zn–N | 1.954  |
| Zn(NH <sub>3</sub> )(OH) <sub>2</sub>               | Zn–N | 2.158  |
| Zn <sub>2</sub> O <sub>2</sub>                      | Zn–O | 1.869  |
| Zn <sub>3</sub> O <sub>3</sub>                      | Zn–O | 1.813  |
| Zn <sub>4</sub> O <sub>4</sub>                      | Zn–O | 1.787  |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | Zn–O | 1.868  |
| Zn(NH <sub>3</sub> )(OH) <sup>+</sup>               | Zn–O | 1.738  |
| Zn(NH <sub>3</sub> )(OH) <sub>2</sub>               | Zn–O | 1.813  |
| Zn <sub>2</sub> S <sub>2</sub>                      | Zn–S | 2.255  |
| Zn <sub>3</sub> S <sub>3</sub>                      | Zn–S | 2.196  |
| Zn <sub>4</sub> S <sub>4</sub>                      | Zn–S | 2.176  |

dipole moments of zinc-containing fragments in which one bond is broken.

## 2. Data Sets and Computational Details

**2.1. Methods and Basis Set.** Four density functionals are assessed in this paper, namely, B3LYP,<sup>95–98</sup> M05-2X,<sup>92</sup> M06,<sup>99,100</sup> and M06-2X.<sup>99,100</sup> B3LYP is a hybrid generalized gradient approximation functional with 20% Hartree–Fock exchange. M05-2X, M06, and M06-2X are hybrid meta-functionals in which the kinetic energy density and improved functional forms are employed in the exchange functional, which in turn allows the correlation functional, which also depends on the kinetic energy density and involves new functional forms, to become more physical.<sup>92,99,100</sup> These functionals contain respectively 56%, 27%, and 54% Hartree–Fock exchange.

The less accurate but faster semiempirical methods that we tested are AM1,<sup>101–104</sup> PM3,<sup>105</sup> PM3(tm),<sup>105–109</sup> MNDO/d,<sup>110,111</sup> PM6,<sup>112</sup> and the new parametrization<sup>84</sup> of the PM3 method for Zn named ZnB. These methods are all based on the neglect of diatomic differential overlap (NDDO) approximation.

PM3 and AM1 are the two most widely used NDDO methods, and their suitability for organic and Zn coordination compounds has been reviewed recently.<sup>79,113</sup> MNDO/d is based on the earlier MNDO<sup>114,115</sup> method but with d-orbitals added for some elements. Due to its closed d-shell, zinc is treated only with s- and p-orbitals in AM1 and PM3.<sup>111</sup> A recent test<sup>79</sup> of AM1, PM3, and MNDO/d for zinc compounds showed that MNDO/d appears to be the most accurate method for the representation of bio-organic complexes containing Zn<sup>2+</sup>, but it exhibits deficiencies in the description of Zn–S interactions. In the same study, PM3 failed to satisfactorily describe Zn–O interactions, but it proved to be the best method for the description of Zn–N complexes.<sup>79</sup>

PM3(tm) is an extension of the standard PM3 Hamiltonian for transition-metal elements, but published applications and evaluations are rare. According to ref 108, PM3(tm) is quite successful in predicting the geometries of transition-metal

**Table 3.** CCSD(T) Benchmark Values (database D1) for Nine Zn–Ligand Bond Angles (in deg), with Corresponding DFT/B2 Values and Mean Unsigned Errors (MUEs)

| compd   | angle  | B3LYP  | M05-2X | M06    | M06-2X | CCSD(T) |
|---|--------|--------|--------|--------|--------|---------|
| Zn(OH) <sup>+</sup>                             | Zn–O–H | 112.31 | 115.39 | 112.82 | 114.51 | 111.89  |
| Zn(OH) <sub>2</sub>                             | O–Zn–O | 174.36 | 176.23 | 174.78 | 176.15 | 175.57  |
| Zn(OH) <sub>2</sub>                             | Zn–O–H | 114.42 | 116.99 | 114.17 | 116.52 | 115.18  |
| Zn(H <sub>2</sub> O) <sub>2</sub> <sup>2+</sup> | Zn–O–H | 124.80 | 125.36 | 125.03 | 125.36 | 125.58  |
| ZnMe <sup>+</sup>                               | Zn–C–H | 91.72  | 90.83  | 90.75  | 90.99  | 91.14   |
| ZnMe  | Zn–C–H | 105.72 | 103.77 | 104.03 | 104.40 | 104.25  |
| ZnSH <sup>+</sup>                               | Zn–S–H | 111.04 | 111.68 | 111.64 | 111.74 | 111.97  |
| Zn(SCH <sub>3</sub> ) <sup>+</sup>              | Zn–S–C | 103.56 | 104.16 | 104.05 | 104.07 | 104.01  |
| Zn(NH <sub>3</sub> ) <sub>2</sub> <sup>2+</sup> | Zn–N–H | 107.71 | 107.33 | 106.93 | 108.82 | 108.74  |
| MUE   |        | 0.85   | 0.98   | 0.68   | 0.60   |         |

complexes. PM6 is a very recent method; it has been parametrized against a large training set.<sup>112</sup> The new ZnB (Zinc Biological) parameter set of PM3 was proposed by Brothers et al.<sup>84</sup> to improve the ability of PM3 to model biological zinc coordination sites.

Note that all NDDO methods evaluated here involve a “very large” core (28 electrons for AM1, PM3, PM6, and ZnB) or a “large” core [18 electrons for PM3(tm) and MNDO/d] for Zn, whereas the density functional and coupled cluster calculations involve a “small” core (10 electrons). For DFT and coupled cluster calculations, we use a relativistic effective core potential (ECP) and a previously<sup>89</sup> designed basis set for Zn, referred to as B2. In this basis, Zn is represented by a supplemented version of the basis set called 6-311+G(d,p)<sup>116–118</sup> in Gaussian 03,<sup>119</sup> which is constructed from the earlier work of Wachters<sup>107</sup> and Hay<sup>117</sup> and further augmented by two additional f functions specified by Raghavachari and Trucks,<sup>118</sup> with exponents of 0.486 and 5.40. The ECP used here is the MEFIT,<sup>R</sup> pseudopotential<sup>120</sup> of Preuss et al., which replaces the 10 innermost electrons.

