Empirical and Accurate Method for the Three-Dimensional Electrostatic Potential (EM-ESP) of Biomolecules

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The electrostatic potential (ESP) is an important property of interactions within and between macromolecules, including those of importance in the life sciences. Semiempirical quantum chemical methods and classical Coulomb calculations fail to provide even qualitative ESP for many of these biomolecules. A new empirical ESP calculation method, namely, EM-ESP, is developed in this study, in which the traditional approach of point atomic charges and the classical Coulomb equation is discarded. In its place, the EM-ESP generates a three-dimensional electrostatic potential $V_{EM}(r)$ in molecular space that is the sum of contributions from all component atoms. The contribution of an atom k is formulated as a Gaussian function $g(r_k;\alpha_k,\beta_k) = \alpha_k/r_k^{\beta k}$ with two parameters (α_k and β_k). The benchmark for the parameter optimization is the ESP obtained by using higher-level quantum chemical approaches (e.g., CCSD/TZVP). A set of atom-based parameters is optimized in a training set of common organic molecules. Calculated examples demonstrate that the EM-ESP approach is a vast improvement over the Coulombic approach in producing the molecular ESP contours that are comparable to the results obtained with higher-level quantum chemical methods. The atom-based parameters are shown to be transferrable between one part of closely related aromatic molecules. The atom-based ESP formulization and parametrization strategy can be extended to biological macromolecules, such as proteins, DNA, and RNA molecules. Since ESP is frequently used to rationalize and predict intermolecular interactions, we expect that the EM-ESP method will have important applications for studies of protein−ligand and protein−protein interactions in numerous areas of chemistry, molecular biology, and other life sciences.

1. Introduction

The molecular electrostatic potential (ESP) has became a powerful predictive and interpretive tool in disparate areas of chemistry and biology, such as protein−ligand and protein−protein interactions, protein folding, and rational drug design.[1] The use of electrostatic potentials in predicting sensitivities of energetic compounds was pioneered by Murray et al in a series of papers in Molecular Physics in the late 1990s; this was clearly stated by Rice et al.[2,3] They simply applied the method of Murray et al. to a large number of molecules. In almost all computer software programs for computer-aided drug design and other life sciences applications, colorful plots of ESPs are used to rationalize trends in organic reactivity[4] and binding in host−guest complexes.[5−10] Quantitative ESP-based reactivity descriptors have also emerged, offering alternatives to traditional substituent constants.[11−16] Accurate computational ESPs have also been used to explore trends as important and as diverse as impact sensitivities of explosive compounds[17] and toxicity in polychlorinated biphenyls.[18]

In quantum chemistry, the ESP value $V(r)$ at position r in molecular space is defined and calculated according to the following equation

$$V_{QM}(r) = \left\langle \Psi \left| \frac{1}{r} \right| \Psi \right\rangle = \sum_{A=1}^{n} \frac{Z_A}{|R_A - r|} - \sum_{\mu,\nu} P_{\mu\nu} \int \frac{\phi_\mu^*(r')\phi_\nu(r')\nu dr'}{|r' - r|} \quad (1)$$

where Ψ is the wave function of molecule A, Z_A and R_A are the charge and position of nucleus A, respectively, n is the number of component atoms, $P_{\mu\nu}$ are elements of density matrix, and μ and ν are indices of basis functions ϕ_μ and ϕ_ν, all in atomic units. The integral in eq 1 runs over all molecular space. The electrostatic interaction energy between molecule A and a point charge q_k can be easily evaluated as follows

$$E_A(r_{A,k}) = V_A(r_{A,k})q_k \quad (2)$$

where $V_A(r_{A,k})$ is the ESP of molecule A at distance $r_{A,k}$ between molecule A and charge q_k. Therefore, the ESP is widely used to explain the electrostatic interactions in molecular interactions.

The ESP is a one-electron property and can be obtained quite accurately with the Hartree−Fock procedure and small basis sets.[4] However, it is still difficult to apply such ab initio quantum chemical calculations to macromolecules. The semiempirical quantum chemical approach cannot provide totally accurate ESPs because these kinds of methods use atom pseudopotentials. The electrostatic potentials computed using the classical Coulomb equation and atomic partial charges are

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TABLE 1: Atomic Mulliken Charges and ESP-Equivalent Charges[a] Obtained from CCSD/TZVP Calculation and the EM-ESP Parameters for the Atoms in Ethanol

			ESP_{EM} parameter	
atomic type	mulliken charge[a]	ESP charge[a]	α	β
$C_1(-CH_2OH)$	0.0542	0.5648	0.10910	3.84325
$C_2(-CH_3)$	−0.2185	0.1626	0.13026	3.36855
O	−0.4465	−0.7761	0.03218	4.88268
O_{lp}[b]			−0.05542	1.54259
$H_p(OH)$	0.2715	0.4175	0.11673	1.71177
H_{11}	0.0517	−0.1082	0.02424	3.21847
H_{12}	0.0517	−0.1082	0.02424	3.21847
H_{21}	0.0685	−0.0917	0.02424	3.21847
H_{22}	0.0837	−0.0303	0.02424	3.21847
H_{23}	0.0837	−0.0303	0.02424	3.21847

[a] Ab initio CCSD/TZVP calculation. [b] The center of the lone pair electrons is in the sp^3 hybrid direction and centered at a distance of 1.203 Å from the oxygen nucleus.

fundamentally different from the ESPs derived via ab initio quantum chemical methods because the Coulomb law ignores the electron structures of molecules, replacing them with simplified point charges. In section 2, the crude molecular ESP contours calculated using the Coulomb equation and the atomic partial charges are compared with that obtained from more sophistical methods.

