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Citation: The Journal of Chemical Physics **104**, 159 (1996); doi: 10.1063/1.470886
View online: http://dx.doi.org/10.1063/1.470886
View Table of Contents: http://scitation.aip.org/content/aip/journal/jcp/104/1?ver=pdfcov
Published by the AIP Publishing

A chemical potential equalization method for molecular simulations

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(Received 2 June 1995; accepted 28 September 1995)

A formulation of the chemical potential (electronegativity) equalization principle is presented from the perspective of density-functional theory. The resulting equations provide a linear-response framework for describing the redistribution of electrons upon perturbation by an applied field. The method has two main advantages over existing electronegativity equalization and charge equilibration methods that allow extension to accurate molecular dynamics simulations. Firstly, the expansion of the energy is taken about the *molecular* ground state instead of the *neutral* atom ground states; hence, in the absence of an external field, the molecular charge distribution can be represented by static point charges and dipoles obtained from fitting to high-level *ab initio* calculations without modification. Secondly, in the presence of applied fields or interactions with other molecules, the density response can be modeled accurately using basis functions. Inclusion of basis functions with dipolar or higher order multipolar character allows molecules or chemical groups to have correct local anisotropic polarizabilities. A modified semiempirical form of the hardness matrix has been introduced that can be evaluated efficiently using Gaussians, and requires only one parameter per basis function. Applications at two basis-set levels demonstrate the method can accurately reproduce induced dipole moments and estimated chemical potentials obtained from density-functional calculations for a variety of molecules. Inclusion of basis functions beyond the conventional spherical-atom type is essential in some instances. The present formulation provides the foundation for a promising semi-empirical model for polarization and charge transfer in molecular simulations. [S0021-9606(96)02901-7]

I. INTRODUCTION

The development of accurate, computationally tractable methods to model the interactions of atoms and molecules is a major goal of modern theoretical chemistry. High level first-principle methods are generally reliable; however, the compute-intensive nature of the calculations severely limits the range of applications that can be addressed by these techniques. On the other hand, more simplistic empirical models frequently lack sufficient accuracy for many important applications. Conventional molecular mechanical force fields often model charge distributions by static point charges and dipoles[1] and, hence, neglect polarization and charge transfer that generally require consideration of many-body effects. Progress has been made by introducing models that include atomic dipole and higher order multipole polarizability.[2] Nonetheless, the development of new methods that incorporate improved physical models is an ongoing area of active research.

Intrinsic to the nature of molecular interactions is the behavior of the electron density.[3,4] In particular, it is instructive to know how the electron density responds to changes in molecular configuration and chemical environment. Thus, an appealing approach towards modeling chemical systems involves modeling changes in the electron density. Density-functional theory[4–7] (DFT) provides a natural framework for attacking this problem since it treats directly the electron density as the basic variable. Unfortunately, the computational requirement inherent in conventional *ab initio* density-functional methods precludes application to very large molecular systems,[8] especially when coupled with extensive sampling of configuration or phase space. For these systems, approximate methods that are less computationally demanding are required.

A particularly promising class of methods that address this problem are based on the concept of *electronegativity equalization*. Electronegativity equalization was first introduced by Sanderson[9] as a method for estimating atomic charges in molecules based on the relative electronegativities of the atoms before and after equalization (molecule formation). Sanderson's original method, however, had the deficiency that it would not distinguish between like atoms in the same molecule. Later, Gasteiger and Marsili[10] introduced an iterative method for determining atomic charges based on partial equalization of orbital electronegativities.[11] Although these methods proved qualitatively useful as empirical methods for estimating atomic charges, they lacked a rigorous foundation in theory.

Density-functional theory provides a rigorous mathematical definition for many intuitive chemical concepts such as electronegativity[12] and chemical hardness,[13,14] and is the foundation of the electronegativity equalization principle.

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The connection is established through the identification of the electronegativity as the negative of the chemical potential.[15] Analogous to macroscopic thermodynamics, the chemical potential of an equilibrium ground-state electronic system is everywhere equal (a constant).[16] The idea behind the electronegativity equalization methods, as the name suggests, is that when atoms or molecules interact, the electronegativity (chemical potential) must equalize. From the viewpoint of density-functional theory, this follows directly from the variational principle for the ground-state electron density.[4]

A major advance was realized with the development of a rigorous mathematical formalism for electronegativity equalization based on density-functional theory by Nalewajski[17] and Mortier *et al.*[18] Methods derived from this formulation predicted atomic charges and other properties that were geometry and connectivity dependent (for a review, see Ref. 19). Following these developments, several variations have been proposed.[20–25] For the most part, these methods have been used to determine atomic charges,[18–23] model chemical binding,[24] and analyze charge transfer in chemical bond formation.[25] Recently, electronegativity equalization has been used to probe reactivities using charge sensitivity analysis,[26] and provide a method for determining dynamic charges for molecular simulations.[20,27] In general, these methods rely on empirical parameterizations of individual atoms and, hence, have the advantage that they can be applied to any molecule. However, for a highly reliable representation of the electron density, as is required for molecular simulations, it is not clear that any single set of atomic parameters can provide sufficient accuracy for a diverse set of molecules.

In this work, we describe a formulation of the classic chemical potential (electronegativity) equalization principle that can be applied to molecular simulations. We choose to refer to the method explicitly as a chemical potential equalization (CPE) method to emphasize its origin in density-functional theory. The method provides a linear response model for the electron density that employs basis functions. The model gives high accuracy in the presence of relatively large perturbations such as those arising from interactions with other molecules or applied fields, and is ''exact'' in the limit that these interactions vanish. The method has the additional advantage that it can be systematically improved by inclusion of more complete basis functions for the density response. In several important instances, inclusion of basis functions beyond the conventional single spherical-atom type representation is essential. Section II gives a general derivation of the chemical potential equalization equations. Section III outlines how the equations can be solved using basis functions for the density response. Section IV gives formulas for several useful properties derivable from the density. Section V applies the method at two basis-set levels to small molecules in the presence of perturbing fields, and to intermolecular water–water interactions. Section VI discusses the advantages and disadvantages of the present method, and its relation with others proposed in the literature.

II. DERIVATION OF CHEMICAL POTENTIAL EQUALIZATION EQUATIONS

Consider a ground-state molecular system characterized by electron density $\rho_0(\mathbf{r})$. From density-functional theory,[4] the energy can be written as a unique functional of the density in the form

$$E[\rho]=T[\rho]+V_{ee}[\rho]+\int \rho(\mathbf{r})\,\nu_0(\mathbf{r})\,d^3r+V_{NN}$$
$$=F[\rho]+\int \rho(\mathbf{r})\,\nu_0(\mathbf{r})\,d^3r+V_{NN}, \tag{1}$$

where $T[\rho]$ is the kinetic energy functional, $V_{ee}[\rho]$ is the electron–electron interaction energy functional which includes both classical Coulombic and nonclassical exchange and correlation effects, and V_{NN} is the nuclear–nuclear repulsion energy. The functional $F[\rho]$ depends only on the electron density (does not depend implicitly or explicitly on the external potential), and is therefore universal. The variational principle for the ground-state energy in terms of the electron density is[4]

$$E[\tilde{\rho}]\geqslant E[\rho_0]\equiv E_0 \tag{2}$$

for any N-representable trial density $\tilde{\rho}$. The conditions for an N-representability density[28] are that the density is smooth, positive semidefinite, and normalized to the total number of electrons N. From Eq. (2) it is clear that the ground-state electron density satisfies the stationary condition

$$\delta\{E[\rho]-\mu N[\rho]\}=0, \tag{3a}$$

$$N[\rho]=\int \rho(\mathbf{r})\,d^3r, \tag{3b}$$

where the chemical potential μ is the Lagrange multiplier on the normalization constraint $N[\rho]=N$. The Euler–Lagrange equation for the ground-state energy and density is thus

$$\left(\frac{\delta E}{\delta\rho(\mathbf{r})}\right)_{\nu}\Bigg|_{\rho=\rho_0}=\left(\frac{\delta F}{\delta\rho(\mathbf{r})}\right)\Bigg|_{\rho=\rho_0}+\nu_0(\mathbf{r})=\mu_0=\text{const.} \tag{4}$$

If the variations in the space of N-representable densities are replaced by variations of orthonormal spin orbitals, Eq. (4) translates into the conventional Kohn–Sham equations of density-functional theory.[5] The Kohn–Sham method provides an accurate method for obtaining the ground-state molecular density.

