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Direct Evaluation of Nonbonding Interactions from ab Initio Calculations

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Abstract: Nonbonding interatomic interactions underlie a variety of biological events, including ligand binding to proteins and molecular assembly. The rigorous characterization of these interactions is necessary if we are, ultimately, to achieve an understanding of these events in terms of intermolecular forces. Here, we show how fitting of particular second derivatives extracts direct information on atom–atom nonbonding interactions. We present a novel technique based on these derivatives for extracting such properties as atomic partial charge, transferability, anisotropy of atom–atom repulsion and polarizability, as well as the constants that characterize these interactions, from the quantum mechanical energy surfaces.

Nonbonding interactions, including electrostatic, steric repulsion, and dispersion, are crucial to the calculation and understanding of the conformation and interactions of biomolecular systems.[1-9] These intermolecular forces determine to a large extent the results obtained from molecular dynamics and mechanics simulations of proteins, peptide hormones, free energy of ligand binding, and therefore the success of these techniques in such applications as drug design.[10-15] Their importance transcends these applications and extends to the study of condensed phases, including liquid-state properties and crystal packing.[14,15] It is the central importance of these studies that have stimulated such intense effort in recent years, including the effort to describe partial atomic charge distribution in molecules.[4,5,7]

We have recently presented a novel method to derive analytical representations of the energy surface (potential energy functions) from quantum mechanical calculations.[16] In particular, we have shown how the vast quantity of information implicit in analytical first and second derivatives of the ab initio energy provide a powerful tool to derive and explore analytical representations. Here we show how a variation of this technique—the use of particular second derivatives of the energy of dimers—can be utilized in a similar way to explore the important electrostatic and exchange repulsion (steric) interactions in biomolecular and pharmacologic functional groups discussed above. We show how we can simultaneously derive both the characteristic partial atomic charges (in the Coulomb representation) and the repulsion parameters. More importantly, perhaps, we show how the ab initio method can be used to probe the nature of these interactions, including the crucial factors of transferability, anisotropy of the nonbonding repulsion (a property heretofore inaccessible), polarizability, and the reaction of partial charges (electron distribution) to distortion of molecular geometry. We use dimers of some simple model compounds to obtain this information. These systems, shown in Figure 1, constitute a relatively simple case of nonbonding interactions since the charge transfer between the monomers is either zero by symmetry or negligibly small.

To demonstrate the specific information about atom–atom nonbonding interactions that is contained in the second derivatives of the energy, consider the D_{2h} water dimer. A common representation of its total energy is given by eq 1 (see ref 16 for a consideration of more elaborate force fields).

$$
\begin{aligned}
E = {} & \\
& \frac{1}{2}K_{b_{OH}}(b_{O_AH_A} - b^0{}_{OH})^2 + \frac{1}{2}K_b(b_{O_AH_{A'}} - b^0{}_{OH})^2 + \frac{1}{2}K_{\theta_{HOH}}(\theta_{H_AO_AH_{A'}} - \theta^0{}_{HOH})^2 \\
& \qquad\qquad\qquad\qquad \text{I} \\
& + \frac{1}{2}K_b(b_{O_BH_B} - b^0{}_{OH})^2 + \frac{1}{2}K_b(b_{O_BH_{B'}} - b^0{}_{OH})^2 + \frac{1}{2}K_{\theta_{HOH}}(\theta_{H_BO_BH_{B'}} - \theta^0{}_{HOH})^2 \\
& \qquad\qquad\qquad\qquad \text{II} \\
& + A_{OO}/R_{O_AO_B}{}^{12} - C_{OO}/r_{O_AO_B}{}^{6} + q_{O_A}q_{O_B}/r_{O_AO_B} \\
& \qquad\qquad \text{III} \\
& + \sum_{\substack{\text{All}\\ O_AH_BO_BH_A}} \{A_{OH}/r_{OH}{}^{12} - C_{OH}/r_{OH}{}^{6} + q_Oq_H/r_{OH}\} \\
& \qquad\qquad\qquad \text{IV} \\
& + \sum_{\substack{\text{All}\\ H_BH_A}} \{A_{HH}/r_{H_AH_B}{}^{12} - C_{HH}/r_{H_AH_B}{}^{6} + q_{H_A}q_{H_B}/r_{H_AH_B}\} \qquad (1) \\
& \qquad\qquad\qquad \text{V}
\end{aligned}
$$