For H, C, N, O, and F, the NDDO calculations use a two-electron core, and for S and Cl they use a 10-electron core, whereas the DFT and coupled cluster calculations treat all electrons explicitly for these elements. For H, C, N, O, F, S, and Cl, the DFT and coupled cluster calculations are carried out with all electrons explicit and with the MG3S<sup>121</sup> basis set.

We have recently added the Zn B2 basis set to the EMSL Basis Set Exchange,<sup>122</sup> where it is listed as “B2 basis set for Zn”.

**2.2. Software and Hardware.** CCSD, CCSD(T), and DFT calculations in this paper were carried out on the Minnesota Supercomputing Institute core resources using MN-GFM version 3.0,<sup>123</sup> which is a locally modified version of Gaussian 03.<sup>119</sup> AM1, PM3, PM6, and ZnB calculations were performed using MOPAC2007<sup>124</sup> and MOPAC 5.013mn<sup>125</sup> on a Dell OptiPlex 745 machine running under SUSE Linux 10.1. MNDO/d and PM3(tm) calculations were carried out on the Dell OptiPlex 745 using SPARTAN'04 Linux.<sup>126</sup>

## 3. Benchmark Databases

**3.1. Molecules and Clusters.** For evaluation of density functionals and NDDO methods for Zn–ligand compounds, Zn<sub>n</sub> clusters, Zn<sub>n</sub>O<sub>n</sub> clusters, and Zn<sub>n</sub>S<sub>n</sub> clusters, we used two

**Table 4.** M05-2X Benchmark Values for 29 Additional Zn–Ligand Bond Angles (in deg)

| compd   | angle  | M05-2X |
|---|--------|--------|
| Zn <sub>2</sub> O <sub>2</sub>                      | O–Zn–O | 102.17 |
| Zn <sub>3</sub> O <sub>3</sub>                      | O–Zn–O | 142.92 |
| Zn <sub>4</sub> O <sub>4</sub>                      | O–Zn–O | 162.82 |
| Zn <sub>2</sub> S <sub>2</sub>                      | S–Zn–S | 113.44 |
| Zn <sub>3</sub> S <sub>3</sub>                      | S–Zn–S | 156.35 |
| Zn <sub>4</sub> S <sub>4</sub>                      | S–Zn–S | 177.00 |
| ZnMe <sub>2</sub>                                   | Zn–C–H | 110.82 |
| ZnEt  | Zn–C–C | 111.29 |
| ZnEt  | Zn–C–H | 103.98 |
| ZnEt <sub>2</sub>                                   | C–Zn–C | 179.49 |
| ZnEt <sub>2</sub>                                   | Zn–C–C | 114.25 |
| ZnEt <sub>2</sub>                                   | Zn–C–H | 108.10 |
| Zn(NH <sub>3</sub> ) <sub>2</sub> <sup>2+</sup>     | Zn–N–H | 112.53 |
| Zn(NH <sub>3</sub> ) <sub>3</sub> <sup>2+</sup>     | Zn–N–H | 112.76 |
| Zn(NH <sub>3</sub> ) <sub>4</sub> <sup>2+</sup>     | Zn–N–H | 113.11 |
| Zn(NH <sub>3</sub> )(OH) <sup>+</sup>               | N–Zn–O | 171.77 |
| Zn(NH <sub>3</sub> )(OH) <sup>+</sup>               | Zn–N–H | 112.48 |
| Zn(NH <sub>3</sub> )(OH) <sup>+</sup>               | Zn–O–H | 120.84 |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | N–Zn–O | 115.91 |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | O–Zn–O | 145.05 |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | N–Zn–N | 104.59 |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | Zn–O–H | 119.55 |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | Zn–N–H | 91.76  |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | Zn–N–H | 114.09 |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | Zn–N–H | 121.71 |
| Zn(NH <sub>3</sub> )(OH) <sub>2</sub>               | N–Zn–O | 93.24  |
| Zn(NH <sub>3</sub> )(OH) <sub>2</sub>               | O–Zn–O | 161.49 |
| Zn(NH <sub>3</sub> )(OH) <sub>2</sub>               | Zn–O–H | 117.34 |
| Zn(NH <sub>3</sub> )(OH) <sub>2</sub>               | Zn–N–H | 113.66 |

**Table 5.** CCSD Dipole Moment Benchmark Values (relative to center of mass, in D) for 29 Zn Model Compounds (database D1), with Corresponding DFT and CCSD//M05-2X Values and Mean Unsigned Errors (MUEs)

|   | B3LYP | M05-2X | M06-2X | CCSD//M05-2X | CCSD              |
|---|-------|--------|--------|--------------|-------------------|
| ZnO(singlet)  | 5.53  | 6.28   | 5.34   | 5.98         | 5.50 <sup>a</sup> |
| Zn–O(triplet)                                       | 2.43  | 2.37   | 2.60   | 2.53         | 2.73              |
| Zn–S  | 5.09  | 2.67   | 4.68   | 5.58         | 5.48              |
| Zn(OH) <sup>+</sup>                                 | 3.59  | 4.37   | 3.81   | 4.25         | 4.24              |
| Zn(H <sub>2</sub> O) <sup>2+</sup>                  | 0.79  | 0.51   | 0.70   | 0.53         | 0.39              |
| Zn(OH) <sub>2</sub>                                 | 1.87  | 1.71   | 1.90   | 1.64         | 1.65              |
| ZnSH <sup>+</sup>                                   | 3.06  | 3.75   | 3.08   | 3.80         | 3.79              |
| Zn(SCH <sub>3</sub> ) <sup>+</sup>                  | 2.74  | 3.53   | 2.73   | 2.19         | 3.58              |
| ZnH <sup>+</sup>                                    | 1.20  | 1.57   | 1.52   | 1.55         | 1.57              |
| ZnH   | 0.49  | 0.35   | 0.55   | 0.50         | 0.64              |
| Zn(NH <sub>3</sub> ) <sup>2+</sup>                  | 1.82  | 1.36   | 1.67   | 1.40         | 1.20              |
| Zn(NH <sub>3</sub> )(OH) <sup>+</sup>               | 7.05  | 7.35   | 7.09   | 7.33         | 7.27              |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | 3.45  | 3.75   | 3.44   | 3.69         | 3.79              |
| ZnMe <sup>+</sup>                                   | 0.52  | 1.07   | 0.66   | 1.02         | 1.12              |
| ZnMe  | 0.25  | 0.45   | 0.25   | 0.10         | 0.06              |
| ZnCN <sup>+</sup>                                   | 6.61  | 7.59   | 6.78   | 7.48         | 7.62              |
| ZnCN  | 4.50  | 4.54   | 4.69   | 4.61         | 4.69              |
| ZnF   | 3.17  | 3.18   | 3.43   | 3.23         | 3.25              |
| ZnCl <sup>+</sup>                                   | 4.78  | 5.47   | 4.84   | 5.47         | 5.58              |
| ZnCl  | 2.84  | 2.74   | 2.86   | 2.88         | 3.07              |
| MUE   | 0.39  | 0.14   | 0.36   | 0.16         | 0.05              |