Consider now the effect of a perturbation $\delta\nu(\mathbf{r})$ on the ground-state system. The perturbed energy to second order is given by

$$E(\rho_0+\delta\rho,\nu_0+\delta\nu)=E_0+\int\left(\frac{\delta E}{\delta\rho(\mathbf{r})}\right)_\nu\delta\rho(\mathbf{r})d^3r+\int\left(\frac{\delta E}{\delta\nu(\mathbf{r})}\right)_\rho\delta\nu(\mathbf{r})d^3r+\frac{1}{2}\int\int\delta\rho(\mathbf{r})\times\left(\frac{\delta^2E}{\delta\rho(\mathbf{r})\delta\rho(\mathbf{r}')}\right)_\nu\delta\rho(\mathbf{r}')d^3r\,d^3r'+\int\int\delta\rho(\mathbf{r})\left(\frac{\delta^2E}{\delta\rho(\mathbf{r})\delta\nu(\mathbf{r}')}\right)\delta\nu(\mathbf{r}')d^3rd^3r'+\frac{1}{2}\int\int\delta\nu(\mathbf{r})\times\left(\frac{\delta^2E}{\delta\nu(\mathbf{r})\delta\nu(\mathbf{r}')}\right)_\rho\delta\nu(\mathbf{r}')d^3rd^3r'. \tag{5}$$

In Eq. (5) and, hereafter, it is implied that all functional derivative terms are evaluated at the ground state ($\rho=\rho_0$ and $\nu=\nu_0$). Note that the variations $\delta\nu(\mathbf{r})$ and $\delta\rho(\mathbf{r})$ are not independent for a given number of electrons N, but are related through the Euler-Lagrange equation Eq. (4). Examination of Eq. (4) identifies the first functional derivative term in Eq. (5) as the chemical potential μ_0 of the unperturbed system. From the expression for the energy functional in Eq. (1), Eq. (5) simplifies to

$$E(\rho_0+\delta\rho,\nu_0+\delta\nu)=E_0+\mu_0\int\delta\rho(\mathbf{r})d^3r+\int[\rho_0(\mathbf{r})+\delta\rho(\mathbf{r})]\delta\nu(\mathbf{r})d^3r+\frac{1}{2}\int\int\delta\rho(\mathbf{r})\left(\frac{\delta^2F}{\delta\rho(\mathbf{r})\delta\rho(\mathbf{r}')}\right)\delta\rho(\mathbf{r}')d^3rd^3r'. \tag{6}$$

The new Euler–Lagrange equation for the perturbed system is

$$\int\left(\frac{\delta^2F}{\delta\rho(\mathbf{r})\delta\rho(\mathbf{r}')}\right)\delta\rho(\mathbf{r}')d^3r'+\delta\nu(\mathbf{r})=\mu-\mu_0=\Delta\mu. \tag{7}$$

Equation (7) is the fundamental equation from which the present formulation of chemical potential equalization is based. The strategy we employ in the following section is to transform Eq. (7) into an algebraic equation that can be solved for the density response $\delta\rho(\mathbf{r})$ for a given applied field perturbation $\delta\nu(\mathbf{r})$ (and optionally a net charge transfer ΔN).

III. SOLUTION OF THE CPE EQUATIONS IN A FINITE BASIS

In this section, we show how the CPE equations can be solved using basis functions for the density response $\delta\rho(\mathbf{r})$. We further suggest a semiempirical approximation for the second functional derivative term in Eq. (7) that is demonstrated later (Sec. V) to give a simple but useful model for polarization and intramolecular charge transfer.

Consider an expansion of the density response $\delta\rho(\mathbf{r})$ in a basis of normalized functions $\{\varphi_i\}$ such that $\langle\varphi_i|\varphi_i\rangle=1$ and $\int\varphi_i(\mathbf{r})d^3r<\infty$

$$\delta\rho(\mathbf{r})=\sum_i c_i\varphi_i(\mathbf{r}). \tag{8}$$

The coefficients $\{c_i\}$ are determined from matrix form of the stationary condition Eqs. (3),

$$\frac{\partial}{\partial c_i}\{E[\underline{c}]-\mu N[\underline{c}]\}=0, \tag{9}$$

where $E[\underline{c}]$ and $N[\underline{c}]$ are given in matrix notation by

$$E[\underline{c}]=E_0+\langle\rho_0|\,\delta\nu\rangle+\mu_0\underline{c}^T\cdot\underline{d}+\underline{c}^T\cdot\underline{\delta\nu}+\tfrac{1}{2}\underline{c}^T\cdot\underline{\underline{\eta}}\cdot\underline{c}+V_{NN}, \tag{10a}$$

$$N[\underline{c}]=N_0+\underline{c}^T\cdot\underline{d}, \tag{10b}$$

where N_0 is the number of electrons in the unperturbed system. The matrix and vector elements of Eqs. (10) are defined by

$$(\underline{d})_i=\int\varphi_i(\mathbf{r})d^3r, \tag{11a}$$

$$(\underline{\delta\nu})_i=\langle\varphi_i|\,\delta\nu\rangle, \tag{11b}$$

$$(\underline{\underline{\eta}})_{ij}=\left\langle\varphi_i\left|\left(\frac{\delta^2\hat{F}}{\delta\rho\,\delta\rho}\right)\right|\varphi_j\right\rangle. \tag{11c}$$

The matrix $\underline{\underline{\eta}}$ describes the interaction between basis functions which we term the *hardness matrix* in the basis of the density response. Application of Eq. (9) using Eqs. (10) and (11) results in the linear equation

$$\underline{\underline{\eta}}\cdot\underline{c}+\underline{\delta\nu}-\Delta\mu\underline{d}=0 \tag{12}$$

which, assuming $\underline{\underline{\eta}}$ is nonsingular, has solution

$$\underline{c}=\underline{\underline{\eta}}^{-1}\cdot\{\Delta\mu\underline{d}-\underline{\delta\nu}\}. \tag{13}$$

The Lagrange multiplier $\Delta\mu$ is chosen to satisfy the normalization condition $\underline{c}^T\cdot\underline{d}=N-N_0\equiv\Delta N$:

$$\Delta\mu=\frac{\Delta N+\underline{d}^T\cdot\underline{\underline{\eta}}^{-1}\cdot\underline{\delta\nu}}{\underline{d}^T\cdot\underline{\underline{\eta}}^{-1}\cdot\underline{d}}, \tag{14}$$

where ΔN is the amount of net charge transfer that is allowed (zero for fixed total number of electrons).

Thus far, we have not explicitly specified the form of the hardness matrix elements. Recall from Eq. (1), the universal functional $F[\rho]$ is a sum of kinetic energy and electron-electron interaction terms. Within the Kohn–Sham formulation of DFT,[5] this term is written as

$$F[\rho]=T_S[\rho]+J[\rho]+E_{XC}[\rho], \tag{15}$$

TABLE I. Comparison of LDA and experimental permanent dipole moments **D**.

Molecule	$\mathbf{D}^{a}$	$\mathbf{D}_{exp}{}^{b}$
CO	0.23	0.11
HF	1.78	1.83
HCl	1.10	1.11
NaCl	8.53	9.00
HCN	3.01	2.98
H_2O	1.84	1.85
H_2S	1.01	0.97
SO_2	1.50	1.63
OCS	0.85	0.72
CH_3OH	1.59	1.70
CH_3NH_2	1.31	1.31
CH_3F	1.69	1.86
CH_3Cl	1.91	1.89
NH_3	1.50	1.47
PH_3	0.63	0.57
HCOH	2.22	2.33
HCOOH	1.50	1.41
$HCONH_2$	3.81	3.73
$HCOCH_3$	2.73	2.75
CH_3OCH_3	1.13	1.30

[a]LDA permanent dipole moment (Debye).
[b]Experimental permanent dipole moment (Debye) taken from Ref. 41.