Let us now consider the second derivative of the energy with respect to the x coordinates of two oxygens, i.e., $\partial^2E/\partial x_{O_A}\partial x_{O_B}$. When we take the first derivative of E with respect to the x coordinate of the oxygen on molecule A, i.e., $\partial E/\partial x_{O_A}$, all terms not containing the position of oxygen A disappear, since they do not depend on x_{O_A}. In particular, derivatives of the intramolecular interactions in molecule B in the second line (II) and all nonbonding hydrogen–hydrogen terms (V), as well as the two interactions between the hydrogens in molecule A and the oxygen in molecule B (IV), are zero. Then when we take the derivative of this derivative with respect to x_{O_B}, i.e., $(\partial/\partial x_{O_B})(\partial E/\partial x_{O_A}) = (\partial^2E/\partial x_{O_B}\partial x_{O_A})$ all remaining terms not containing the position of x_{O_A}, i.e., all terms but those in III

$$(A/r_{O_AO_B}{}^{12}) + (C/r_{O_AO_B}{}^{6}) + (q_{O_A}q_{O_B}/r_{O_AO_B}) \qquad (2)$$

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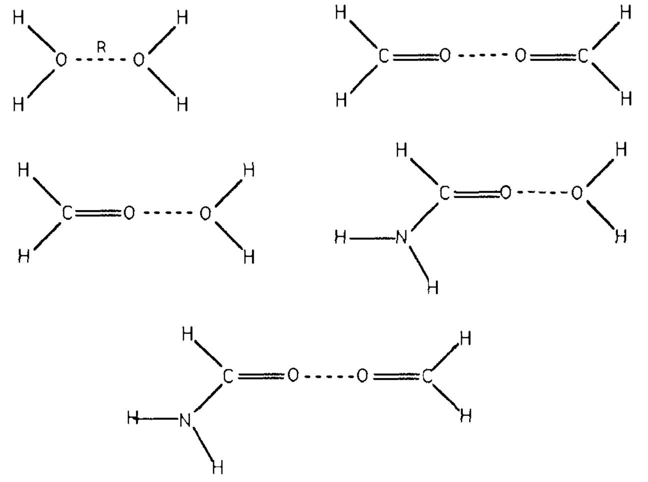

Figure 1.

disappear. Thus, the second derivative with respect to the coordinates of the two oxygens *gives direct information on the pairwise interaction between the two oxygens*. Of course, the same holds true for all the dimers in Figure 1 and for any potential of any form where the intramolecular terms do not depend on the position of an atom in a neighboring molecule, and the nonbonding parameters and partial charges are independent of the intramolecular geometry or of the positions of nearby atoms. This is the case for all potentials currently being applied to biomolecular systems.[1,6,8,9,11]

The key to exploring the properties of the O···O interaction as described above, including partial charges, transferability, anisotropy, etc., is to fit the ab initio second derivatives with an analytical representation of the nonbonding interaction and assess the ability of this analytic representation to describe the energy surface as reflected in those derivatives. We have carried out Hartree–Fock calculations (6-31G** basis set) for the five dimers shown in Figure 1, for various intermolecular distances and extracted all of the second derivatives of the energy as a function of O···O separation. In the following sections we use the derivatives with respect to the coordinates of the oxygen atoms to investigate the oxygen–oxygen steric repulsion and Coulomb interaction. The notation $H^{OO}_{xx'}$ is used for the derivative $\partial^2 E/\partial x_{O_A}\partial x_{O_B}$ since it is an element of the Hessian matrix.