<sup>a</sup> Values published in ref 89.

benchmark databases. One of these (D1) contains CCSD(T) bond distances, bond angles, and bond dissociation energies, and CCSD dipole moments. This database is used for evaluating both density functional and semiempirical methods. The second database (D2) includes all data in D1 plus some M05-2X values for bond distances and bond angles, some CCSD values of dipole moments calculated in single-

**Table 6.** Additional CCSD//M05-2X Benchmark Values for Two Zn Model Compound Dipole Moments (in D)

| compd                                 | CCSD//M05-2X |
|---------------------------------------|--------------|
| ZnEt                                  | 0.46         |
| Zn(NH <sub>3</sub> )(OH) <sub>2</sub> | 2.34         |

point calculations at M05-2X geometries, and some CCSD(T) values of dissociation energies calculated in single-point calculations at M05-2X geometries. The D2 benchmark geometries are used for evaluation of geometries calculated with NDDO methods, while the D2 dipole moments and dissociation energies are used to test both density functional and NDDO dipole moments and dissociation energies.

The CCSD(T) method has been shown to be reliable and accurate for reproducing experimental parameters for small transition-metal compounds.<sup>127–130</sup> Table 1 gives the best estimates of 26 Zn–ligand bond distances in database D1; some of these values were published previously in ref 89. The best estimates of Zn(NH<sub>3</sub>)<sub>3</sub><sup>2+</sup> and Zn(NH<sub>3</sub>)<sub>4</sub><sup>2+</sup> geometric parameters were obtained by extrapolation<sup>89</sup> from MP2/B2 calculations, while all other values in this table are from full CCSD(T)/B2 optimization.

Table 1 shows that the best DFT methods for Zn–ligand geometries are M05-2X and B3LYP; these methods can therefore be used to obtain additional benchmark values to evaluate the performance of less accurate semiempirical calculations for geometric parameters. We enlarged the benchmark database used to assess the accuracy of NDDO methods by adding 17 more M05-2X bond distances (Table 2) plus, as discussed below, 29 more bond angles, seven more dissociation energies, and two more dipole moments. All these additional values are included in the D2 database.

Table 3 gives the best estimates of nine Zn–ligand bond angles yielded by CCSD(T) calculations (database D1). The 29 M05-2X additional bond angle values included in the database D2 are found in Table 4.

The CCSD method yields very accurate geometries (Table 1), and CCSD optimizations are used to calculate best estimates of dipole moments. Table 5 lists CCSD dipole moments for 20 Zn–ligand compounds (database D1). The mean unsigned deviation of CCSD//M05-2X from CCSD is much smaller than the deviation of any of the four DFT methods from CCSD; therefore, CCSD//M05-2X calculations can be used to obtain suitable benchmarks to estimate the accuracy of both DFT and NDDO methods. Table 6 lists two dipole moments obtained by the CCSD//M05-2X method that are included in database D2.

Best estimates of dissociation energies were calculated by the CCSD(T) method. Table 7 lists DFT and CCSD(T)//M05-2X bond dissociation energies (data set D1). The CCSD(T)//M05-2X method gives results very close to full CCSD(T) values; once again, CCSD(T)//M05-2X can justifiably be used to calculate best estimates for systems where full coupled-cluster optimizations are not feasible. These additional benchmark values (included in database D2) are given in Table 8.

**3.2. Coordination Compounds Based on X-ray Structures.** To assess the performance of density functional approximations and NDDO techniques for structures that



**Table 7.** CCSD(T) Benchmarks for Bond Dissociation Energies (BDEs, kcal/mol) for 29 Zn-Containing Small Molecules (database D1), with CCSD(T)/M05-2X and DFT Values, and Mean Unsigned Errors (MUEs)