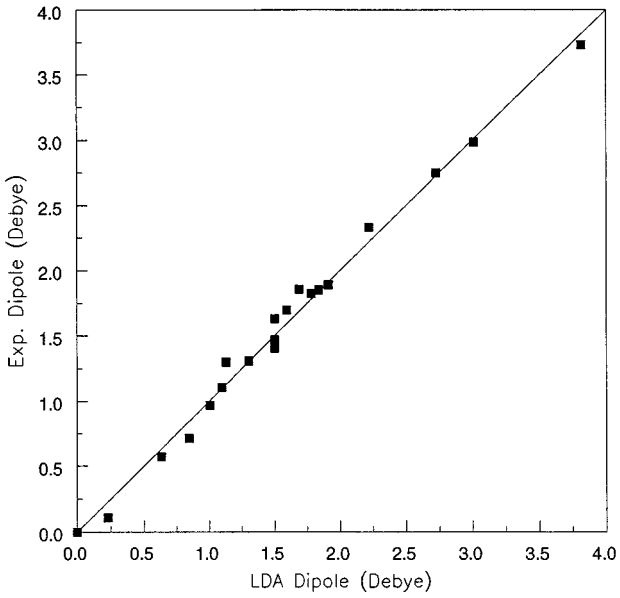

FIG. 1. Linear regression of permanent dipole moments from density-functional LDA calculations and from experiment (Ref. 41). Data is shown for all molecules listed in Table I.

where $T_S[\rho]$ is the Kohn–Sham noninteracting kinetic energy, $J[\rho]$ is the classical electrostatic energy, $E_{XC}[\rho]$ is the exchange-correlation energy. In fact, the form of the two-electron operator

$$\left(\frac{\delta^2 F}{\delta\rho(\mathbf{r})\,\delta\rho(\mathbf{r}')}\right)=\frac{1}{|\mathbf{r}-\mathbf{r}'|}+\left(\frac{\delta^2 T_S}{\delta\rho(\mathbf{r})\,\delta\rho(\mathbf{r}')}\right)+\left(\frac{\delta^2 E_{XC}}{\delta\rho(\mathbf{r})\,\delta\rho(\mathbf{r}')}\right) \tag{16}$$

is not known because the kinetic energy and exchange correlation functionals are not known exactly in terms of the density. We therefore introduce the following extended Hückel–like approximation[29] for the elements of the hardness matrix:

$$(\underline{\eta})_{ii}=f_i+\langle\varphi_i|\frac{1}{|\mathbf{r}-\mathbf{r}'|}|\varphi_i\rangle, \tag{17a}$$

$$(\underline{\eta})_{ij}=\frac{1}{2}\kappa(f_i+f_j)\langle\varphi_i|\varphi_j\rangle+\langle\varphi_i|\frac{1}{|\mathbf{r}-\mathbf{r}'|}|\varphi_j\rangle \quad \text{for} \quad i\neq j, \tag{17b}$$

where the $\{f_i\}$ are empirical parameters, and κ is taken to be unity. Thus, long-range interactions are treated as purely Coulombic, and the kinetic and exchange correlation energy contributions are modeled by a term proportional to the overlap of the density basis functions. For localized basis functions, the model assumes the kinetic energy and exchange-correlation contributions are short range. This treatment is also analogous to a Mulliken-type approximation[30] using density basis functions.

Construction of a CPE force field for molecular dynamics simulations requires selection of a density basis set $\{\varphi_i\}$ and parametrization of the hardness matrix parameters $\{f_i\}$ (one per basis function). Once this has been accomplished, the procedure for determining the linear density response $\delta\rho(\mathbf{r})$ of a system for a given perturbing potential $\delta\nu(\mathbf{r})$ with the CPE method is as follows:

(i) Construct the vectors $\underline{d}$ and $\underline{\delta\nu}$ from Eqs. (11a) and (11b).

(ii) Construct the hardness matrix [Eq. (11c)] using the form Eqs. (17).

(iii) Solve for the Lagrange multiplier $\Delta\mu$ from Eq. (14); this requires inversion of the hardness matrix.

(iv) Solve for the coefficients $\underline{c}$ from Eq. (13) using the value for $\Delta\mu$ determined in the previous step.

The basis set coefficients define the density response $\delta\rho(\mathbf{r})$ through Eq. (8) and are used to determine the total energy Eqs. (10). The CPE equations [Eqs. (10)–(14)] are valid for any set of normalized basis functions of the form Eq. (8). In the following section, we outline how other chemical properties can be obtained from the CPE procedure.

IV. CHEMICAL PROPERTIES DERIVABLE FROM THE DENSITY

Several useful derivatives can be computed directly from the CPE method presented earlier. Perhaps the simplest is the chemical potential μ, defined from density-functional theory to be the functional derivative of the energy with respect to the electron density (at constant external field ν), or alternately, the derivative of the energy with respect to the total number of electrons[6]

$$\mu=\left(\frac{\delta E}{\delta\rho(\mathbf{r})}\right)_{\nu}=\left(\frac{\partial E}{\partial N}\right)_{\nu}. \tag{18}$$

TABLE II. Comparison CPE induced dipole moment (**D**), chemical potential (μ), and polarizability (α) results using *S* and *SP* basis sets with corresponding LDA and experimental values. Relative percent errors of the CPE and LDA induced dipole moments (err **D**) and chemical potentials (err μ) are given. LDA chemical potentials were estimated by the highest occupied KS orbital eigenvalue ϵ_{HOMO}. Static polarizabilities (α) are given in Å^3.

Molecule	err $\mathbf{D}_S$	err $\mathbf{D}_{SP}$	err μ_S	err μ_{SP}	α_S	α_{SP}	α_{exp}[a]
H_2[b]	63.8	7.0	0.4	0.5	0.33	0.79	0.80
N_2	70.2	10.2	0.4	0.1	0.75	1.75	1.74
O_2	70.0	10.4	0.2	1.0	0.71	1.60	1.58
F_2	51.3	0.7	0.1	0.2	0.62	1.30	1.38
Cl_2	73.2	9.1	0.4	0.3	2.17	4.60	4.61
Na_2	77.5	18.1	3.1	5.9	14.5	36.9	39
CO	74.5	7.3	0.6	0.6	0.79	2.00	1.95
HF	79.6	4.5	0.2	0.4	0.33	0.92	0.80[c]
HCl	81.2	5.0	0.2	0.5	0.94	2.81	2.77
NaCl	82.8	5.9	0.4	0.9	2.07	5.38	
HCN	64.2	5.1	0.1	0.3	1.14	2.58	2.59
H_2O	63.4	7.7	0.8	0.7	1.00	1.57	1.45
H_2S	64.2	10.7	1.0	0.7	2.38	3.92	3.95
CO_2	58.8	1.8	0.1	0.1	1.29	2.57	2.91
SO_2	45.1	6.5	0.4	0.3	2.61	3.71	3.72
CS_2	61.9	2.7	0.1	0.3	4.61	8.48	8.74
OCS	65.2	5.5	0.3	0.5	2.51	4.94	5.2
CH_4	17.6	2.6	0.5	0.5	2.26	2.35	2.59
CH_3OH	18.4	10.6	2.5	1.1	3.10	3.22	3.29
CH_3NH_2	12.7	10.5	2.9	1.3	3.98	4.00	4.01
CHCH	69.5	4.7	0.1	0.4	1.50	3.53	3.33
CH_2CH_2	56.5	9.5	0.9	1.2	3.07	4.35	4.25
CH_3CH_3	8.6	8.0	0.3	0.4	4.40	4.52	4.43
CH_3F	18.2	9.9	1.1	0.7	2.46	2.55	2.97
CH_3Cl	31.2	5.6	0.9	0.4	4.63	4.64	4.72
NH_3	21.9	10.9	0.6	0.6	2.36	2.28	2.26
PH_3	23.2	6.7	1.1	0.8	4.49	4.70	4.84
HCOH	43.1	6.8	0.9	0.8	1.99	2.70	2.8
HCOOH	43.1	9.8	0.3	1.1	2.73	3.51	3.4
$HCONH_2$	45.3	6.3	0.8	0.7	3.31	4.31	4.2
$HCOCH_3$	19.5	7.7	3.9	3.0	4.41	4.64	4.6
CH_3OCH_3	14.1	7.5	0.5	0.7	5.18	5.14	5.16

[a]Experimental static polarizabilities in Å^3 taken from Ref. 41.
[b]For H_2, the *SP* basis consisted of one *s*-type and one isotropic *p*-type Gaussian on each hydrogen. For all other molecules, only a single *s*-type function was used for hydrogens.
[c]Experimental static polarizability taken from Ref. 42, and discussed in Ref. 43.