In this study, we propose an empirical ESP calculation method (EM-ESP), in which the concept of traditional atomic charges and the classical Coulomb equation approach are replaced with the empirical EM-ESP method. In this case, the three-dimensional ESP $V_{EM}(r_i)$ in molecular space is computed based on the molecular structures (PDB data of proteins) and using empirical equations and a set of atomic ESP parameters. In contrast to the higher-level quantum chemical methods, these calculations can be performed on a personal computer in only a few seconds. The electrostatic potentials calculated using the empirical equations and the atomic ESP parameters compare favorably with the ab initio electrostatic potentials, for example, CCSD/TZVP.

2. Theory and Methods

In molecular dynamics (MD),[19,20] the nonbonded electrostatic interaction is computed according to Coulomb's law

$$\Delta E_{elec}(r_{i,j}) = \frac{q_i q_j}{r_{i,j}} = V_{CL}(r_{i,j}) q_j \tag{3}$$

where the q_i and q_j are atomic partial charges, $r_{i,j}$ is the distance between atoms i and j, and $V_{CL}(r_{i,j}) = q_i/r_{i,j}$ is the Coulomb ESP of charge q_i at distance $r_{i,j}$. On the basis of eq 3, the electrostatic interaction is a long-range property, decaying slowly as a function of $1/r_{i,j}$. Therefore, the electrostatic interaction is the dominant factor in the molecular interactions, and the atomic charges are the most important parameters in the force field for the MD simulations.[19,20]

The atomic partial charges can be directly derived from higher-level theoretical calculations or by fitting the theoretical or experimental potentials using a least-squares technique. For example, the Mulliken atomic charges are obtained from the Mulliken population analysis[21] of the quantum mechanical molecular orbitals (MO), and the ESP-equivalent atomic charges[22−25] are obtained by fitting the quantum chemical electrostatic potentials on the molecular surface. Table 1 lists the atomic Mulliken charges and ESP-equivalent charges of ethanol obtained from ab initio quantum chemical calculations using the CCSD[26−28] method and TZVP basis set.[29]

In the empirical method EM-ESP, the electrostatic potential of a molecule is the sum of atomic contributions from all component atoms. The atomic ESP contribution of atom k is evaluated using a Gaussian function

$$g_k(r_{i,k};\alpha_k,\beta_k) = \frac{\alpha_k}{|r_i - r_k|^{\beta_k}} \tag{4}$$

where r_k is the position of atom k, r_i is a point in molecular space, and $r_{i,k}$ is the distance between r_k and r_i. The Gaussian type function $g(r_{i,k};\alpha_k,\beta_k)$ of atom k has two parameters α_k and β_k. The former is similar to the atomic charge, and the latter controls the speed with which ESP decays with the distance $r_{i,k}$. For the atoms in a π-conjugate system, such as carbon, nitrogen, and oxygen, two Gaussian functions are used; one is above the π-plane and the other below the π-plane. For the atoms with lone electron pairs, more Gaussian functions are used for the lone electron pairs. Thus, the electrostatic potential of a molecule at position r_i is the sum of contributions from all components of all of the atoms (including the Gaussian functions for lone electron pairs and the additional Gaussian functions for π-conjugate atoms)

$$V_{EM}(r_i) = \sum_{i=1}^{Atoms} g_k(r_{i,k};\alpha_k,\beta_k) = \sum_{i=1}^{Atoms} \frac{\alpha_k}{|r_i - r_k|^{\beta_k}} \tag{5}$$

The atom-based ESP parameters $\{\alpha_k,\beta_k\}$ are classified into atomic types (e.g., terminal aliphatic carbon and methyl group hydrogens), and the parameters are optimized based on benchmark quantum chemical calculations performed on a molecular training set consisting of common organic molecules.

3. Calculation Results

In this section, the detailed optimizations of ESP parameters are introduced using ethanol as an example. In the quantum chemical benchmark calculations, the coupled cluster theory with single and double excitations (CCSD) method[28,29] and the TZVP (triple-ζ valence and polarization) basis set[30,31] is used. The structure and orientation of ethanol are shown in Figure 1A, which is optimized at the CCSD/TZVP level.