| compd   | products  | B3LYP  | M05-2X | M06    | M06-2X | CCSD(T)/M05-2X | CCSD(T)              |
|---|---|--------|--------|--------|--------|----------------|----------------------|
| ZnO(singlet)  | Zn, O(singlet)  | 90.02  | 76.66  | 81.23  | 81.38  | 80.32          | 80.32 <sup>a</sup>   |
| ZnO(singlet)  | Zn, O(triplet)  | 26.62  | 19.77  | 20.04  | 21.60  | 29.14          | 29.14                |
| ZnO(triplet)  | Zn, O(singlet)  | 91.14  | 80.59  | 82.31  | 88.87  | 75.18          | 75.37                |
| ZnO(triplet)  | Zn, O(triplet)  | 27.73  | 23.70  | 21.11  | 29.09  | 23.99          | 24.18                |
| ZnS   | Zn, S(singlet)  | 64.82  | 66.95  | 61.28  | 66.30  | 58.54          | 58.56 <sup>a</sup>   |
| ZnS   | Zn, S(triplet)  | 26.41  | 30.20  | 25.71  | 30.24  | 27.84          | 27.87                |
| Zn <sub>2</sub>                                     | Zn, Zn  | -0.05  | 0.60   | 1.90   | 0.52   | 0.41           | 0.43                 |
| Zn <sub>3</sub>                                     | Zn <sub>2</sub> , Zn  | 0.17   | 2.16   | 5.01   | 1.75   | 1.22           | 1.22                 |
| Zn <sub>4</sub>                                     | Zn <sub>3</sub> , Zn  | 2.84   | 6.69   | 10.88  | 4.43   | 6.43           | 8.00                 |
| ZnH <sub>2</sub>                                    | ZnH, H  | 79.11  | 80.70  | 80.41  | 75.46  | 78.88          | 78.90 <sup>a</sup>   |
| Zn(OH) <sup>+</sup>                                 | Zn <sup>2+</sup> , OH <sup>-</sup>                                | 446.96 | 436.57 | 443.12 | 437.76 | 435.56         | 435.67 <sup>a</sup>  |
| Zn(OH) <sub>2</sub>                                 | Zn(OH) <sup>+</sup> , OH <sup>-</sup>                             | 257.03 | 262.42 | 261.24 | 260.45 | 260.00         | 258.71 <sup>a</sup>  |
| Zn(H <sub>2</sub> O) <sup>2+</sup>                  | Zn <sup>2+</sup> , H <sub>2</sub> O                               | 106.89 | 104.12 | 104.12 | 104.55 | 99.79          | 99.78                |
| ZnSH <sup>+</sup>                                   | Zn <sup>2+</sup> , SH <sup>-</sup>                                | 434.53 | 420.75 | 434.63 | 421.23 | 417.50         | 417.51               |
| Zn(SCH <sub>3</sub> ) <sup>+</sup>                  | Zn <sup>2+</sup> , SCH <sub>3</sub> <sup>-</sup>                  | 448.80 | 433.69 | 446.97 | 433.36 | 430.42         | 433.84 <sup>a</sup>  |
| Zn(NH <sub>3</sub> ) <sup>2+</sup>                  | Zn <sup>2+</sup> , NH <sub>3</sub>                                | 143.20 | 136.51 | 139.99 | 136.74 | 133.12         | 134.15 <sup>a</sup>  |
| Zn(NH <sub>3</sub> ) <sub>3</sub> <sup>2+</sup>     | Zn(NH <sub>3</sub> ) <sub>2</sub> <sup>2+</sup> , NH <sub>3</sub> | 58.91  | 64.31  | 61.30  | 64.02  | 62.07          | 60.67 <sup>a,b</sup> |
| Zn(NH <sub>3</sub> ) <sub>4</sub> <sup>2+</sup>     | Zn(NH <sub>3</sub> ) <sub>3</sub> <sup>2+</sup> , NH <sub>3</sub> | 43.24  | 49.00  | 46.70  | 49.23  |                | 46.06 <sup>a,b</sup> |
| Zn(NH <sub>3</sub> )(OH) <sup>+</sup>               | Zn(OH) <sup>+</sup> , NH <sub>3</sub>                             | 76.97  | 79.77  | 80.67  | 79.11  | 78.87          | 81.14 <sup>a,b</sup> |
| Zn(NH <sub>3</sub> ) <sub>2</sub> (OH) <sub>2</sub> | Zn(NH <sub>3</sub> )(OH) <sub>2</sub> , NH <sub>3</sub>           | 8.76   | 15.63  | 12.12  | 16.32  | 12.95          | 8.87 <sup>a,b</sup>  |
| ZnMe <sup>+</sup>                                   | Zn <sup>2+</sup> , Me   | 496.87 | 483.52 | 494.47 | 482.78 | 480.73         | 480.77               |
| ZnMe  | Zn, Me  | 11.28  | 12.39  | 9.02   | 16.57  | 13.30          | 13.60                |
| ZnCN <sup>+</sup>                                   | Zn <sup>2+</sup> , CN <sup>-</sup>                                | 398.88 | 383.68 | 397.42 | 385.97 | 385.85         | 386.52               |
| ZnCN  | Zn, CN  | 50.08  | 53.76  | 42.90  | 57.08  | 54.24          | 54.87                |
| ZnF   | Zn, F   | 63.14  | 61.50  | 57.85  | 66.09  | 63.88          | 63.90                |
| ZnF <sub>2</sub>                                    | ZnF, F  | 114.64 | 123.79 | 118.14 | 115.75 | 116.75         | 116.77               |
| ZnCl <sup>+</sup>                                   | Zn <sup>2+</sup> , Cl <sup>-</sup>                                | 404.23 | 393.20 | 404.16 | 393.77 | 390.01         | 390.04               |
| ZnCl  | Zn, Cl  | 43.36  | 45.40  | 40.49  | 51.20  | 45.77          | 45.88                |
| ZnCl <sub>2</sub>                                   | ZnCl, Cl  | 95.24  | 105.85 | 101.85 | 100.42 | 99.08          | 99.11                |
| MUE   |   | 6.04   | 3.13   | 5.54   | 3.36   | 0.63           |                      |

<sup>a</sup> Values published in ref 89. <sup>b</sup> Values published in ref 89 and estimated by extrapolation from MP2/B289.

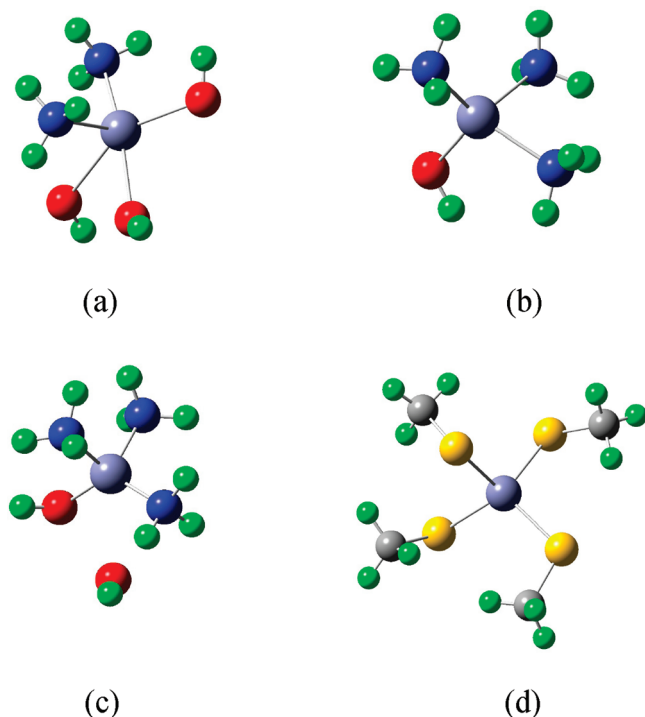
**Table 8.** Additional CCSD(T)/M05-2X Benchmark Values for Bond Dissociation Energies (in kcal/mol) for Seven Zn-Containing Compounds

| compd   | products  | CCSD(T)/M05-2X |
|---|---|----------------|
| Zn <sub>2</sub> O <sub>2</sub>                  | 2 ZnO (singlet)   | 94.00          |
| Zn <sub>2</sub> O <sub>2</sub>                  | 2 ZnO (triplet)   | 104.29         |
| Zn <sub>2</sub> S <sub>2</sub>                  | 2 ZnS   | 93.97          |
| Zn(NH <sub>3</sub> ) <sub>2</sub> <sup>2+</sup> | Zn(NH <sub>3</sub> ) <sub>2</sub> <sup>2+</sup> , NH <sub>3</sub> | 109.08         |
| ZnMe <sub>2</sub>                               | ZnMe, Me  | 73.16          |
| ZnEt  | Zn, Et  | 8.98           |
| ZnCN <sub>2</sub>                               | ZnCN, CN  | 115.86         |