Since the most common analytical representation of interatomic potential is as given in eq 2, namely a Lennard-Jones potential and a Coulomb type interaction with partial atomic charges placed on the nuclei, we first tested the ability of this form to account for the O···O intermolecular interaction. The dispersion interactions are not accounted for by Hartree–Fock calculations, and the R^{-6} term was accordingly omitted from fitting the ab initio second derivatives. A linear least-squares method was employed so that the charge product in (2), rather than the atomic charges, was obtained from the fitting.

Self-Polarization

The first observation that emerged from the calculations was that the partial charges and characteristic repulsive parameter, A, which best fit the second derivatives of a single dimer in different directions $H^{OO}_{xx'}$, $H^{OO}_{yy'}$, and $H^{OO}_{zz'}$ were significantly different. On the basis of the assumptions underlying current analytic potential functions as outlined above, this cannot occur. Further analysis revealed that the "problem" stems from different self-polarizations of the monomers along the different axes. Thus, displacing the oxygen in a water molecule from its equilibrium position (which is implicit in the second derivative discussed above) changes the electron distribution and this change has a different magnitude along the x, y, and z axes. In force-field nomenclature this would mean that we cannot assign a fixed partial charge to an atom as currently done but would need to make this charge a function of the intramolecular geometry. This effect, which is the polarization of the monomer by its own vibration, is closely related to the well-known fact that partial atomic charges derived from IR intensities of the isolated monomer are anisotropic.[17] Here we find that it affects the interaction in the dimer as well. A simple demonstration is provided in Figure 2. In this case two water molecule are considered at the D_{2h} orientation as in Figure 1. At large distances the interaction between the monomers is purely electrostatic and the coupling second derivative of (2) enables the determination of the atomic charges (i.e., the repulsive part is negligible). Figure 2 shows q, as obtained from $H^{OO}_{xx'}$, $H^{OO}_{yy'}$, and $H^{OO}_{zz'}$, as a function of the distance between the oxygens. Clearly, there are three limiting values, significantly different from each other. In accordance with the analysis[17] these values are found to be identical with the three diagonal elements of the atomic polar tensor, namely, $\partial\mu_x/\partial x$, $\partial\mu_y/\partial y$, and $\partial\mu_z/\partial z$.

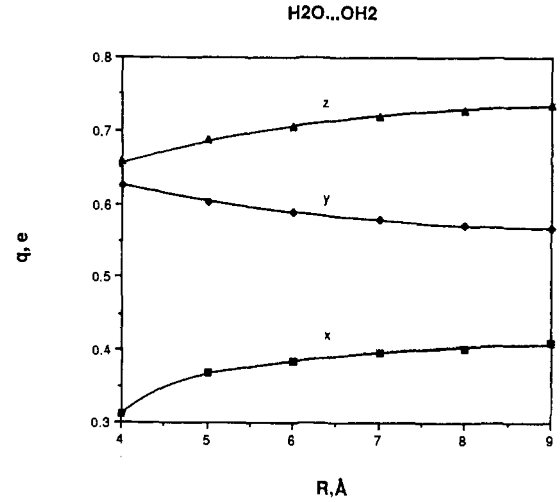

Figure 2. Partial atomic charge on the oxygen in H_2O as derived from $H^{OO}_{zz'}$ of the D_{2h} H_2O···OH_2 dimer in Figure 1. The abscissa is the distance between the two oxygens. At large distances the interaction is purely electrostatic and $H^{OO}_{zz'} \rightarrow q_O{}^2/R^3$.

Table I. O···O Parameters[a] As Obtained from Derivatives of an ab Initio Energy Surface

dimer	Q^2	A	rel dev
H_2O···OH_2	0.4193	61 552.3	0.003
CH_2O···OCH_2	0.2541	128 683.5	0.035
CH_2O···OH_2	0.3120	85 674.8	0.019
NH_2CHO···OH_2	0.3326	73 230.5	0.011
NH_2CHO···OCH_2	0.2583	107 584.1	0.029

[a] 6-31G** Hartree–Fock calculations. The distance between the oxygens was varied from 2.3 to 3.1 Å while the geometries of the monomers were held fixed at the equilibrium values. Q^2 is the charge product q_Aq_B and is given in e^2, A in kcal·Å^{12}/mol.