3.1. Optimization of ESP Parameters. In Figure 1A, the five atoms, C_1, C_2, O, H_p (polar hydrogen), and H (nonpolar hydrogen) are in the X−Y plane. A square grid (7.0×7.0 Å^2) is set up on the X−Y plane with a 0.035 Å increment, for a total of 40400 points. The electrostatic potentials at the 40400 points are calculated at the CCSD/TZVP level. The contour map of the ESP_{QM} in the X−Y plane is shown in panel (B).

For a better optimization result, we selecte five special radial directions, which are indicated in Figure 1A by green arrows. These directions are important for chemical reactions and molecular interaction. In each radial direction, 1000 points from 0.6 to 10 Å are used for ESP_{QM} calculations at

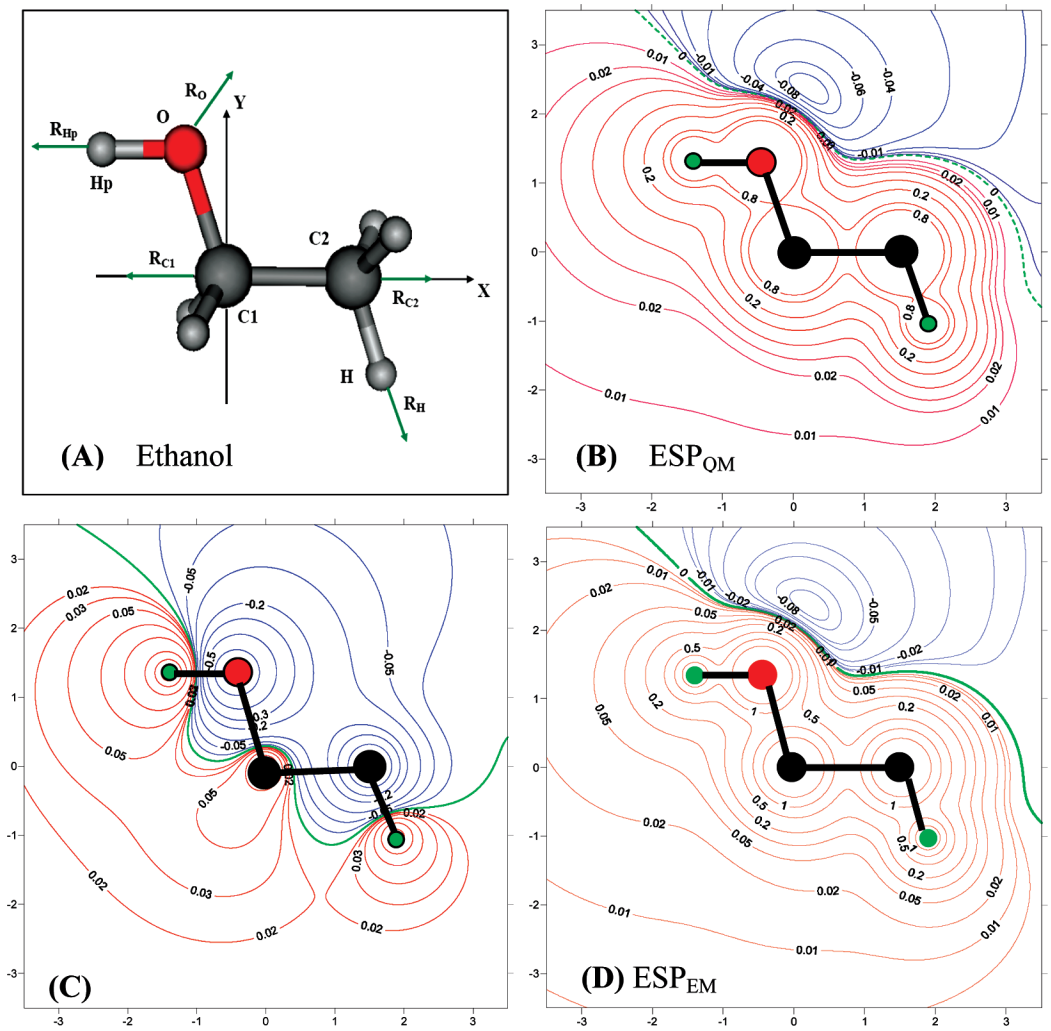

Figure 1. (A) The geometry of ethanol is optimized at the CCSD/TZVP level. The five atoms C_1, C_2, O, H_p (polar hydrogen), and H (nonpolar hydrogen) on the X−Y plane represent five types of atoms. The five green arrows indicate the radial directions in which the EM-ESP is calculated and optimally parametrized for each of the five atoms in the X−Y plane. (B) The quantum chemical contour map of ESP_{QM} calculated at the CCSD/TZVP level. (C) The ESP_{CL} contour map of ethanol in the X−Y plane calculated using the Coulomb equation and Mulliken atomic charges. (D) The ESP_{EM} contour map of ethanol in the X−Y plane calculated using empirical method EM-ESP and atom-based parameters optimized by the authors.