In the CPE framework, the chemical potential follows directly from Eq. (14). The chemical potential of an atom or molecule corresponds to minus the electronegativity.[15] Another intuitive chemical property is the global or absolute hardness η,[13,14] defined as the second derivative of the energy with respect to the total number of electrons,[13] and can be evaluated with the CPE method from the matrix equation

$$\eta=\left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu}=\left(\frac{\partial \mu}{\partial N}\right)_{\nu}=(\underline{d}^T\cdot\underline{\underline{\eta}}^{-1}\cdot\underline{d})^{-1}. \tag{19}$$

A related property, the softness *S*, is defined as the inverse of the hardness

$$S=\left(\frac{\partial N}{\partial \mu}\right)_{\nu}=(\underline{d}^T\cdot\underline{\underline{\eta}}^{-1}\cdot\underline{d})=\frac{1}{\eta}. \tag{20}$$

Hardness and softness are fundamental concepts in acid/base and inorganic chemistry,[14] and are global quantities for a given molecule. It is possible to define related local quantities and kernels that give additional insight into regions of likely chemical reactivity. The local *softness* is defined as[31]

$$s(\mathbf{r})=\left(\frac{\partial \rho(\mathbf{r})}{\partial \mu}\right)_{\nu}=\underline{s}^T\cdot\underline{\varphi}(\mathbf{r}), \tag{21}$$

where

$$\underline{s}=\left(\frac{\partial \underline{c}}{\partial \mu}\right)_{\nu}=\underline{\underline{\eta}}^{-1}\cdot\underline{d} \tag{22}$$

and $\underline{\varphi}(\mathbf{r})$ is the vector of basis functions $\varphi_i(\mathbf{r})$. Note the integral of the local softness gives the global softness *S*. A closely related quantity to the local softness is the so-called *Fukui function*. The Fukui function $f(\mathbf{r})$ is an index of reactivity that measures the response of the chemical potential to a variation in the external field.[32] The necessary connection between the local softness and the Fukui function can be established through the identity

$$\left(\frac{\partial \rho(\mathbf{r})}{\partial \mu}\right)_{\nu}=\left(\frac{\partial \rho(\mathbf{r})}{\partial N}\right)_{\nu}\left(\frac{\partial N}{\partial \mu}\right)_{\nu}, \tag{23}$$

which identifies the relationship $f(\mathbf{r})=s(\mathbf{r})/S$.

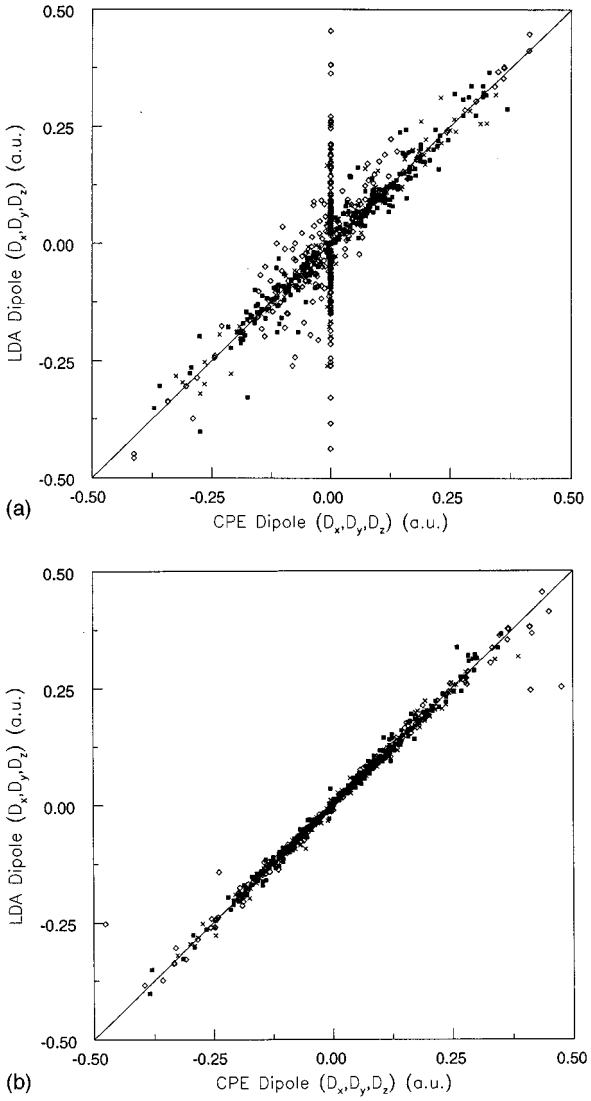

FIG. 2. Linear regression of CPE and LDA induced dipole moments: (a) CPE results obtained with the *S* basis set; (b) CPE results obtained with the *SP* basis set. Individual components (D_x, D_y, D_z) are shown for each molecule listed in Table II. Linear, planar, and nonplanar molecules are depicted by diamond symbols, crosses, and solid squares, respectively. Units are atomic units.

Hardness and softness can be further broken down into two-variable kernels,[7] which, in the basis of the density response, are simply $\underline{\underline{\eta}}$ and $\underline{\underline{\eta}}^{-1}$, respectively. Similarly, the two-variable *linear response function*[7] is defined as

$$\left(\frac{\delta\rho(\mathbf{r})}{\delta\nu(\mathbf{r}')}\right)_N = \left(\frac{\delta^2 E}{\delta\nu(\mathbf{r})\delta\nu(\mathbf{r}')}\right)_N = \left(\frac{\delta\rho(\mathbf{r}')}{\delta\nu(\mathbf{r})}\right)_N = \underline{\varphi}^T(\mathbf{r})\cdot\underline{\underline{P}}\cdot\underline{\varphi}(\mathbf{r}'), \tag{24}$$

where

$$\underline{\underline{P}} = \left(\frac{\underline{\underline{\eta}}^{-1}\cdot\underline{d}\otimes\underline{d}^T\cdot\underline{\underline{\eta}}^{-1}}{\underline{d}^T\cdot\underline{\underline{\eta}}^{-1}\cdot\underline{d}} - \underline{\underline{\eta}}^{-1}\right) \tag{25}$$

and the symbol $\otimes$ indicates the direct product. Note the linear response function given by Eq. (24) satisfies the exact condition

$$\int \left(\frac{\delta\rho(\mathbf{r})}{\delta\nu(\mathbf{r}')}\right)_N d^3r' = 0. \tag{26}$$

A closely related quantity to the linear response function is the static polarizability tensor $\underline{\underline{\alpha}}$, defined as minus the second derivative of the total energy with respect to components of the electric field $\vec{F}=(F_1,F_2,F_3)$,[33]

$$(\underline{\underline{\alpha}})_{\alpha\beta} = -\left(\frac{\partial^2 E}{\partial F_\alpha \partial F_\beta}\right). \tag{27}$$

Here Greek subscripts are used for elements in three-dimensional Cartesian space. In the limit of small uniform electric fields, the interaction of the response density with the field can be written as the scalar product:

$$-\sum_{\alpha=1}^{3}\mu_\alpha^{\mathrm{ind}}F_\alpha = \sum_{\alpha=1}^{3}\left(\int x_\alpha\delta\rho(\mathbf{r})d^3r\right)F_\alpha = \sum_{\alpha=1}^{3}\underline{c}^T\cdot\underline{x}_\alpha F_\alpha, \tag{28}$$

where $\mu_\alpha^{\mathrm{ind}}$ $(\alpha=1,2,3)$ are the Cartesian components of the induced dipole moment, x_α $(\alpha=1,2,3)$ are the components of the position vector $\vec{r}=(x,y,z)$, and $\underline{x}_\alpha$ $(\alpha=1,2,3)$ are vectors defined by

$$(\underline{x}_\alpha)_i = \int x_\alpha\varphi_i(\mathbf{r})d^3r. \tag{29}$$

It follows directly from Eqs. (28) and (29) that the static polarizability tensor in the CPE model is simply

$$(\underline{\underline{\alpha}})_{\alpha\beta} = -\underline{x}_\alpha^T\cdot\underline{\underline{P}}\cdot\underline{x}_\beta \tag{30}$$

It should be emphasized that the CPE method employed here is a linear response model. The energy has been constructed as a quadratic function of the electron density; hence the energy and its derivatives are continuous functions of the number of electrons N. This is in contrast to the known discontinuities of derivatives of the form $\partial/\partial N$ when N is an integer. Examples include the chemical potential $(\partial E/\partial N)_\nu$ and Fukui functions $[\partial\rho(\mathbf{r})/\partial N]_\nu$ (in fact, from this prospective, the absolute hardness of a molecule with integer number of electrons is not well defined). Nonetheless, chemical potential equalization methods have been demonstrated to provide a useful qualitative description of these properties for a variety of systems.[26]

V. NUMERICAL APPLICATION

In this section we apply the CPE formalism to model the linear density response. In Sec. V A the method is parametrized and applied to a series of small molecules in the presence of perturbing fields. Induced dipole moments and chemical potentials calculated with the CPE method are compared with corresponding LDA and experimentally de-