more closely represent Zn biocenters, we created four model compounds based on Zn metalloprotein centers: anthrax toxin lethal factor, abbreviated LF (PDB ID 1PWU);<sup>73</sup> matrix metalloproteinase-1, abbreviated MMP-1, also known as collagenase-1 (PDB ID 2CLT);<sup>74</sup> matrix metalloproteinase-3, abbreviated MMP-3, also known as stromelysin-1, (PDB ID 1SLN);<sup>75</sup> and *Saccharomyces cerevisiae* YNR046W, a Zn-finger protein from the ERF1 methyltransferase complex (PDB ID 2J6A)<sup>76</sup> (Figure 1). Inclusion of these structures enables the accuracy of DFT and NDDO methods to be tested at geometries that are relevant to metalloprotein dynamics. To increase the diversity of our test set, we chose two pentacoordinate catalytic Zn centers (LF and MMP-3) and two tetracoordinate structural Zn centers (MMP-1 and the Zn-finger). In the anthrax toxin lethal factor enzyme, the catalytic Zn is ligated by two histidines and one glutamic acid; in 1PWU, this zinc is further coordinated by two oxygens in the hydroxamate moiety of the cocrystallized inhibitor ilomastat, forming the pentacoordinate system.

Similarly, the catalytic zinc in stromelysin-1 (MMP-3) is coordinated by three histidine residues, and in 1SLN the two additional coordination sites are occupied by hydroxamate oxygens in the cocrystallized inhibitor. The structural zinc centers in the MMP-1 and Zn-finger enzymes are both tetracoordinate, with the four coordination sites occupied, respectively, by three histidines and one aspartic acid (2CLT), and four cysteine residues (2J6A).

The metal–ligand distances in the metalloproteins are often quite different from those in small gas-phase molecules. For example, the Zn–N distances in LF are 2.25–2.32 Å and those in MMP-3 are 1.78–1.87 Å, as compared to 1.94–2.06 Å in Zn(NH<sub>3</sub>)<sub>n</sub><sup>2+</sup>. The Zn–O distances in the crystal structure sites studied here are 2.24, 2.23, and 2.52 Å (LF); 2.08 Å (MMP-1); and 1.75 and 2.87 Å (MMP-3) vs 1.76–1.85 Å in Zn(OH)<sub>n</sub><sup>+2-n</sup> and Zn(H<sub>2</sub>O)<sup>2+</sup>. The Zn–S distances in the Zn-finger structural site are 2.295–2.40 Å vs 2.17 Å in Zn(SCH<sub>3</sub>)<sup>+</sup>. Note that the geometries of the crystal-site compounds are *not* optimized in the gas phase. The Zn–ligand distances were fixed at their values in the crystals, and the biological ligands were represented as follows: imidazoles were replaced with ammonia, cysteines were replaced with SCH<sub>3</sub>, and each oxygen of glutamate or aspartate was replaced by an OH. The SCH<sub>3</sub> groups were placed so that the S and C were at the same positions as in cysteine. The atoms on NH<sub>3</sub>, SCH<sub>3</sub>, and OH were placed at standard distances and default orientations by the GaussView program; the default methyl C–H bond length is 1.07 Å, the default N–H bond length in NH<sub>3</sub> is 1.00 Å, and the default OH distance is 0.96 Å. The default bond angles for



**Figure 1.** Zn model compounds representing structural and catalytic zinc centers in four relevant metalloproteins: (a) the anthrax toxin lethal factor (LF) (catalytic site),<sup>73</sup> (b) matrix metalloproteinase-1 (MMP-1) (structural site),<sup>74</sup> (c) matrix metalloproteinase-3 (MMP-3) (catalytic site),<sup>75</sup> and (d) a *S. cerevisiae* Zn-finger protein (structural site).<sup>76</sup> Light blue = Zn, red = O, dark blue = N, yellow = S, gray = C, and green = H.

ligand geometries in GaussView are obtained by AM1 optimizations.

Dissociation energies were calculated for each Zn–ligand bond, and dipole moments were calculated for each model compound as follows: first at the crystal structure geometry and then at the Zn-containing product of the dissociation process for breaking each Zn–ligand bond. In addition, we calculated the change in energy when the bond distance (to Zn) of each ligand was stretched by 0.2 Å as compared to its value in the X-ray structure. (The stretch was carried out along the bond axis with the remainder of the molecule held rigid.) The calculations were done using the same DFT and NDDO methods that were tested for small molecules, and the results were compared with CCSD(T)/B2 values for energies and CCSD/B2 values for dipole moments for the LF and MMP-1 crystal structure site models. In addition, the NDDO methods were tested over all four X-ray structures against benchmark values of bond dissociation energies and

dipole moments, including M05-2X values for the MMP-3 and Zn-finger crystal structure models.

## 4. Results and Discussion

**4.1. Small Molecules and Clusters.** Table 1 shows that the B3LYP functional is the most accurate one for reproducing Zn–ligand bond lengths, particularly Zn–Zn bond distances. The energetic surface of Zn–Zn bonds in the vicinity of the optimized value is very flat, i.e., large changes in bond distance often lead to a very small energy change. The mean unsigned error in Zn–Zn bond length is therefore quite large in comparison with MUEs for other Zn–ligand bonds. Therefore in Table 1 we also show bond-distance MUEs excluding Zn–Zn bonds. If one excludes compounds with Zn–Zn bonds, the MUE in bond distance for B3LYP differs from M05-2X by only 0.002 Å.

Among the NDDO methods, ZnB shows the best performance for bond lengths evaluated against the D1 database, but Table 9 shows that its performance is not superior to other methods if compounds containing Zn–Zn bonds are excluded. The ZnB parametrization accurately reproduces the lengths of Zn–S bonds, but not Zn–O bond lengths. The most accurate NDDO method for Zn–ligand bond lengths without Zn–Zn bonds is PM3. PM3(tm) improves upon PM3 for Zn–O and Zn–S bonds, but does not do well for Zn–N bonds. However, AM1 performs particularly well for Zn–N bonds. As was determined in previous work,<sup>89</sup> we found that MNDO/d does not accurately reproduce Zn–S bond distances. The PM6 method is generally not accurate for our test data. Table 10 illustrates that the broadening of our test set to larger systems by inclusion of M05-2X bond lengths does not alter these conclusions.

