

Atomic Charge Calculation of Metallobiomolecules in Terms of the ABEEM Method

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Abstract: Applying the atom-bond electronegativity equalization method (ABEEM) to metallobiomolecules, the ABEEM parameters for transition metals (V, Cr, Mn, Fe, Co, Ni, Cu, and Zn) were calibrated through linear regression and least-squares optimization by choosing more than 300 training molecules. The quality of the ABEEM charge calculated in terms of the optimized electronegativity and hardness parameters for the training set is assessed by comparison with B3LYP/6-31G* charges. For a check, the ABEEM charges of some large metallobiomolecules have been calculated, and the obtained results correlate quite well to those calculated with the B3LYP/6-31G* method. The linear correlation coefficients R are all over 0.98. This shows that the ABEEM method can predict the charge distributions of large metallobiomolecules with high accuracy.

Introduction

Electron density determines all properties of a molecular system. Therefore, atomic charges of a molecule, as concentrated electron density distribution, are of great importance. On the one hand, atomic charges certainly show Coulomb interactions between different molecular sites. The atomic charges are useful indexes of molecular reactivity, particularly for electrophilic and/or nucleophilic reactions. Furthermore, atomic charges are indicators of molecular sites between which the hydrogen bonds may form for both intramolecular and intermolecular cases. On the other hand, atomic charges are also used in many packages, where they may be treated on an equal footing as important parameters, such as bond lengths, etc. The electronegativity equalization method based on DFT^{1–4} is such an approach that allows fast calculation of atomic charges in a large set of molecules. In this field, a noteworthy one is Mortier and Nalewajski's electronegativity equalization method (EEM), which has been used to predict atomic charges in molecules, electron population normal modes, etc.^{5–6} Besides, the charge equili-

bration method (Qeq) was developed by Rappé et al.⁷ Cioslowski et al. analyzed electron flow and electronegativity equalization by using charge-constrained calculations.⁸ York and Yang presented the chemical potential equalization principle to describe the redistribution of electrons upon perturbation by an applied field.⁹ De Proft et al. presented a nonempirical electronegativity equalization scheme.¹⁰ Ghosh put forward a semiempirical electronegativity equalization procedure to predict bond energies of diatomic molecules.¹¹ No et al. proposed a partial equalization of the orbital electronegativity method.¹² In order to explicitly treat the chemical bonds, Yang et al. developed an atom-bond electronegativity equalization method (ABEEM),^{13–22} which has been applied to predict charge distributions for large molecules and aqueous solutions.

Recently, Bultinck et al. have reformulated and validated the EEM approach with showing its necessity and amenability to fast calculation of atomic charges over a molecule.^{23,24} They also pointed out there was a need to extend those EEM approaches to comprise more elements in order to use them in more extensive large molecular systems. To our knowledge, there is little work that involves transition metals in those EEM methods. However, it has been estimated that a lot of proteins and enzymes purified to apparent homogeneity

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require transition-metal ions as cofactors for biological function. These transition metals include V, Mn, Fe, Co, Ni, Cu, and Zn.²⁵ At present, two chromium-containing biomolecules in nature have been known.²⁶ All of these transition metals play an important role in a variety of biological systems. Thus to investigate metallobiomolecules is very interesting. The focus of the current paper is to further develop the ABEEM method so that it can be widely applied to metallobiomolecules. In this paper, the metallobiomolecules involving the first row of transition metals including V, Cr, Mn, Fe, Co, Ni, Cu, and Zn are investigated.

This article is organized as follows. First, a brief formalism of the ABEEM method is given. Second, a large set of the training molecules that contains the common organic groups as well as some transition metals is chosen and then a large amount of *ab initio* calculations on the training molecules in order to calibrate the ABEEM parameters is done. Third, the ABEEM parameters calibrated for transition metals, quality of the ABEEM atomic charges, and applicability of the ABEEM are discussed. Finally, a brief summary is given.