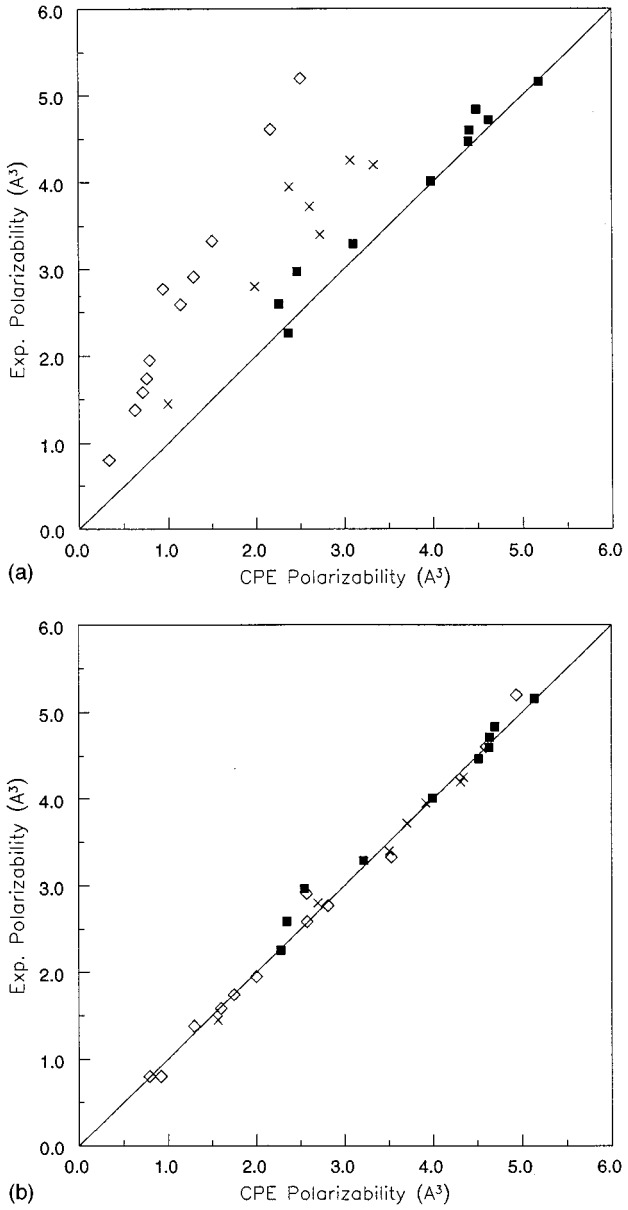

FIG. 3. Linear regression of CPE and experimental static polarizabilities: (a) CPE results obtained with the *S* basis set; (b) CPE results obtained with the *SP* basis set. Static polarizabilities are shown for each molecule listed in Table II. Linear, planar, and nonplanar molecules are depicted by diamond symbols, crosses, and solid squares, respectively. Experimental values were taken from Ref. 41. Polarizabilities are in $Å^3$.

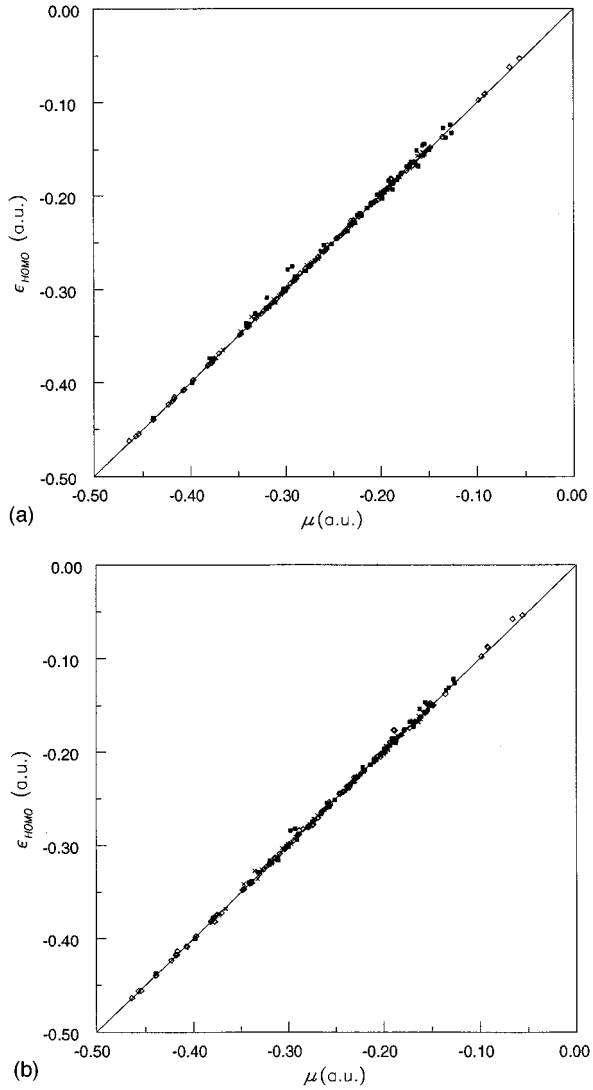

FIG. 4. Linear regression of CPE chemical potentials (μ) and LDA estimated chemical potentials (ϵ_{HOMO}): (a) CPE results obtained with the *S* basis set; (b) CPE results obtained with the *SP* basis set. Chemical potentials are shown for each molecule listed in Table II. Linear, planar, and nonplanar molecules are depicted by diamond symbols, crosses, and filled squares, respectively. Units are atomic units.

rived values. In Sec. V B we examine in detail intermolecular water–water interactions within the CPE framework.

A. Computational procedure

1. Density-functional calculations

Density-functional calculations were performed using the Kohn–Sham (KS) formulation of density-functional theory[5] implemented in a numerical self-consistent-field (SCF) algorithm.[34] Electron correlation was treated using the Vosko–Wilk–Nusair local density approximation (LDA).[35] Atomic orbital basis functions were generated as numerical LDA solutions of the KS equations for the isolated atoms, similar to that of Delley.[36] Extensive diffuse functions and polarization functions were employed in order to obtain accurate moments of the electron density for a series of applied field perturbations. A basis set of $3s$, $3p$, and $3d$ (polarization) functions were used for hydrogen atoms, and $5s$, $4p$, $4d$, and $2f$ (polarization) functions for second and third row atoms. The numerical integration mesh was chosen such that the error in evaluation of the matrix elements was (approximately) less than 10^{-6} Hartree. The convergence criterion for the SCF procedure was 10^{-6} Hartree for the total energy and 10^{-5} Hartree for the classical electrostatic component of the energy. The latter was necessary to achieve convergence of induced dipole moments.

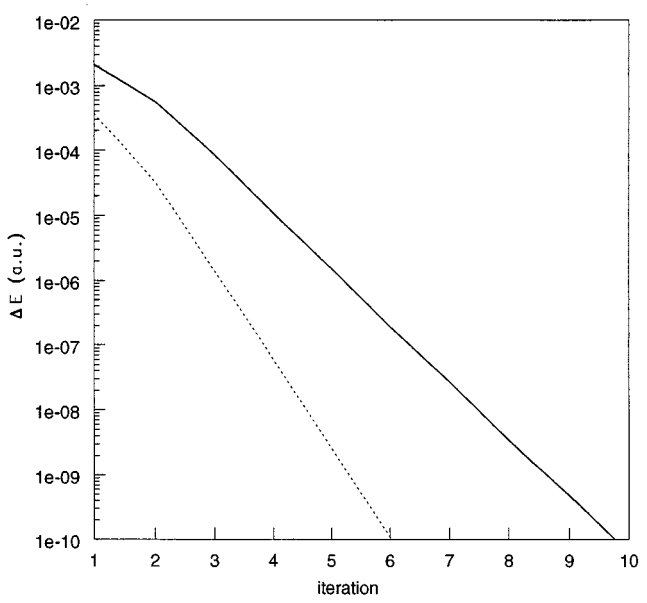

FIG. 5. Convergence of change in total energy ΔE (a.u.) as a function of iteration for linear water dimer (solid line) and bifurcated water dimer (dashed line). ΔE_i for each iteration i is defined by $\Delta E_i = E_i - E_{i-1}$, where E_i is the total energy at iteration i, and E_0 is zero (hence ΔE_1 is the interaction energy of the static charge distributions).