The best NDDO methods for Zn–ligand bond angles in our training set are PM3 and AM1, while the least accurate method is PM6 (Table 11). For the enlarged benchmark database for bond angles, the PM3 method no longer exhibits the best performance, and the best methods against the D2 database benchmarks are AM1 and ZnB (which is also shown in Table 11).

The best density functional for dipole moments relative to the CCSD benchmarks is M05-2X (Table 5), followed closely by M06-2X, while the best NDDO method for dipole moments is PM3 (Table 12). Adding CCSD//M05-2X benchmarks (D2 database) does not change the leadership of M05-2X (Table 12). DFT methods with a lower percentage *X* of Hartree–Fock exchange, including B3LYP and M06, are less accurate for dipole moments than M06-2X and M05-2X (*X* = 56% and 54%, respectively). PM3 exhibits

**Table 9.** Mean Unsigned Errors (MUEs) in Zn–Ligand Bond Distances (in Å) for Various NDDO Methods Relative to D1 Benchmark Database Values<sup>a</sup>

| method  | Zn–H | Zn–C | Zn–N | Zn–O | Zn–S | Zn–halogen | Zn–Zn | all compds | excluding Zn–Zn bonds |
|---------|------|------|------|------|------|------------|-------|------------|-----------------------|
| ZnB     | 0.12 | 0.03 | 0.04 | 0.11 | 0.08 | 0.09       | 0.57  | 0.14       | 0.08                  |
| MNDO/d  | 0.12 | 0.08 | 0.04 | 0.04 | 0.15 | 0.02       | 0.93  | 0.17       | 0.07                  |
| PM3     | 0.02 | 0.04 | 0.04 | 0.04 | 0.16 | 0.02       | 1.18  | 0.18       | 0.05                  |
| PM3(tm) | 0.04 | 0.04 | 0.08 | 0.03 | 0.11 | 0.03       | 1.21  | 0.18       | 0.05                  |
| AM1     | 0.06 | 0.07 | 0.02 | 0.09 | 0.07 | 0.03       | 1.11  | 0.18       | 0.06                  |
| PM6     | 0.13 | 0.08 | 0.07 | 0.15 | 0.10 | 0.15       | 1.54  | 0.28       | 0.12                  |

<sup>a</sup> MUE is based on 26 CCSD(T) values in Table 1.

**Table 10.** Mean Unsigned Errors (MUEs) in Zn-Ligand Bond Distances (in Å) for Various NDDO Methods Relative to Augmented Benchmark Database Values (database D2)<sup>a</sup>

| method  | Zn-H | Zn-C | Zn-N | Zn-O | Zn-S | Zn-halogen | Zn-Zn | all compds | excluding Zn-Zn bonds |
|---------|------|------|------|------|------|------------|-------|------------|-----------------------|
| ZnB     | 0.12 | 0.03 | 0.07 | 0.09 | 0.09 | 0.09       | 0.57  | 0.11       | 0.08                  |
| PM3     | 0.02 | 0.04 | 0.06 | 0.04 | 0.09 | 0.02       | 0.93  | 0.13       | 0.05                  |
| MNDO/d  | 0.12 | 0.08 | 0.06 | 0.04 | 0.14 | 0.03       | 1.11  | 0.13       | 0.07                  |
| PM3(tm) | 0.04 | 0.04 | 0.12 | 0.03 | 0.09 | 0.02       | 1.18  | 0.14       | 0.06                  |
| AM1     | 0.06 | 0.07 | 0.03 | 0.11 | 0.05 | 0.03       | 1.21  | 0.14       | 0.07                  |
| PM6     | 0.13 | 0.10 | 0.11 | 0.14 | 0.06 | 0.15       | 1.54  | 0.21       | 0.11                  |

<sup>a</sup> MUE is based on 43 CCSD(T) and M05-2X values in Tables 1 and 2.**Table 11.** Mean Unsigned Errors (MUEs) in Zn-Ligand Bond Angles (in deg) for Various NDDO Methods, Relative to Databases D1 and D2

| method  | D1 <sup>a</sup> | D2 <sup>b</sup> |
|---------|-----------------|-----------------|
| AM1     | 3.0             | 4.3             |
| ZnB     | 3.6             | 4.8             |
| MNDO/d  | 8.6             | 6.2             |
| PM3     | 2.4             | 6.8             |
| PM3(tm) | 6.9             | 8.4             |
| PM6     | 10.4            | 10.1            |

<sup>a</sup> MUE for database D1 is relative to nine CCSD(T) values in Table 3. <sup>b</sup> MUE for augmented database D2 is relative to 38 CCSD(T) and M05-2X values in Tables 3 and 4.**Table 12.** Mean Unsigned Errors (MUEs) in Dipole Moments (D) for Various DFT and NDDO Methods, Relative to Databases D1 and D2

| method  | D1 <sup>a</sup> | D2 <sup>b</sup> |
|---------|-----------------|-----------------|
| M05-2X  | 0.14            | 0.14            |
| M06-2X  | 0.16            | 0.15            |
| M06     | 0.36            | 0.36            |
| B3LYP   | 0.39            | 0.37            |
| PM3     | 0.80            | 0.86            |
| AM1     | 0.89            | 0.91            |
| MNDO/d  | 0.94            | 1.07            |
| ZnB     | 1.16            | 1.17            |
| PM3(tm) | 1.47            | 1.52            |
| PM6     | 1.94            | 2.02            |

<sup>a</sup> MUE for database D1 is relative to 20 CCSD values in Table 5. <sup>b</sup> MUE for database D2 is relative to 22 CCSD and CCSD//M05-2X values in Tables 5 and 6.**Table 13.** Mean Unsigned Errors (MUEs) in Bond Dissociation Energies (kcal/mol) for Various DFT and NDDO Methods, Relative to Databases D1 and D2

| method  | D1 <sup>a</sup> | D2 <sup>b</sup> |
|---------|-----------------|-----------------|
| M05-2X  | 3.1             | 3.7             |
| M06-2X  | 3.4             | 3.8             |
| M06     | 5.5             | 5.2             |
| B3LYP   | 6.0             | 6.0             |
| MNDO/d  | 14.2            | 13.8            |
| ZnB     | 18.1            | 18.3            |
| PM3     | 21.5            | 20.5            |
| AM1     | 29.6            | 27.8            |
| PM6     | 26.8            | 28.9            |
| PM3(tm) | 71.6            | 65.1            |