Nonbonding Parameters for Interactions between Rigid Bodies

While a detailed study of the importance and possible analytical representation of the self-polarization effect will be deferred to a later stage, we note that in the case of the planar symmetry of the water dimer discussed here (D_{2h}) a small movement of the oxygen in the z direction, perpendicular to the plane, corresponds to a rigid rotation of the molecule, whereas in-plane displacements along the x and y directions involve intramolecular deformation. As a result, a small displacement along the z direction does not change the intramolecular charge distribution. Thus, we can study the nonbonding interaction between *rigid bodies*, corresponding to the approximations used in the literature, by fitting the *perpendicular* derivatives $\partial^2 E/\partial z_{O_A}\partial z_{O_B}$. Elsewhere[17] we show that this is a property of planar systems in general and not just the water dimer discussed above. The partial charges and repulsive parameters obtained in this way for all the dimers in Figure 1 are given in Table I. These values correspond to fitting the perpendicular coupling second derivatives of the energy in the

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Table II. Test of Combination Rules

monomer	$-q = (Q^2)^{1/2}$	$A^{1/2}$
H_2O	0.6475	248.1
CH_2O	0.5041	358.7
NH_2CHO^a (from $NH_2CHO\cdots OH_2/H_2O\cdots OH_2$)	0.5136	295.2

dimer	Q^2	qq'	A	$A^{1/2}A'^{1/2}$
$CH_2O\cdots OH_2$	0.3120	0.3264	85674.8	88998.7
$NH_2CHO\cdots CH_2O$	0.2583	0.2589	107584.1	105884.2

[a] Parameters derived by dividing those obtained for $NH_2CHO\cdots OH_2$ by the parameters obtained for $H_2O\cdots OH_2$.

range 2.3–3.0 Å, focusing on the repulsive term. As is evident, the optimized analytical expression fits the energy derivatives within 3.5% or less.

Transferability and Combination Rules

On the basis of the physics of the interaction and the representation of the electron distribution by partial atomic charges, the value of the charge $q_{O(H_2O)}$ obtained from the energy derivatives of the homogeneous dimer from the square root of Q^2 ($= q_{O(H_2O)}q_{O(H_2O)}$) should be transferable to the mixed-dimer interaction . That is, the value obtained for the charge product $Q_{AB}{}^2$ should be equal to q_Aq_B, where the latter are obtained from the homogeneous dimers. As is seen from Table II, this is the case. Although this may seem trivial, it is reassuring to find that there are not significantly different polarizations in the mixed dimers.

The combination rule for the steric constant A is not as fundamental as that for the charge product.[1] Most potential functions used in biomolecular applications of molecular mechanics and dynamics assume some relationship such as $A_{AB} = A_A{}^{1/2}A_B{}^{1/2}$. The information provided by the ab initio energy derivatives allows us to probe this question as well, and again it is reassuring to find, as seen from Table II, that the above combination rule is obeyed reasonably well for these dimers. Of course, the more stringent test of this will be for totally different atoms.

Anisotropy of Nonbonding Interactions

All current potentials used in simulations of proteins and other biomolecular interactions assume the interactions are spherically symmetric. Recent studies in crystal structures[18,19] suggest however that anisotropy is of importance. In the past it has been difficult to test the validity of the spherically symmetric potentials, as the data used to probe the nonbonding interactions were not sensitive enough or too sparse to yield such information. (In fact, it is difficult to get unique values for the parameters themselves due to a severe correlation problem[10] as demonstrated by the variety of parameter sets existing in the literature.[1]) We have carried out a calculation of ab initio energy derivatives for the usual H-bonded water dimer (C_s orientation) and extracted the oxygen–oxygen interaction through their second derivatives in the same way as presented above. The value of the repulsive constant, A, found in this orientation is 220 000 kcal/(mole·Å^{12}), or 4 times the value found for the head-to-head orientation. Thus, we find a huge anisotropy, which could have significant implications for the representation of these interactions in biomolecular simulations. These could be due to an inherent anisotropy in the atoms' electron distribution caused by chemical bonding or to polarization arising from the hydrogen-bond interaction. Further calculations for other configurations of the dimer (such as a stacked configuration) should help define this effect. In that respect note that the repulsive parameter of the water oxygen in the head-on orientation (Figure 1) is smaller than that of the carbonyl oxygens (see Tables I and II), contrary to the order in standard parameterization such as OPLS and TIP4P.[6,20] However, the latter corresponds to the hydrogen-bonded oxygen for which the repulsive parameter is found to increase significantly.