the CCSD/TZVP level. Then, the 5000 ESP_{QM} values are used as the benchmarks for atomic ESP parameter optimizations using the SIMPLEX method.[32] The nine atoms of ethanol are classified into six atomic types C_1, C_2, O, O_{lp} (lone electron pair of oxygen), H, and H_p (polar hydrogen), as listed in Table 1. Careful examination of the ESP_{QM} contour map reveals that the negative ESP area is located around the positions of lone electron pairs of the oxygen atom. Therefore, the lone electron pair of oxygen has its own ESP parameters and positions that are different from the oxygen atom per se. The central positions of two oxygen lone electron pairs are determined according to sp^3 hybridization of the oxygen atom. The optimization results of the total 12 parameters of ethanol are listed in Table 1. All five atomic types (C_1, C_2, O, H_p, and H) possess positive α parameters, and only in the region of the lone electron pairs of oxygen O_{lp} is there a negative α parameter. The most surprising result is that distance-decaying parameters β for the six atomic types are much larger than 1, denoting that the ESP_{QM} decreases with distance much faster than the simple Coulomb equation approach would suggest.

In order to check the effects of the optimized parameters and the EM-ESP equations, the ESP_{EM} contour map of ethanol was generated using the parameters listed in Table 1 and eq 5, which in this case is

$$V_{EM}(r_i) = \sum_{k=1}^{11} \frac{\alpha_k}{|r_i - r_k|^{\beta_k}} \tag{6}$$

The summation in eq 6 runs over nine atoms and the two lone electron pairs of oxygen. The ESP_{EM} contour map of ethanol is shown in Figure 1D, which is almost exactly the same as the quantum chemical ESP_{QM} contour map.

For comparison, the contour map of the classical electrostatic potential ESP_{CL} was generated using the Coulomb equation

$$V_{CL}(r_i) = \sum_{k=1}^{9} \frac{q_k}{|r_i - r_k|} \tag{7}$$

where q_k are the atomic Mulliken charges obtained from CCSD/TZVP calculations. The associated ESP_{CL} contour map for ethanol in the X−Y plane is shown in Figure 1C. In the quantum chemical contour map in Figure 1B, the areas surrounding all

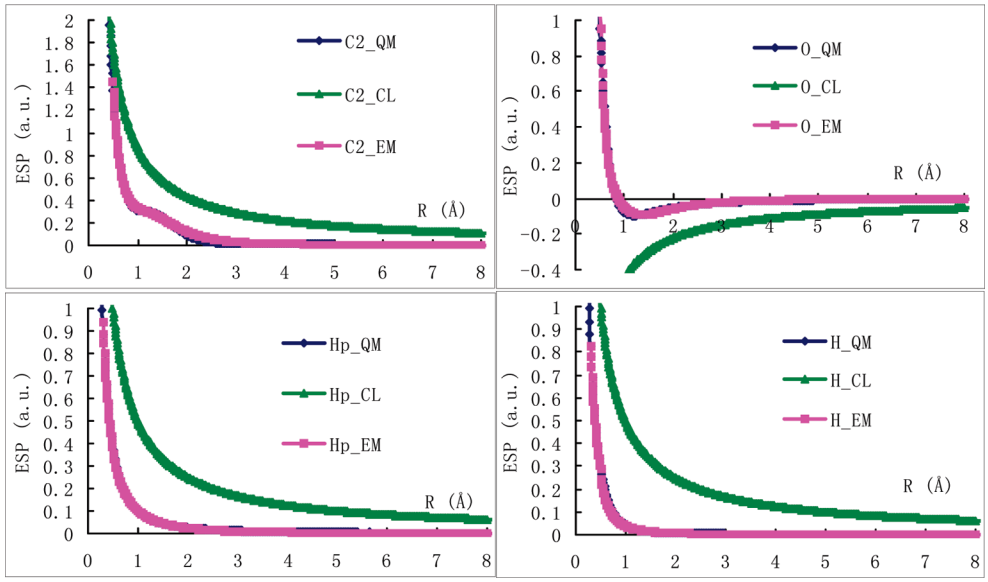

Figure 2. The plots of ESP versus *R* (radial distance) of four atoms C_1, O, H_p (polar hydrogen), and H (nonpolar hydrogen) of ethanol computed using three methods, quantum mechanics (QM), the EM-ESP method (EM), and the classical Coulomb equation (CL). The radial ESP curves of atoms C_1, H_p, and H are positive and exponentially decay with the radial distance, much faster than the Coulomb equation does. However, the ESP curve of the oxygen atom has a negative minimum like the van der Waals potential, which is caused by lone electron pairs. The curve shapes and values of the EM-ESP (EM) method and the quantum chemical (QM) method are in good agreement. However, the curves calculated using the Coulomb equation are significantly different than those of the quantum chemical method.