ABEEM Formalism

The electronegativity equalization principle formulated by Sanderson²⁷ states that when a molecule is formed, electronegativities of the constituent atoms become equal, yielding molecular, equalized electronegativity. Several formalisms mentioned above have been developed from this principle. In the ABEEM method, a molecule is divided into atom regions *c*, bond regions, and lone-pair electron regions *t*. By using a definition of electronegativity in light of DFT, we can express the effective electronegativity χ_c of any atom and χ_t of any bond or lone-pair electron as

$$\chi_c = \chi_c^* + 2\eta_c^* q_c + k \left[\sum_{d \neq c} \frac{q_d}{R_{c,d}} + \sum_t \frac{q_t}{R_{c,t}} \right] \quad (1)$$

$$\chi_t = \chi_t^* + 2\eta_t^* q_t + k \left[\sum_c \frac{q_c}{R_{t,c}} + \sum_{s \neq t} \frac{q_s}{R_{t,s}} \right] \quad (2)$$

In eq 1, χ_c^* and $2\eta_c^*$ are valence state electronegativity and valence state hardness of atom *c*, respectively; q_c and q_d are the partial charges of atom *c* and atom *d*, respectively; q_t is the partial charges of bond or lone-pair electron *t*; $R_{c,d}$ represents the distance between atom *c* and atom *d*, and $R_{c,t}$ represents the distance between atom *c* and bond or lone-pair electron *t*; and *k* is an overall correction coefficient in this formalism. As for the symbols in eq 2, the meanings are analogous to those of the symbols in eq 1. The electronegativity equalization principle demands $\chi_c = \chi_t = \bar{\chi}$, with $\bar{\chi}$ being the electronegativity of the molecule. When an arbitrary molecule is partitioned into *m* regions, one has *m*+1 unknown quantities (*m* charges of *q* and one value $\bar{\chi}$) in the *m* equations. These equations, along with the constraint equation on its total charge, can be solved to give $\bar{\chi}$ and the charge distribution *q* in the molecule if all parameters χ^* and $2\eta^*$ are known.

Calibration of the ABEEM Parameters for Metallobiomolecules

Choice of Training Set. Here we are mainly concerned with metallobiomolecules, so lots of molecules including transition metals were chosen as a training set. The initial structures of all model metallobiomolecules that include transition metals were taken directly from PDB and the Cambridge Crystallographic Data Center (CCDC). In most cases of metallobiomolecules, metal ions are coordinated with nitrogen, oxygen, and/or sulfur atoms of biological ligands, thus amino, imidazolyl, carbonyl, carboxylate, phenolate, alkoxide, thiolate, thioether, porphyrin, and others are chosen as ligands. Indeed, the ligands also play an important role in the calibration process, which will be discussed in detail in the Results and Discussion section. The calibration set consists of 387 metallobiomolecules, holding 30 molecules containing a V atom, 20 molecules containing a Cr atom, 50 molecules containing a Mn atom, 80 molecules containing an Fe atom, 60 molecules containing a Co atom, 47 molecules containing a Ni atom, 56 molecules containing a Cu atom, and 64 molecules containing a Zn atom. The frame structures of some metallobiomolecules used in the training set are available in part (I) of the Supporting Information. These molecules should ensure the calibration process and the chemical relevance.

Quantum Chemical Calculations. The organic ligand molecules like amido acid were optimized by the DFT (B3LYP/6-31G*) method. The initial structures of metallobiomolecules were taken from PDB and CCDC. Hydrogen atoms were added with the GaussView program of the Gaussian 03 package. In order to keep up the experimental structure, the heavy atoms of the crystal structures were not optimized, and the hydrogen atoms were locally optimized at the B3LYP/6-31G* level, using the Gaussian 03 program.²⁸ At the same time, the B3LYP/6-31G* method was used to calculate the charge distribution via Mulliken population analysis in this study for both the calibration training set and the metallobiomolecules for check.

Calibration of Parameters. The ABEEM parameters (χ^* and $2\eta^*$) related to C, H, O, and N atoms are mainly based on the previous studies by Yang et al.^{13–16,20,21} The metal–ligand bond is dependent on the detailed nature of the valence state or orbitals of the ligands as well as the effective nuclear charge, coordination numbers, and geometry of the metal ion. In order to deal simply with the metal–ligand bond charges, we assume that there is only one bond charge between a ligand and a metal ion. The method for the bond charge allocation between the metal ion and the coordinated atom of the ligand is the same as the σ bond allocation between them. The detail of this method can be found in refs 13–16. Mulliken charges of the molecules in the training set were calculated by the B3LYP/6-31G* method and then were brought into eqs 1 and 2 in order to determine the ABEEM parameters by the least-square-root algorithm.