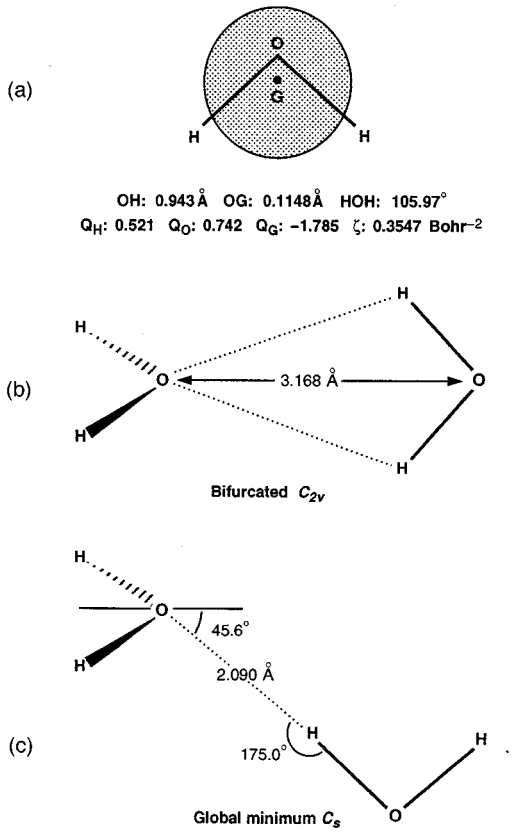

FIG. 6. Water and water dimer geometric and electrostatic parameters: (a) isolated water molecule; (b) bifurcated water dimer; (c) global minimum (linear) water dimer. Parameters for the isolated water molecule were taken directly from Hall and Smith (Ref. 45). Relative geometries of the water dimers were taken from Marsden *et al.* (Ref. 46).

2. Estimation of the CPE parameters

Chemical potential equalization parameters were calculated for molecules by fitting to induced dipole moments and estimated chemical potentials obtained from LDA calculations. For each molecule, LDA calculations were performed in the absence and presence of a series of applied field perturbations at the molecular surface (described below). The LDA induced dipole and chemical potential results provided the reference data used to obtain the CPE parameters. CPE parameters $\{f_i\}$ in Eqs. (17) were determined by introducing identical applied field perturbations and fitting parameters to best reproduce (in a least squares sense) corresponding LDA values. The purpose of the fitting procedure was to demonstrate that the CPE method can adequately reproduce well-defined quantities (dipole moments and chemical potentials) for a diverse set of molecules subject to applied field perturbations, with relatively simple basis sets. These parameters are later shown to be transferable to intermolecular interactions as demonstrated in the case of water dimers. The parameters are not intended to represent rigorously derived force field parameters; hence they are not all listed, but are available upon request.[37]

The chemical potential from the LDA calculations were estimated by the highest occupied KS orbital eigenvalue ϵ_{HOMO}.[7] For each molecule, dipole moments were induced by introducing a perturbing field at points outside the molecular surface as follows. A ''solvent-accessible surface'' was defined as the surface generated by the van der Waals radii of the atoms plus a probe radius of $2.65a_0$ (1.4 Å, approximately the radius of a water molecule). Points roughly evenly spaced on the surface were chosen at a density of $0.05a_0^{-2}$ (i.e., this corresponds to 18 points for H_2O). At each surface point R_k a Gaussian probe density was added of the form

$$\rho_{\mathrm{probe}}(\mathbf{r}) = \pm Q \cdot \left(\frac{\zeta}{\pi}\right)^{3/2} e^{-\zeta|\mathbf{r}-\mathbf{R}_k|^2} \tag{31}$$

where the exponent ζ was $1.0a_0^{-2}$, and the net charge Q was alternately $0.25e$ and $0.5e$. The sign $\pm$ was chosen such that the electrostatic interaction of the probe with the unperturbed molecule was favorable. At each surface point, the static potential of the probe was used as an applied field, and the corresponding perturbed molecular density was computed from SCF solution of the KS equations. Hence, the number of perturbations used to collect induced dipole moment and chemical potential data was $2M$, where M is the number of surface points (the factor 2 comes from the Q values $0.25e$ and $0.5e$ at each point).

Basis functions for representation of the CPE density response Eq. (8) were chosen as normalized atom-centered Gaussian functions. Two different sets of basis function were considered. The first set, denoted the S set, consisted of a single spherical (s-type) Gaussian on each atom. This set represents each atom as a spherical charge density similar to the electronegativity equalization method of Mortier *et al.*[18] and the charge equilibration method of Rappé and

TABLE III. Water molecule CPE parameters.

CPE parameters[a]	H_s	O_s	O_p
	S basis		
ζ	0.937	0.226	
f	0.0	14.13	
η	13.41	69.65	
	SP basis		
ζ	0.883	0.255	0.262
f	0.0	0.0	26.86
η	14.23	49.25	42.82

[a]Parameters for the CPE procedure: the Gaussian exponent (ζ) and the f parameter [Eqs. (17)]. Also listed are the diagonal elements of the hardness matrix (η) (which can be computed from the other parameters, but conveys more intuitive physical meaning). The type of Gaussian (*s* or *p* type) is indicated by atom subscripts in the column headings. Note there are no basis functions on the off-center Gaussian site (Fig. 6). All units are atomic units.

Goddard.[20] The second set, denoted the *SP* set, contained an *s*-type function on each atom in addition to three Gaussian functions with dipolar (*p*-type) symmetry on all nonhydrogen atoms.

The Gaussian exponents of the basis functions along with the $\{f_i\}$ parameters of Eqs. (17) were determined by least squares fitting of the LDA and CPE chemical potentials and induced dipole moments. In all fitting procedures, parameters for each *p*-type basis function for a given atom were constrained to be equal, and parameters of *topologically* equivalent atoms (atoms with the same covalent connectivity) were constrained to be identical.

One additional parameter per molecule is required, the molecular chemical potential μ_0 in the absence of an applied field [Eq. (10a)]. Note, this term is only needed for the evaluation of the total energy in the case where there is a net charge transfer ($\Delta N = \int \delta\rho(\mathbf{r}) d^3r \neq 0$). If no net charge transfer is allowed, explicit dependence of this term vanishes, and only the Lagrange multiplier $\Delta\mu$ [Eq. (14)] is required. Since we have estimated the LDA chemical potentials by the ϵ_{HOMO} values for molecules in the presence of applied fields, it is natural that we take μ_0 to be the corresponding ϵ_{HOMO} for the system in the absence of an applied field (no probe perturbation).[7]

B. Linear response to applied field perturbations

Kohn–Sham density-functional theory in conjunction with the LDA has been used extensively and with great success for the computation of dipole moments[38,39] and polarizabilities.[33,40] This is based largely on the observation that the LDA gives a very good description of the electron density, despite the known errors in the corresponding total energies. We exploit the strength of LDA for predicting reliable densities to parameterize Eqs. (17) and, hence, gain access to a wealth of chemical information within the CPE framework.

Table I compares the experimental and calculated LDA dipole moments for several small molecules. The agreement between the two data sets is quite close (Fig. 1). The overall root-mean-square (rms) deviation is 0.14 D and the linear correlation coefficient is 0.999. The largest rms error occurs for NaCl (0.5 D), with a relative error of 5.2%. These results support the assertion that the LDA is sufficiently accurate for describing moments of the electron density.