five atomic nuclei (C_1, C_2, O, H_p, and H) have positive electrostatic potentials, denoted by red lines. However, in the area where the lone pair electrons of the oxygen atom are located, the ESPs are negative (blue lines). This result is quite different from the picture derived from the classical viewpoint, in which the traditional MD parametrization results in the oxygen and carbon atoms often being assigned negative charges. However, the results are quite consistent with our previous findings,[33−37] which showed that the molecular surfaces of hydrophobic hydrocarbon chains ($-CH_2CH_3$) are surrounded by ESPs with the same sign, which is the reason for the molecular hydrophobicity. In the contour map of ESP_{CL}, the areas surrounding the nuclei O and C_2 are negative ESPs, which adjoin the positive ESP areas surrounding the nuclei of H_p, C_1, and H, resulting in regions of positive and negative potential within the chemical bonds C_1-C_2 and C_1-O. Therefore, the ESP_{CL} contour map is significantly different from the ESP_{QM} map, both qualitatively and quantitatively, implying that the Coulomb equation and the traditional atomic charges of MD cannot describe the electrostatic interactions correctly.

In the next step, the EM-ESP parameters and eq 6 were used to calculate the ESP values in the five radial directions shown in Figure 1. The plots of ESP_{EM} versus *R* (radial distance) are shown in Figure 2. For comparison, the plots of ESP_{QM} versus

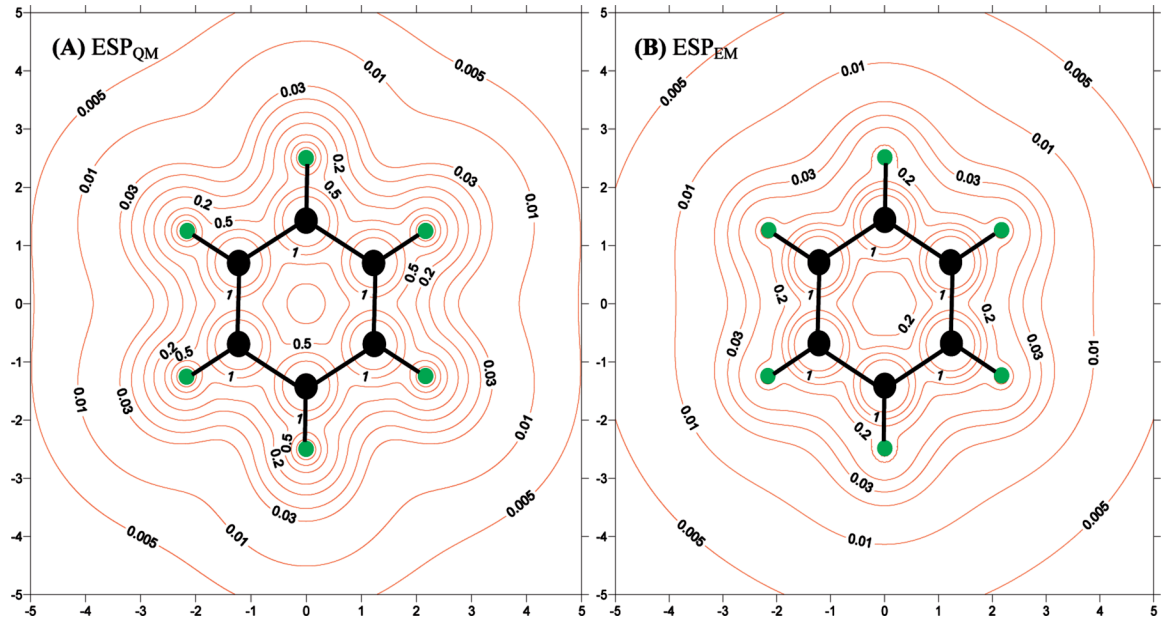

Figure 3. (A) The quantum chemical ESP_{QM} contour map of benzene is computed using the CCSD/TZVP method. (B) The empirical electrostatic potential ESP_{EM} contour map of benzene is calculated using the EM-ESP equation and optimized atomic parameters for aromatic molecules. The two contour maps agree quite well qualitatively (in shape) and quantitatively (in ESP values), implying the reliability of EM-ESP parameters.

TABLE 2: Optimized EM-ESP Parameters and Classification for Common Organic Compounds and Proteins

atomic type	atomic group	ESP_{EM} parameter		note
	compound	α	β	
Aliphatic[a]				
C	$-CH_3$	0.06763	3.04364	
C	$-CHR_2$	0.09118	3.53658	
C	$-CR_3$	0.11473	4.02952	
C	$-CH_2X$	0.21181	2.04698	
O	OH	0.13536	2.24529	
O_{lp}	OH	−0.13650	1.75200	sp^3
O	=O	0.02806	6.24596	
O_{lp}	=O	−0.08028	1.17021	sp^2
H	C (sp^3)	0.03989	1.87601	
H_p	OH	0.08832	1.85337	
H_p	NH	0.09854	1.22210	
N	AL_2-NH	0.11392	3.34279	
N	$AL-NH_2$	0.11392	3.34279	
N_{lp}	AL_2-NH	0.07241	1.88272	sp^2
Aromatic[b]				
C	$=CR_2$	0.10690	7.70388	$h = \pm 0.6$ Å
C	=CRX	0.10690	7.70388	$h = \pm 0.6$ Å
H	C (sp^2)	0.01288	1.74505	
N	>N−R	0.12664	6.45006	$h = \pm 0.6$ Å
H	−HN−R	0.09854	1.22210	