Results and Discussion

Calibrated Parameters. The calibration of the ABEEM parameters for transition metals and their bonds proves to be a highly cumbersome task. Each additional element and

Table 1. Defined Atom and Bond Types and the Optimized Values of Parameters of Valence Electronegativity χ^* and Valence Hardness $2\eta^*$ in the ABEEM^a

code ^b	atom and bond type	description ^c	χ^*	$2\eta^*$
2303	V ³⁺	V ³⁺ coordinates O, N and/or S atom in ligands	8.76	1.88
2305	V ⁵⁺	V ⁵⁺ coordinates O and/or S atom in ligands	13.81	2.15
2307	V ⁵⁺	V ⁵⁺ coordinates N atom in ligands	13.81	2.11
2403	Cr ³⁺	Cr ³⁺ coordinates O and/or S atom in ligands	9.33	2.03
2407	Cr ³⁺	Cr ³⁺ coordinates N atom in ligands	9.33	2.20
2406	Cr ⁶⁺	Cr ⁶⁺ coordinates O, N and/or S atom in ligands	15.30	1.93
2502	Mn ²⁺	Mn ²⁺ coordinates O and/or N atom in ligands	7.81	3.08
2515	Mn ²⁺	Mn ²⁺ coordinates O atom in phosphoric ligands	7.96	2.84
2503	Mn ³⁺	Mn ³⁺ coordinates O and/or N atom in ligands	10.57	3.02
2602	Fe ²⁺	Fe ²⁺ coordinates O, N and/or S atom in ligands	7.86	3.05
2603	Fe ³⁺	Fe ³⁺ coordinates O, N and/or S atom in ligands	11.50	3.50
2612	Fe ³⁺	Fe ³⁺ coordinates O atom in carbonic ligands	12.30	3.65
2616	Fe ³⁺	Fe ³⁺ coordinates S atom in Cys ligands	12.30	3.65
2702	Co ²⁺	Co ²⁺ coordinates O, N and/or S atom in ligands	8.06	3.01
2716	Co ²⁺	Co ²⁺ coordinates S atom in Cys ligands	8.11	2.72
2703	Co ³⁺	Co ³⁺ coordinates N atom in ligands	13.15	4.05
2802	Ni ²⁺	Ni ²⁺ coordinates O, N and/or S atom in ligands	8.40	3.14
2901	Cu ⁺	Cu ⁺ coordinates O and/or N atom in ligands	5.66	2.91
2902	Cu ²⁺	Cu ²⁺ coordinates O and/or N atom in ligands	8.42	3.45
2916	Cu ²⁺	Cu ²⁺ coordinates S atom in Cys ligands	8.46	3.13
3002	Zn ²⁺	Zn ²⁺ coordinates O and/or N atom in ligands	8.60	3.54
3016	Zn ²⁺	Zn ²⁺ coordinate S atom in Cys ligands	8.66	3.20
8125	M–O	V (Cr, Mn, Fe, Co, Ni, Cu, and Zn)-O single bond	4.31	25.49
7125	M–N	V (Cr, Mn, Fe, Co, Ni, Cu, and Zn)-N single bond	3.81	16.94
1625	M–S	V (Cr, Mn, Fe, Co, Ni, Cu, and Zn)-S single bond	5.21	35.03

^a The unit of χ^* is Pauling unit; the unit of $2\eta^*$ is Pauling/electron. ^b "Code" denotes the label defined in the the ABEEM program to identify the atom or bond type. ^c In this description, taking V⁵⁺ as an example, "V⁵⁺ coordinating by N atom in ligands" stands for V⁵⁺ coordinating by N atom not including O and/or S atoms in ligands. If V⁵⁺ ion coordinates by N and S and/or O atoms, then the atom type can be adopted by the atom type which coordinates by S and/or O atoms. As for the other metal atom types, the meanings are analogous to those mentioned above.

different atom type would require new ABEEM parameters. This is also due to the sensitivity of the fitness function for the parameters. The new defined atom and bond types as well as the calibrated valence state electronegativity and hardness of the ABEEM parameters related to the transition metals are listed in Table 1. The unlisted ABEEM parameters and their atom type codes related to this paper are available in parts (II) and (III) of the Supporting Information. Besides, from our experience of calibration, it is known that the geometrical parameters like bond stretching, angle bending, and others, in practice, only have very small effects on the charges, and they mainly determine the geometries.