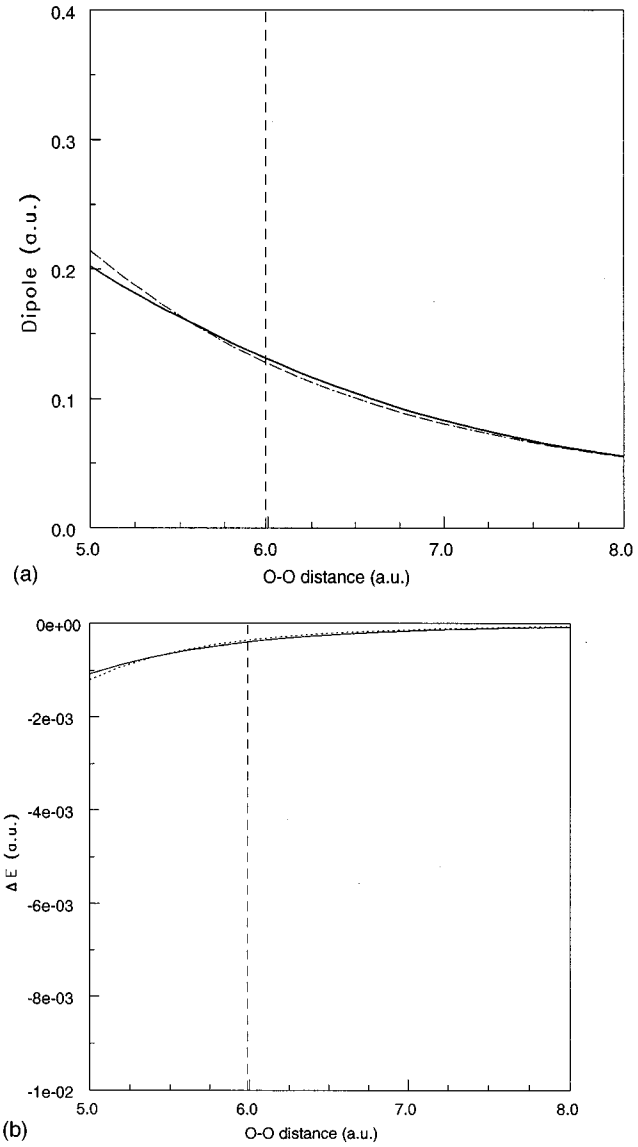

FIG. 7. Bifurcated water dimer properties as a function of O–O distance: (a) CPE induced dipole moments calculated with *S* (dotted line) and *SP* (dashed line) basis sets and corresponding LDA values (solid line); (b) CPE stabilization energies ΔE calculated with *S* (dotted line) and *SP* (dashed line) basis sets. For the dipole moments, the *S* and *SP* curves are almost indistinguishable. All units are atomic units.

The CPE basis functions and parameters (*S* and *SP* sets) were optimized to fit the LDA induced dipole moments and estimated chemical potentials. Relative errors in the CPE dipole moments and chemical potentials, along with the calculated isotropic polarizabilities are listed in Table II.

The CPE induced dipole moments calculated using the *S* basis set show a wide range of relative errors [Fig. 2(a)]. This results from the inability of the spherical functions to

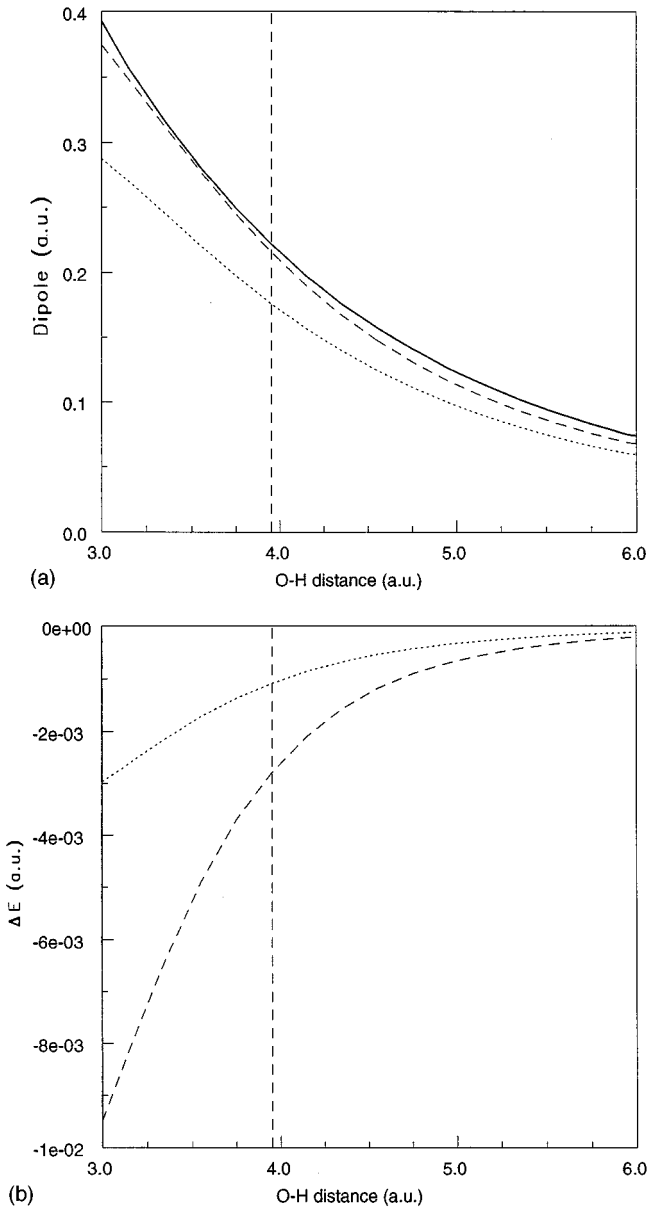

FIG. 8. Global minimum (linear) water dimer properties as a function O–H distance: (a) CPE induced dipole moments calculated with *S* (dotted line) and *SP* (dashed line) basis sets and corresponding LDA values (solid line); (b) CPE stabilization energies ΔE calculated with *S* (dotted line) and *SP* (dashed line) basis sets. All units are atomic units.

adequately accommodate the density response for a diverse set of field perturbations, and is reflected by the corresponding molecular polarizabilities [Fig. 3(a)]. In the worst case of linear molecules, the CPE method with the *S* basis set allows polarization only along the C_∞ axis. The corresponding polarizabilities are, in general, underestimated by approximately 2/3, since effectively only one component of the static polarizability tensor is represented. In the case of planar molecules, the situation with the *S* basis set is similar, except that polarization is now restricted to the molecular plane. The corresponding polarizabilities are underestimated by approximately 1/3. For nonplanar molecules, the *S* basis set is able to reproduce fairly well the LDA induced dipole moments and polarizabilities.

TABLE IV. Water dimer results. Dipole moments (D_y, D_z) in Debye of water dimers at "equilibrium" geometry [Figs. 6(b) and 6(c)]. The *z* direction in the bifurcated dimer is taken along the C_∞ axis; the *x* direction in the linear dimer is taken to be perpendicular to the symmetry plane, and hence has no dipole component. Stabilization energies ΔE resulting from chemical potential equalization are also listed in atomic units.

	D_y	D_z	$\lvert D\rvert$	ΔE
Bifurcated C_{2v}				
S basis		4.01	4.01	-3.6×10^{-3}
SP basis		4.04	4.04	-4.0×10^{-3}
LDA		3.99	3.99	
Global min. C_s				
S basis	1.80	2.04	2.72	-1.1×10^{-2}
SP basis	1.81	2.18	2.84	-2.8×10^{-2}
LDA	1.82	2.15	2.81	

The *SP* basis set, which includes isotropic *p*-type functions on nonhydrogen atoms, overcomes the deficiencies of the *S* set by accommodating out-of-line and out-of-plane polarization for all molecules. The resulting fit to the induced dipole moments is significantly improved [Fig. 2(b)]. These results suggest the *SP* basis set representation is sufficient to capture the essential dipolar density response for small perturbations at the molecular surface. The molecular polarizabilities calculated with the *SP* basis set agree well with the experimental values [Fig. 3(b)].

The total error associated with the polarizability results relies in a multiplicative fashion on the error in the LDA induced dipole moments, and the error in the CPE model in reproducing the LDA results. The latter, of course, depends on the basis set used in the CPE method to model the density response. The strong correlation of the experimental and predicted polarizabilities indicates that both the LDA and CPE approximation using the *SP* basis set are reliable. These results are encouraging that the CPE method may be used to model polarization in molecular simulations by allowing a dynamical representation of the charge density.

In addition to the induced dipole moments and polarizabilities, it is interesting to consider the chemical potentials estimated from the LDA calculations and from the CPE model. We have estimated the LDA chemical potential by the highest occupied KS eigenvalue ϵ_{HOMO}.[7] The CPE chemical potentials μ were calculated directly from the hardness matrix via Eq. (14), and μ_0 was chosen as the LDA ϵ_{HOMO} value for the unperturbed system. These two quantities, ϵ_{HOMO} and μ, are remarkably well correlated for both *S* and *SP* density basis sets [Figs. 4(a) and 4(b)]. The maximum relative error for the *S* and *SP* sets occurs for Na_2 (3.1% and 5.9%, respectively), which has by far the largest observed polarizability ($\sim$37 Å^3). The striking agreement of the estimated CPE and LDA chemical potentials is intriguing. Moreover, it is suggestive that coupling of the CPE procedure with density-functional methods, for example in hybrid quantum mechanical/molecular mechanical simulation force fields, may be possible.

C. Water–water interactions

The close fit between the LDA and CPE induced dipole moments and chemical potentials is encouraging. It remains to demonstrate that the method can be used to accurately describe intermolecular interactions. In this subsection we apply the CPE method to water–water interactions, using the parametrization procedure described in the previous section for the isolated molecules.