[a] R represents any group linked through carbon. X represents O, S, N, and halogen. A_{lp}: Subscript lp represent the lone electron pair of atom A. The position of the lone electron pair is determined according to the hybrid of master atom. [b] The atoms in a π-conjugate system have two Gaussian functions; one is above the π-plane, and the other is below the π-plane. The h is the distance with the π-plane.

R and ESP_{CL} versus R are also shown in Figure 2. The radial ab initio ESP_{QM} curves in the directions from atoms C_1, H_p, and H are positive and exponentially decay with the radial distance much faster than the ESP_{CL} does. However, the ESP_{QM} curve in the direction from the oxygen atom has a negative minimum like the L-J van der Waals equation, which is caused by the presence of the lone electron pairs. The shapes of the curves for the EM-ESP and QM methods match each other very well. However, again, the curves calculated using the Coulomb equation are significantly different from the QM curves, decaying with the distance too slowly.

3.2. Transferability of EM-ESP Parameters for Aromatic Molecules. The transferability of atom-based EM-ESP parameters for aromatic molecules is a significant problem in empirical approaches to quantum mechanical calculations. In this section, we optimize the EM-ESP parameters for benzene (C_6H_6) and then apply those values to phenol (C_6H_5OH), thereby assessing the transferability of the EM-ESP parameters for closely related aromatic molecules.

In the aromatic molecules, the majority of electron density is not in the π-plane but concentrates in the regions above and below the π-plane. In the benzene molecule, two Gaussian functions are used for each aromatic carbon atom; one depicts the behavior above the π-plane, and the other describes the condition below the π-plane, separated by 1.2 Å and perpendicular to π-plane. The EM-ESP parameters of the carbon and hydrogen atoms are optimized based on the CCSD/TZVP benchmark calculations. In the parameter optimization, the ESP_{QM} benchmark values include the ESPs in the π-plane and on four molecular surfaces.[38,39] One is the standard van der Waals surface, and the other three surfaces are built using scaling factors of 0.8, 1.5, and 2.0.

Next, eq 5 and EM-ESP parameters of aromatic carbon and hydrogen were used to calculate the ESP_{EM} values of benzene in the π-plane. The ESP_{QM} and ESP_{EM} contour maps of benzene are shown in Figure 3A and B, respectively. The two contour maps agree quite well, suggesting that the optimized aromatic EM-ESP parameters are reliable. The most surprising finding in the aromatic EM-ESP parameter optimization is that the aromatic carbon atom has a very large β parameter ($\beta = 7.7039$), implying that the ESPs of the π-electron density highly concentrate surrounding the carbon atoms. It also implies that the transferability of aromatic EM-ESP parameters to related