In the calibration process, there are two main factors that influence the ABEEM parameters. On one hand, the chemical surrounding should be taken into account. It is very important for metal atoms to be coordinated by different atoms. For example, Cu and Zn atoms coordinating by an S atom in cysteine have different properties from coordinating by other atoms, such as N and O. In this paper, atom types can be also classified mainly according to these ligands atoms that form different geometric environments, like tetrahedral, square planer, octahedral, etc. For instance, the Fe(II) atom is six-coordinate with three His residues, two Asp residues, and a hydroxyl in the hemerythrin compound. The iron ion coordinates with trigonal-bipyramidal geometry by three His residues, an Asp residue, and solvent molecules in an Fe-containing superoxide dismutase. The iron ion coordinates with a square plane by nitrogen atoms of porphyrin in iron-

Table 2. Absolute Electronegativity (χ) and Hardness (η) Parameters for Some Metal Ions^a

metal ions	Cu ⁺	Mn ²⁺	Fe ²⁺	Ni ²⁺	Cu ²⁺	Zn ²⁺	Fe ³⁺
χ	14.0	24.4	23.4	26.7	28.6	28.8	43.7
η	6.3	9.3	7.3	8.5	8.3	10.8	13.1

^a All values are in eV.

containing protoporphyrin. In our calibration, hemerythrin, superoxide dismutase, and protoporphyrin have been chosen as the model molecules. Obviously, a different training set has a somewhat different effect on the parameters. But the effect is very limited if the training set contains a sufficient number of training molecules and atom types. On the other hand, how to obtain atomic charges to calibrate electronegativity and hardness is also expected to play an important role, because charge distributions are strongly dependent on the choice of basis sets. However, the atomic charges from a different choice of basis sets have a similar trend and correlate to each other nearly linearly. The B3LYP/6-31G* method is used for calibrations in this paper. The HF/STO-3G method was used in some previous calibrations for largely reducing the huge computational work.^{5,13–16}

In order to compare the valence state electronegativity values of the transition metals, Table 2 lists the so-called absolute electronegativity and hardness that were calculated from the experimental ionization potentials and electron affinities by Pearson^{2,29} for some metal ions. A correlation of the absolute electronegativity and hardness with our

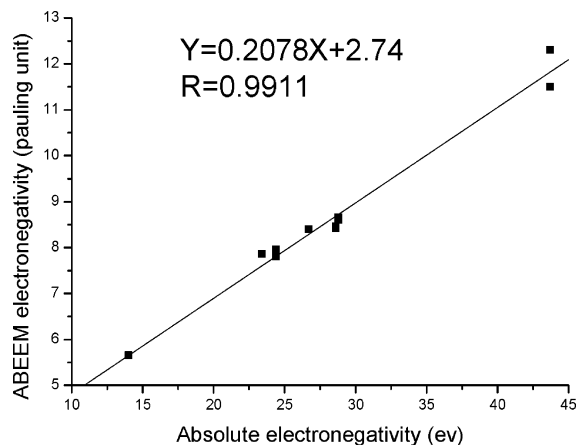


Figure 1. The correlation diagram between the absolute electronegativity parameters and the ABEEM parameters χ^* for some metal ions.

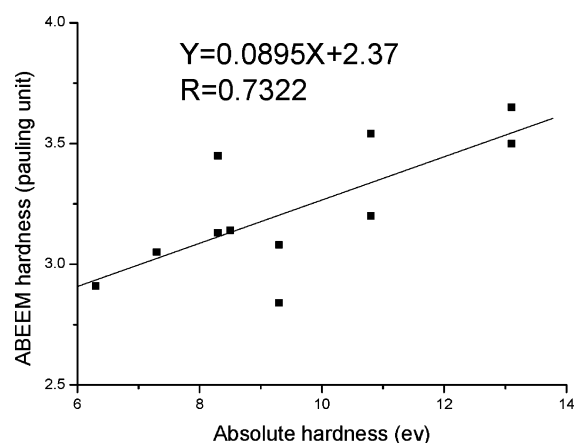


Figure 2. The correlation diagram between the absolute hardness parameters and the ABEEM parameters $2\eta^*$ for some metal ions.

parameters is shown in Figures 1 and 2, respectively. It is noted that the ABEEM parameter values from the current calibration have the same trend with those from the experimental quantities. The same trend and the good correlation also show our ABEEM parameters are reasonable.

Quality of the ABEEM Atomic Charges. The quality of the ABEEM atomic charges is assessed by comparison

with the DFT charges for the training molecules. Figure 3 gives the ABEEM atomic charge distributions versus the B3LYP/6-31G* atomic charge distributions for the training molecules that contain Mn ion. Also included are the correlation constants for the best fitting linear function between both types of the charges in these figures. In fact, the ABEEM charge distributions versus the B3LYP/6-31G* charge distributions for the Mn ion in Figure 3(b) are only a magnification of a small piece of that of all atoms, including H, C, N, O, and so on, in the Mn training molecules in Figure 3(a). In the same way, a comparison of ABEEM and DFT charge distributions about Fe training molecules is shown in Figure 4. And the correlation diagrams for other ions are available in part (IV) of the Supporting Information.