<sup>a</sup> MUE for database D1 is relative to 29 CCSD(T) values in Table 7. <sup>b</sup> MUE for database D2 is relative to 37 CCSD(T) and CCSD(T)/M05-2X values in Tables 7 and 8.

the smallest MUE among the semiempirical methods for the large database (D2) of dipole moments. In our previous work, PM3(tm) was not evaluated for dipole moments, because it was not parametrized for these, but our present calculations

**Table 14.** Balanced Mean Unsigned Errors (BMUEs) for Zn-Containing Molecules and Clusters, Based on Comparing DFT and NDDO Bond Distances, Bond Dissociation Energies, and Dipole Moments to CCSD(T) Bond Distances, CCSD(T) Bond Dissociation Energies, and CCSD Dipole Moments Values in the D1 Database

| method  | molecules <sup>a</sup> | molecules and clusters <sup>b</sup> |
|---------|------------------------|-------------------------------------|
| M05-2X  | 0.21                   | 0.21                                |
| M06-2X  | 0.29                   | 0.29                                |
| B3LYP   | 0.35                   | 0.32                                |
| M06     | 0.35                   | 0.41                                |
| MNDO/d  | 1.08                   | 1.05                                |
| ZnB     | 1.30                   | 1.11                                |
| PM3     | 1.01                   | 1.13                                |
| AM1     | 1.26                   | 1.30                                |
| PM6     | 2.03                   | 1.93                                |
| PM3(tm) | 2.13                   | 2.25                                |

<sup>a</sup> BMUE calculated excluding Zn-Zn bond lengths. <sup>b</sup> BMUE calculated including Zn-Zn bond lengths.**Table 15.** Balanced Mean Unsigned Errors (BMUEs) in NDDO Bond Distances, Bond Angles, Bond Dissociation Energies, and Dipole Moments for Zn-Containing Molecules and Clusters, Validated against the Enlarged Benchmark Database (D2)

| method  | BMUE                         |                              |
|---------|------------------------------|------------------------------|
|         | excluding Zn-Zn <sup>a</sup> | including Zn-Zn <sup>b</sup> |
| ZnB     | 0.84                         | 0.76                         |
| MNDO/d  | 0.80                         | 0.79                         |
| PM3     | 0.76                         | 0.82                         |
| AM1     | 0.81                         | 0.82                         |
| PM6     | 1.42                         | 1.40                         |
| PM3(tm) | 1.37                         | 1.41                         |

<sup>a</sup> BMUE calculated excluding Zn-Zn bond lengths. <sup>b</sup> BMUE calculated including Zn-Zn bond lengths.

show that its performance for dipole moments is indeed quite poor. As the dipole moment may be seen as the leading indicator of charge distribution, one must view with caution a method that does not yield reasonable dipole moments.

M05-2X is also the top DFT method for bond dissociation energies (Table 7), with M06-2X in second place. MNDO/d predicts the most accurate dissociation energies among NDDO methods tested (Table 13). The new ZnB parametrization of PM3 for Zn also shows very good performance for dissociation energies. These results differ from the conclusion drawn in ref 112, where PM6 is reported as the most accurate method for dissociation energies. Testing bond dissociation energies against the augmented benchmark database D2, which includes CCSD(T)/M05-2X values (Table 13), does not change the ranking of DFT methods,

**Table 16.** Balanced Mean Unsigned Errors (BMUEs) in DFT and NDDO Dissociation Energies and Dipole Moments for Zn-Containing Molecules and Clusters, Evaluated against the Enlarged Benchmark Database (D2)

| method  | BMUE |
|---------|------|
| M05-2X  | 0.18 |
| M06-2X  | 0.18 |
| M06     | 0.34 |
| B3LYP   | 0.37 |
| MNDO/d  | 0.98 |
| PM3     | 1.03 |
| ZnB     | 1.16 |
| AM1     | 1.25 |
| PM6     | 1.92 |
| PM3(tm) | 2.57 |

<sup>a</sup> Based on 81 geometric data, 36 energetic data, and 22 dipole moments.

but the rank of PM6 is improved, and its MUE becomes smaller than the MUE for AM1.

The balanced mean unsigned error (BMUE) is a unitless quantity that normalizes MUEs for each parameter against the average error over all methods for that parameter. Thus, BMUE serves as a criterion to evaluate the overall performance of each technique. For the sake of simplicity, we first restricted BMUE to incorporate bond distances, dissociation energies, and dipole moments for database D1. This initial BMUE is defined as

$$\text{BMUE} = \{[\text{MUE (in \AA)}/\text{AMUE (in \AA)}] + [\text{MUE (in D)}/\text{AMUE (in D)}] + [\text{MUE (in kcal/mol)}/\text{AMUE (in kcal/mol)}]\}/3 \quad (1)$$

where AMUE is the average mean unsigned error, i.e., the mean of all MUEs for bond distances (in Å), dipole moments (in D), or bond dissociation energies (in kcal/mol). Table 14 lists BMUEs for all methods tested in this paper calculated relative to CCSD(T) bond distances and dissociation energies and relative to CCSD dipole moments (that is, over the D1 database). M05-2X is found to be the best density functional, while MNDO/d is the best NDDO method (mainly due to highly accurate bond dissociation energies in comparison with other NDDO methods). Among the NDDO methods, ZnB also demonstrates very good performance. M06-2X is found to be in second place overall. Excluding Zn–Zn bond distances from the BMUE calculations does not change the ranking of density functionals; however, without Zn–Zn bond distances, MNDO/d and ZnB rank below PM3.