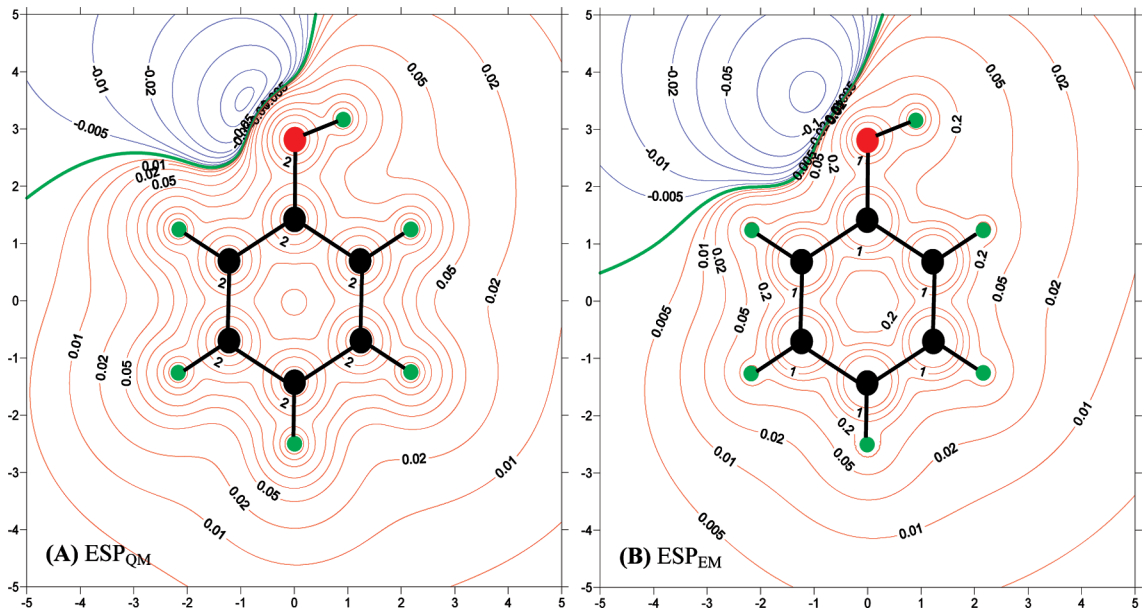

Figure 4. (A) The quantum chemical ESP_{QM} contour map of phenol is computed using the ab initio CCSD/TZVP method. (B) The empirical electrostatic potential ESP_{EM} contour map of phenol is calculated using the EM-ESP method and atomic parameters for aromatic molecules. The two contour maps match very well in shapes and in ESP values, implying the reliability and the transferability of aromatic EM-ESP parameters.

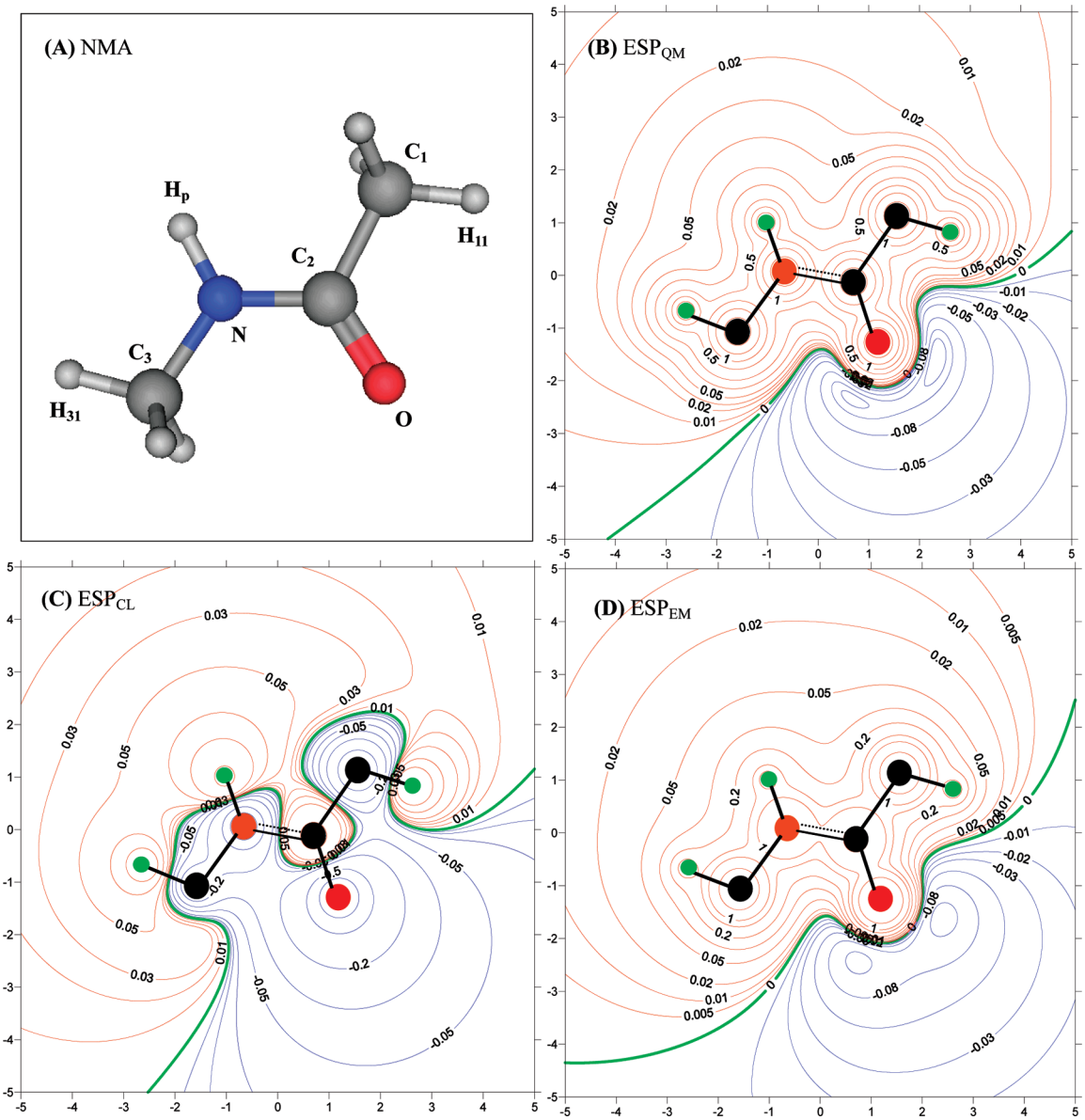

Figure 5. (A) The geometry of NMA (*N*-methyl acetamide) optimized at the CCSD/TZVP level. The atoms C_2, N, and O form a peptide bond, which is a partial double bond (quasi π-bond). The atoms H_{11}, C_1, C_2, O, N, H_p (polar hydrogen), C_3, and H_{31} are in the X−Y plane. (B) The ESP_{QM} contour map in the X−Y plane of NMA is calculated using the quantum chemical CCSD/TZVP method. (C) The ESP_{CL} contour map in the X−Y plane of NMA is calculated using the classical Coulomb equation and atomic Mulliken charges. (D) The ESP_{EM} contour map of NMA is calculated using the empirical method EM-ESP and parameters. The ESP_{EM} contour map agrees very well with the quantum chemical map ESP_{QM}, in marked contrast to the ESP_{CL} map.