The linear correlation coefficients R containing all atoms over 0.99 are in Figures 3 and 4. It is obvious that the ABEEM charges can well reproduce the DFT charges. But there are also some deviations for Mn and Fe ions between the ABEEM charges and the DFT charges. These deviations may be greatly reduced considering the detailed atom types and the coordination numbers (geometric environments) as well as the multiplicities in different metallobiomolecules. It is well-known that Fe is a very important element in these biomolecules like protoporphyrin, superoxide dismutase, hemerythrin, and so on. For reducing the number of the parameters, however, only one atom type for Fe(II) is assumed in this paper. So the ABEEM charges show some deviations from DFT charges in some compounds. For example, the ABEEM charge of Fe(II) is 1.23 e , and the DFT charge is 1.08 e in the hemerythrin compound (PDB code 1HMD). But, if only one metallobiomolecule is considered, then the trend of the ABEEM charges is in fair accordance with the trend of the DFT charges. In order to obtain better fitting and to make this kind of deviation decrease for metallobiomolecules, adding more atom types that can reflect more complicated geometric environments may be required.

Anyway, in this kind of correlation, the metal ions are in various molecules and their positive charges are quite large. The fact that the ABEEM adequately predicts atomic charges for the transition metals, using the same parameters and fewer

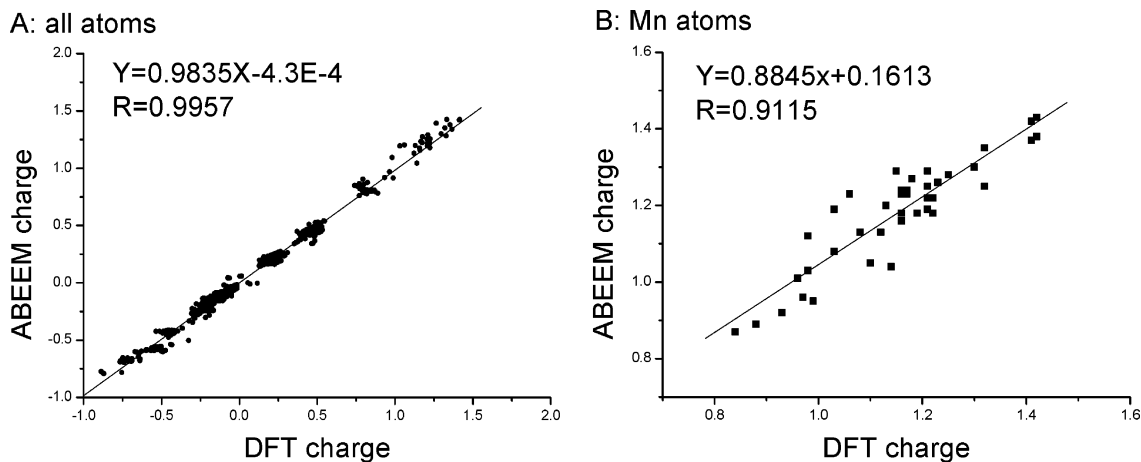


Figure 3. Comparison of the ABEEM and the DFT charge distributions for Mn training molecules.