For database D2, we incorporated bond angles into eq 1 by adding a fourth term, MUE (in deg)/AMUE (in deg), to the average. BMUEs calculated relative to the D2 augmented benchmark database for Zn–ligand bond distances and angles, dipole moments, and dissociation energies are listed in Table 15. ZnB proves superior here due to its accurate rendering of Zn–Zn bonds and dissociation energies; however, removing the Zn–Zn bond distances from the test set raises the PM3 method to first place, as it ranks best for bond distances (without Zn–Zn bonds) and for dipole moments. Despite its good performance for bond distances, PM3(tm) fails to give accurate dissociation energies or dipole moments; therefore, its overall rank is very low. Table 16 lists BMUEs of all tested methods against the D2 database

**Table 17.** Balanced Mean Unsigned Errors (BMUEs) for Two Coordination Compounds Based on Metalloenzyme Crystal Structures (LF and MMP-1) Determined by Comparing DFT and NDDO Bond Dissociation Energies, Bond-Stretch Energies, Dipole Moments, and Fragment Dipole Moments to CCSD(T) Dissociation Energies and CCSD Dipole Moments<sup>a</sup>

| method  | MUE               |                                | BMUE |
|---------|-------------------|--------------------------------|------|
|         | dipole moment (D) | dissociation energy (kcal/mol) |      |
| M06-2X  | 0.04              | 3.2                            | 0.32 |
| M05-2X  | 0.09              | 2.8                            | 0.33 |
| M06     | 0.38              | 3.1                            | 0.72 |
| PM3     | 0.33              | 4.7                            | 0.78 |
| MNDO/d  | 0.23              | 6.6                            | 0.82 |
| ZnB     | 0.50              | 5.0                            | 1.02 |
| B3LYP   | 0.42              | 6.5                            | 1.04 |
| AM1     | 0.47              | 6.0                            | 1.15 |
| PM6     | 0.85              | 5.5                            | 1.48 |
| PM3(tm) | 0.79              | 17.1                           | 2.36 |

<sup>a</sup> Based on 18 energetic data and 11 dipole moments.

**Table 18.** Mean Unsigned Errors (MUEs) and Balanced Mean Unsigned Errors (BMUEs) for Four Coordination Compounds Representing Metalloenzyme Crystal Structure Zn Centers (LF, MMP-1, MMP-3, and Zn-finger), Incorporating Bond Dissociation Energies, Bond-Stretch Energies, Dipole Moments, and Fragment Dipole Moments<sup>a</sup>

| method  | MUE               |                                | BMUE |
|---------|-------------------|--------------------------------|------|
|         | dipole moment (D) | dissociation energy (kcal/mol) |      |
| PM3     | 0.44              | 5.7                            | 0.60 |
| ZnB     | 0.81              | 6.3                            | 0.85 |
| AM1     | 0.90              | 6.7                            | 0.92 |
| PM6     | 0.99              | 7.1                            | 1.00 |
| MNDO/d  | 0.97              | 9.3                            | 1.12 |
| PM3(tm) | 0.99              | 15.5                           | 1.50 |

<sup>a</sup> Based on 36 energetic data and 22 dipole moments.

when BMUE is restricted to dissociation energies and dipole moments; once again, the ranking of density functionals does not change, but now MNDO/d ranks above PM3 due to its excellent performance for bond dissociation energies.

**4.2. Metalloprotein Zn Center Models.** The MUEs for dissociation energies and dipole moments and corresponding BMUEs against CCSD(T) values of dissociation energies and bond-stretch energies and CCSD values of dipole moments for the Zn-center models obtained from the LF and MMP-1 X-ray structures are given in Table 17. These tests are consistent with the results of section 3.1 in that the best density functionals are M05-2X and M06-2X, but B3LYP shows surprisingly poor performance for the large crystal-site coordination compounds; its rank is lower than the ranks of three NDDO methods (PM3, MNDO/d, and ZnB). The poor performance of B3LYP in these cases casts doubts on methods such as SCC-DFTB<sup>131</sup> that were parametrized<sup>132</sup> against B3LYP for Zn-containing compounds.

Including M05-2X benchmark values of dissociation energies, bond-stretch energies, and dipole moments, we calculated MUEs and BMUEs for all four crystal-structure model compounds (Table 18). These results support our



conclusion that the most suitable NDDO method for Zn compounds is PM3.

**4.3. Other Transition Metals.** When M05-2X<sup>92</sup> and M06-2X<sup>99</sup> were developed, it was specifically indicated that they were not designed to treat transition metals because the accurate treatment of the multireference character<sup>133</sup> of transition metals usually requires 70–100% local exchange and no more than 30% Hartree–Fock exchange. Nevertheless, in our previous paper<sup>89</sup> we tested these functionals and found that M05-2X gives the best performance for Zn chemistry. Perhaps this should not be too surprising, because the closed shell (3d<sup>10</sup>4s<sup>2</sup>) of Zn means that it has little multireference character in many of its complexes. Apparently Zn acts more like a main-group metal than a transition metal in its terms of its requirements for accurate electronic structural treatment. Recent tests and discussions of tests of density functionals for complexes of other transition metals may be found elsewhere.<sup>92,99,100,134–144</sup>

## 5. Summary and Concluding Remarks

We have presented databases of CCSD(T)/B2 geometric parameters and bond dissociation energies and CCSD/B2 dipole moments for a set of Zn model compounds. This database, D1, is supplemented by M05-2X/B2 geometries, CCSD(T)/B2 single-point dissociation energies, and CCSD single-point dipole moments calculated at M05-2X geometries, forming a larger database called D2. Four density functionals and six semiempirical parametrizations of the NDDO method were tested relative to all benchmark values.

As expected, the density functionals we tested prove much more accurate than the semiempirical NDDO methods for the small-molecule Zn compounds. For all calculated features of small compounds, the BMUE for the worst density functional is at least a factor of 2 smaller than the BMUE for the best NDDO method. This also holds true for the metalloprotein site models with exception of B3LYP, which does not perform as well as PM3, MNDO/d, or ZnB for these structures.

Our conclusions agree with those of ref 89 in that M05-2X is the most suitable density functional method for accurate calculations of geometries, dipole moments, and energetics of Zn compounds. This conclusion is further supported by the fact that the database used for testing in the present study is now larger, more diverse, and more broadly representative of the larger structures that occur in important Zn environments such as clusters and metalloproteins.

PM3 and MNDO/d are found to be, on average, the best NDDO methods for describing Zn centers. The recently proposed<sup>84</sup> ZnB parametrization of PM3 is an improvement upon PM3 for Zn–Zn bond distances and energies, but in general does not improve upon that method for other geometrical parameters and dipole moments.

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**Supporting Information Available:** CCSD(T) and M05-2X Cartesian geometries of all Zn–ligand compounds studied in this paper; DFT and NDDO Zn–ligand bond distances, bond angles, dipole moments and bond dissociation energies; X-ray structural coordinates for the Zn biocenters studied in this paper; bond dissociation energies, bond-stretch energies, and dipole moments of coordination compounds based on X-ray structures and their dissociation products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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