aromatic structures may be useful, as well. All optimized EM-ESP parameters are summarized in Table 2.

The transferability was tested using phenol as an example. Specifically, the ESP_{QM} contour map was calculated using the CCSD/TZVP method, and the ESP_{EM} contour map of phenol was generated using the EM-ESP method and parameters. In the EM-ESP calculations for phenol, the parameters of aromatic carbon and hydrogen are the same as those in benzene, and the parameters of the hydroxyl group (−OH) are the same as those in ethanol. The ESP_{QM} and ESP_{EM} maps, which are shown in Figure 4A and B, respectively, are in close agreement, illustrating the reliability and transferability of EM-ESP parameters.

3.3. Application of EM-ESP Parameters to a Peptide. A current list of atomic types and their associated EM-ESP parameters is shown in Table 2. So far, the number of such atomic types with EM-ESP parameters is insufficient to generate ESP_{EM} calculations for complete proteins. However, more atomic types and EM-ESP parameters will be added in the coming months.

In the meantime, *N*-methyl acetamide (NMA) can be considered a mini peptide, containing a single peptide bond. As an example, the EM-ESP method and parameters were used to calculate the ESP_{EM} of NMA. The geometry of NMA is shown in Figure 5A, which is optimized at the CCSD/TZVP level. The atoms C_2, N, and O form the peptide bond, which has a partial double-bond character (a quasi π-bond). The atoms H_{11}, C_1, C_2, O, N, H_p (polar hydrogen), C_3, and H_{31} are in the X−Y plane. The quantum chemical ESP_{QM} contour map in the X−Y plane of NMA is calculated using the CCSD/TZVP method, shown in Figure 5B. For comparison, the ESP_{CL} contour map of NMA is calculated using the classical Coulomb equation and atomic Mulliken charges and is shown in Figure 5C. The ESP_{EM} contour map of NMA is shown in Figure 5D, which is calculated using empirical method

EM-ESP and parameters listed in Table 2. The ESP_{EM} contour map compares quite well with the quantum chemical map ESP_{QM}, which again is in marked contrast to the ESP_{CL} map.

4. Discussion and Conclusion

The electrostatic potential is one of the dominant factors in molecular interactions. Molecules are collections of positive nuclei held together by complex electronic interactions. Merely assigning partial charges to the nuclei to account for the presence of the electrons in order to use simple Coulombic interaction methods cannot accurately describe the electrostatic interaction between molecules. Our use of the EM-ESP method and parameters, in lieu of partial charges, to study molecular interaction reveals that the molecular ESPs are not a long-range property, as suggested by the Coulombic approach, but rather, they decay at a much faster rate with distance. For atoms in aliphatic molecules the decaying factors (the β parameters in the exponent) are between 2 and 4, and for atoms in aromatic molecules, the decaying factors are between 6 and 7.

The transferability of atom-based charge parameters of aromatic molecules is often questioned for many molecular properties. The large β parameters of aromatic atoms in a conjugated π-system imply tight ESP distributions around the aromatic atoms and, therefore, good transferability of ESP_{EM} parameters in aromatic molecules. Several research groups[40−43] have demonstrated that most substituents have no significant effect on the ESPs of benzene. Their conclusion agrees well with our findings. However, this question needs more examination than the single example that we have reported so far, and it will be the focus of future work.

In the calculation examples, α parameters of all atomic types are positive, even for electronegative atoms oxygen and nitrogen. Only the lone electron pairs have negative α parameters, and the areas of negative ESP are always in the region of the lone electron pairs.

Unlike ESP-equivalent atomic charges,[22−25] which are obtained by fitting the QM electrostatic potentials only on the molecular van der Waals surface, the EM-ESP parameters are obtained by fitting the QM electrostatic potentials in all molecular interaction space. The empirical ESP equation has a simple mathematical form so that there is no need for complex calculations and large computational resources. In fact, the EM-ESP calculation can be performed on a personal computer in only a few seconds. The ESP parameters are classified according to the atomic types. Therefore, it can be built up and applied to more complex systems.

Furture work will include expanding on the library of ESP parameters that are available for different atomic types. The intent is to extend the method so that interaction between complex systems, such as protein molecules and other biological macromolecules, can be confidently studied in many areas of chemistry and molecular biology.

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