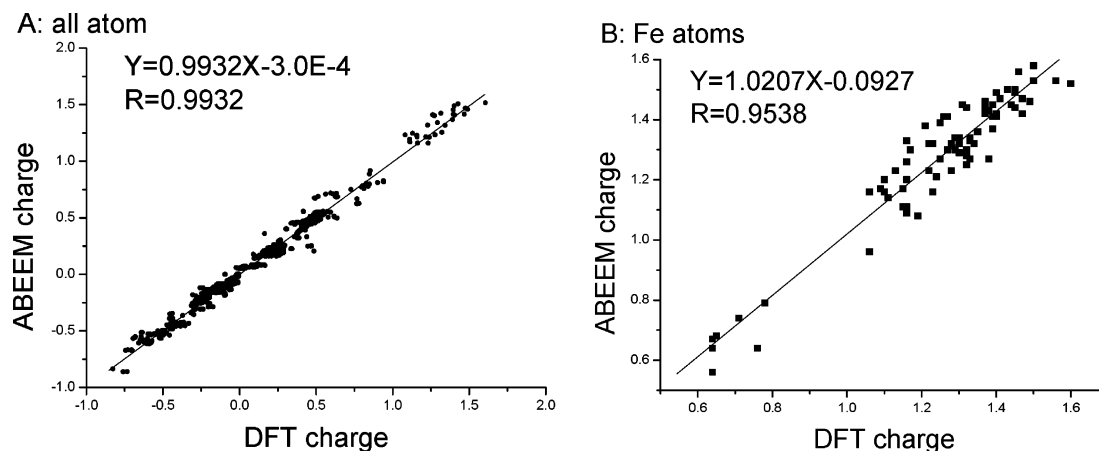


Figure 4. Comparison of the ABEEM and the DFT charge distributions for Fe training molecules.

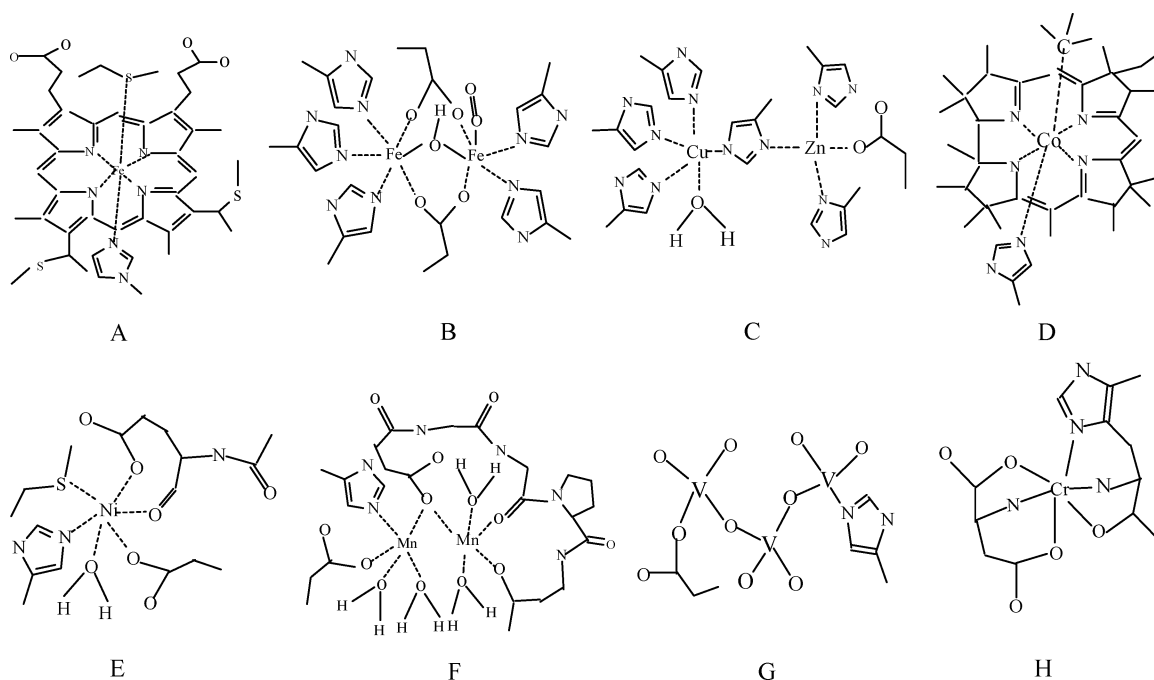


Figure 5. The frame structures of eight metallobiomolecules: A = $C_{43}H_{52}FeN_6O_4S_3$, B = $C_{26}H_{14}Fe_2N_{10}O_7$, C = $C_{27}H_{42}CuN_{12}O_3^- Zn$, D = $C_{40}H_{62}CoN_6$, E = $C_{19}H_{36}N_4NiO_7S$, F = $C_{26}H_{48}Mn_2N_7O_{15}$, G = $C_7H_{11}N_2O_{10}V_3$, H = $C_{10}H_{13}CrN_4O_6$.