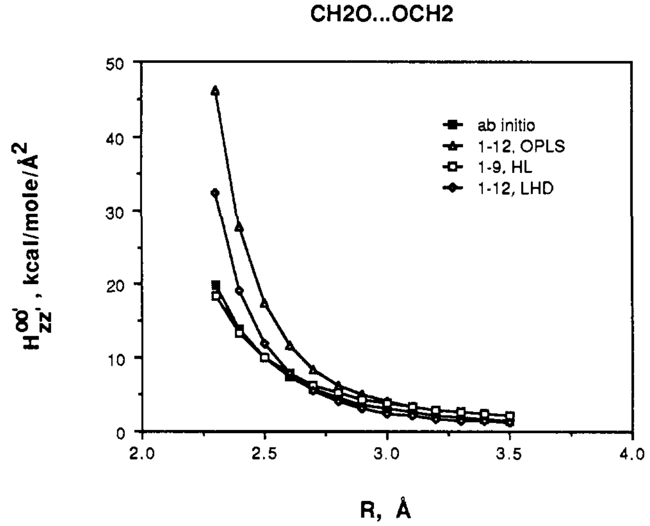

Figure 3. Second derivative of the energy with respect to the z coordinates of the two oxygens in the formaldehyde dimer. The two monomers are in the xy plane as shown in Figure 1 (D_{2h} symmetry). The abscissa is the distance between the two oxygens. OPLS, ref 6; HL, ref 21; LHD, ref 15. The C_6/R^6 contribution was omitted from these curves.

Comparison with Parameters Obtained from Fitting Experimental Observables

It is of interest to compare the nonbonding parameters obtained from the ab initio energy surface with those obtained from experimental data and utilized in common analytical force fields. The repulsive coefficients A, given in Table I, are in fact lower than the latter, and this can be seen in Figure 3, where the ab initio second derivative $H^{OO'}_{zz'}$ is plotted as a function of the O–O distance along with corresponding curves based on published 1–12 and 1–9 potentials. As can be seen, the major difference between the intratomic interaction curves occurs at short interatomic distances, those not usually sampled in equilibrium intermolecular interactions. However, it is just the lack of enough experimental data in that region that renders uncertain the determination of the repulsive parameter. Thus, the three experimentally derived potentials in Figure 3 are similar at long O···O distances but differ significantly at short distances. This has ramifications for the transferability of the nonbonding parameters. Interestingly, the old 1–9 potential agrees quite well with the ab initio calculations. However, the intrinsic errors in the ab initio calculations (such as basis set superposition error) and the uncertainty in the experimentally derived value are such that this agreement may be fortuitous. Further work is required to establish the scaling factors between the ab initio and the experimental results. Finally we note that short nonbonding distances may be present in intramolecular interatomic interactions as well—*cis*-glyoxal is an example of a case where two nonbonded oxygens are in relatively close contact. It will be interesting to see if the parameters derived here from intermolecular interactions are transferable to the intramolecular regime.

Summary

In summary, we have presented a new method for exploring the nature of nonbonding interatomic interactions. This method utilizes particular second derivatives of a quantum mechanical energy surface. In the example discussed here it has been used to derive characteristic potential constants including the charge and repulsive coefficient for oxygen–oxygen interactions. More importantly, the technique provides an opportunity to study the nature of interatomic interactions, their functional form, and their transferability from one molecular system to another.

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