Table 3. Correlation Equations of the ABEEM Charge Distribution Y versus the DFT (B3LYP/6-31G*) Charge Distribution X^a

molecules (PDB code ^b and total charge)	$Y = AX + B$	R	S	U
$C_{43}H_{52}FeN_6O_4S_3$ (1CXC, -2)	$Y = 0.9982X - 1.2E-05$	0.9915	0.0270	0.1086
$C_{26}H_{14}Fe_2N_{10}O_7$ (1HMO, +1)	$Y = 0.9739X + 2.3E-04$	0.9948	0.0262	0.1396
$C_{27}H_{42}CuN_{12}O_3Zn$ (2SOD, +2)	$Y = 0.9741X - 1.1E-03$	0.9932	0.0353	0.1220
$C_{40}H_{62}CoN_6$ (1BMT, 0)	$Y = 1.0049X - 8.8E-09$	0.9862	0.0322	0.1334
$C_{19}H_{36}N_4NiO_7S$ (2TDX, 0)	$Y = 0.9980X + 2.0E-06$	0.9909	0.0354	0.1447
$C_{26}H_{48}Mn_2N_7O_{15}$ (1DQ6, +2)	$Y = 1.0106X - 3.2E-04$	0.9928	0.0373	0.1735
$C_7H_{11}N_2O_{10}V_3$ (1H2F, -2)	$Y = 0.9728X - 7.6E-04$	0.9930	0.0435	0.1481
$C_{10}H_{13}CrN_4O_6$ (-2)	$Y = 1.0153X + 5.6E-06$	0.9951	0.0309	0.1466

^a $Y = AX + B$. R being the correlation coefficient, S being the standard error, and U being the maximum error. ^b The framework structures of $C_{10}H_{13}CrN_4O_6$ can be found in ref 30.

atom types, shows the calibrated parameters are applicable within a large range of metallobiomolecules.

Applicability of the ABEEM. In order to check these calibrated parameters, we applied the optimal atomic electronegativity and hardness parameters to calculate charge distributions of some large metallobiomolecules that do not

belong to the calibration set. These metallobiomolecules include haloperoxidase, hemoglobin, hemocyanin, hemerythrin, vitamin B₁₂, carboxypeptidase, carbonic anhydrase, and so on. Most of their framework structures are also directly taken from PDB. Eight of these metallobiomolecule framework structures are shown in Figure 5. These metal-

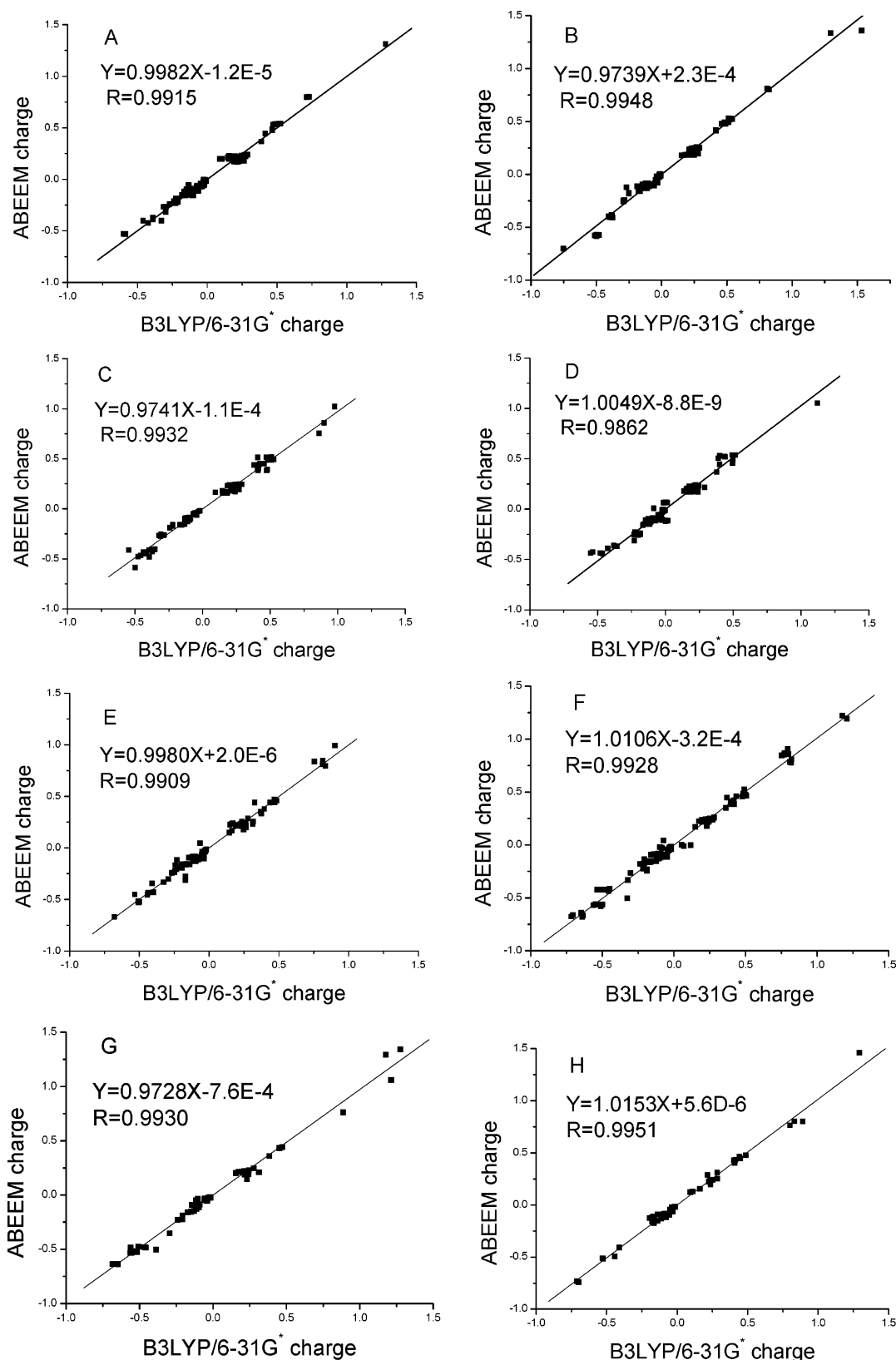


Figure 6. Correlation of the ABEEM and the B3LYP/6-31G* charge distributions for metallobiomolecules: A = $C_{43}H_{52}FeN_6O_4S_3$, B = $C_{26}H_{14}Fe_2N_{10}O_7$, C = $C_{27}H_{42}CuN_{12}O_3Zn$, D = $C_{40}H_{62}CoN_6$, E = $C_{19}H_{36}N_4NiO_7S$, F = $C_{26}H_{48}Mn_2N_7O_{15}$, G = $C_7H_{11}N_2O_{10}V_3$, and H = $C_{10}H_{13}CrN_4O_6$.

lobiomolecules are quite complicated in their structures. The correlation equations about the ABEEM charge distribution versus the DFT (B3LYP/6-31G*) charge distribution for the eight metallobiomolecules are listed in Table 3. The linear

correlation coefficients R are all over 0.98, the standard errors S are smaller than 0.045, and the maximum errors U are smaller than 0.18 that mainly relate to metal ions that have the largest charges. At the same time, Figure 6 gives the

schematic diagrams of the ABEEM charges versus the DFT (B3LYP/6-31G*) charges of these metallobiomolecules. Remarkably, these diagrams show that the ABEEM method can well reproduce the DFT charges. This means that the calibrated ABEEM parameters involving the transition metals of the fourth row in the periodic table of the elements are applicable to more metallobiomolecules.

Atomic charges are very important indicators. Fast calculation of atomic charges for a large molecule or for a large number of molecules could be very useful. For a comparison, speed of the ABEEM calculation of atomic charges is very fast, about 2000 times faster than the usual Mulliken population analysis in the usual SCF MO procedure. Thus, charge calculations with high accuracy and high speed for large metallobiomolecules become an outstanding advantage of the ABEEM method. Once the configuration of a molecular system is determined, its atomic charge distributions will be calculated quickly.

Summary

We have extended the ABEEM method to involve the transition metals. The ABEEM parameters, the valence state electronegativity and hardness, of the transition metals such as V, Cr, Mn, Fe, Co, Ni, Cu, and Zn were calibrated. Although only a few transition-metal atom types are involved, the quality of the ABEEM charges of transition metals and other atoms in the training molecules is good. For the investigated metallobiomolecules, the charge distributions obtained by the ABEEM method are in fair correlation with those obtained from the B3LYP/6-31G* method. The linear correlation coefficients R of the charge distributions for more than 300 training molecules and the above-mentioned eight large metallobiomolecules are all over 0.98. The present study shows the calibrated parameters are reasonable and applicable, and the ABEEM method can predict and calculate charge distribution of metallobiomolecules with high accuracy and high speed. At present, more applications of the ABEEM method in this respect are in progress.

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Supporting Information Available: Frame structures of some model molecules (I) (Figure S1); some optimized values of parameters of χ^* and $2\eta^*$ in the ABEEM (II) (Table S1); atom type codes in ligands (III) (Figure S2); and comparisons of the ABEEM and the DFT charge distributions for V, Cr, Co, Ni, Cu, and Zn training molecules (IV) (Figure S3). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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