The CPE model described here is a linear response theory for predicting the response of the molecular electron density to an applied field. In the case of interacting molecules, the ''applied field'' felt by a given molecule arises from the charge distributions of the surrounding molecules. Solving the CPE equations requires inversion of the global hardness matrix, which has dimensions equal to the total number of density basis functions. For small systems this is trivial; however, for larger systems this will become a severely limiting problem. Although this limitation will not be realized in the case of the water dimers examined here, we outline a fast iterative procedure that does not require inversion of the global hardness matrix.

We define the external field felt by a single molecule to be that due to the charge distributions of all the other molecules in the system multiplied by one half. The factor of one half arises because we require the sum of the molecular energies (intramolecular+field interaction) to be equal to the correct total energy of the system. With this definition, we can solve the CPE equations for each molecule separately, by inverting the local molecular hardness matrices, and obtain the linear response. Since determination of the density response for one molecule changes the field felt by the other molecules, the chemical potential equilibration process proceeds iteratively until a certain level of convergence is reached. The procedure converges rapidly for systems where the induced field is small compared to the static field such as in the case of the water dimers (Fig. 5). Convergence is linear; that is the change in energy decays exponentially with iteration. Similar iterative procedures are routinely used to calculate dipole polarization in molecular simulations.[44]

Another aspect of the CPE procedure when applied to interacting molecules involves the normalization conditions. If only global normalization is enforced, the chemical potential is allowed to everywhere equalize, and intermolecular charge transfer, in general, occurs. However, there has been some criticism of this method as being unrealistic in practical applications.[27] For instance, consider two water molecules very far separated, and subject to different applied fields. The chemical potentials of the molecules before equalization will in general be different and, hence, equalization will be accompanied by a net intermolecular charge transfer. If indeed the system is in a stationary state, this is the correct quantum mechanical result within the Born–Oppenheimer approximation (fixed nuclei). However, the tunneling probability for an electron to jump from one molecule to the other is so small that, for any dynamic system, charge transfer would be kinetically forbidden. In this way, the solvent bath would act as an infinite reservoir of electrons for a solute molecule. An alternative approach that has been applied to liquid water simulations[27] involves individual normalization constraints for each molecule. This reduces the global chemical potential equalization process to that of many local molecular chemical potential equalization processes, and prohibits by definition intermolecular charge transfer. Since there is no computational disadvantage to this convention, we adopt it in our application to water dimers. For ionic systems, however, this approximation may not be appropriate; in this case, an intermediate procedure for regulating intermolecular charge transfer as a function of distance is required.

In order to obtain the total potential due to the charge density $\rho_0+\delta\rho$ of a water molecule in a perturbing field, the CPE method assumes a knowledge of the static potential of the unperturbed ground-state density ρ_0. We have chosen to represent the static ground-state potential of the isolated water molecule by the simple point charge/Gaussian model proposed by Hall and Smith[45] [Fig. 6(a)]. CPE parameters for the isolated water molecule were obtained for the S and SP basis sets using the procedure outlined in the previous subsection and are summarized in Table III (note: no basis functions were placed on the off-center Gaussian site). Two water dimer structures were considered [Figs. 6(b) and 6(c)], the bifurcated C_{2v} structure, and the global minimum C_s structure. Water dimers were constructed to have geometries similar to that given by Marsden *et al.*,[46] with the exception that the internal geometries of each water molecule are the same as that of the isolated molecule.[45] Both S and SP basis sets were considered.

Figure 7(a) compares the LDA and CPE bifurcated water dimer induced dipole moments as a function of O–O distance. The agreement is remarkably close. The dipole moments for the S and SP basis sets are virtually indistinguishable. This is because polarization occurs only along the O–O (C_2) axis, which lies in the molecular plane of both molecules and, hence, can be accommodated equally well by the S and SP basis sets. Figure 7(b) shows the corresponding CPE energy curves. The energy associated with the linear response is fairly small, and the two curves are very similar. It should be pointed out that the bifurcated water dimer has been predicted to be a transition state near the Hartree–Fock limit, and does not correspond to the global minimum structure.[46]

The global minimum (C_s) water dimer structure is shown in Fig. 6(c). Polarization will clearly be out-of-plane for one of the water molecules. Figure 8(a) compares the LDA induced dipole moments with the CPE values for the water dimer as a function of the H···O hydrogen bond distance. The S basis set underestimates the LDA induced dipole moment by about 15–25 % in the region near the predicted equilibrium distance. This is a direct result of the inability of the S basis set to allow polarization out of the plane of the molecule. Inclusion of the SP basis set effectively overcomes this difficulty and gives the correct induced dipole moment behavior. The discrepancy between the two methods manifests itself even more distinctly upon examination of the response energy curves [Fig. 8(b)]. The response energy at the equilibrium distance differs by more than 100%

(Table IV). Since many hydrogen bonds have a similar angular dependence to that of the (C_s) water dimer, this may be an important concern for hydrogen-bonded systems such as biological macromolecules.

VI. RELATION TO OTHER CHEMICAL POTENTIAL EQUALIZATION MODELS

Two related methods based on chemical potential equalization have been proposed by Mortier *et al.*[18] and later by Rappé and Goddard.[20] The former has been employed mainly as a method for estimating atomic charges in molecules based on parametrization to STO-3G Mulliken charges,[18] and more recently for probing reactivity using sensitivity coefficients from density-functional theory.[26] The latter method[20] has been developed to provide a dynamic charge model for molecular simulations. Both methods are based on the approximation of the *molecular* energy as a second order Taylor expansion about the *neutral* atoms. The molecular charge distribution and energy are obtained as solutions to the CPE equations of the neutral atoms assembled to form a molecule. Hence, these methods treat a molecule as a perturbation of an assembly of noninteracting neutral atoms. The methods require two parameters per atom: an effective electronegativity (negative of the chemical potential), and hardness (in the latter method, the hardness appears as the atomic electrostatic self-energy). These atomic parameters are assumed to be transferable for all molecules. Mortier *et al.*[18,19] have demonstrated that this approximation is remarkably robust, and gives useful qualitative, and sometimes even quantitative insight to a variety of chemical problems. Nonetheless, the representation of the molecular energy and charge distribution as an expansion about the neutral atoms is considerably limited in its ability to give high accuracy. Consequently, a new method that provides high accuracy and can be systematically improved is required for reliable molecular simulations.

The CPE formulation presented here accommodates these difficulties. Since the total molecular energy is expanded about the ground-state molecular density, the exact energy and charge distribution are recovered in the absence of an applied field. This is convenient for molecular simulations that routinely obtain atomic point charges and dipoles from *ab initio* calculations of molecules in the gas phase. For a system of interacting molecules, the CPE method provides a model for the linear density response of each molecule in the field of the other molecules, with the possibility of charge transfer. As demonstrated in the preceding section, this method reproduces well the density response, even with very simple basis function representations. More importantly, systematic improvement of the methodology is straight forward by inclusion of more complete density basis functions, which may include off-center functions in bond regions or functions with higher angular momentum (multipolar) symmetry.

The methods proposed by Mortier *et al.*[18] and Rappé and Goddard[20] are, in fact, particular cases of the general formalism developed here. To illustrate this, consider the integral Taylor expansion Eq. (5) to be chosen about the neutral-atom ground-state densities. If the density basis functions are chosen to be delta functions at the atomic positions (neglecting the infinite electrostatic self-energy term in the diagonal elements of the hardness matrix), the present model reduces to that proposed by Mortier.[18] In this case, the empirical parameters are the effective atomic chemical potentials and hardnesses. Alternately, if atom-centered ns Slater-type functions are used as basis functions, and the empirical parameters $\{f_i\}$ of Eqs. (17) are set to zero, the present model reduces to that proposed by Rappé and Goddard.[20] The latter method parametrizes the diagonal elements of the hardness matrix by adjusting the Slater exponents of the density basis functions. The corresponding electrostatic self-energies play the same role as the atomic hardness parameters of Mortier.[18] Note both of these methods treat the off-diagonal elements of the hardness matrix as being purely Coulombic in nature.

The present chemical potential equalization method provides a particularly convenient framework for modeling polarization in molecular simulations. Electrostatic fields in molecular simulations are typically modeled by static charge distributions obtained from fitting to gas-phase electrostatic potentials. For such models that do not attempt to take into account polarization implicitly, the present method is ideal. This derives from the fact that the static charge distribution is chosen to directly reflect the zero order term in the Taylor expansion Eq. (5) corresponding to the ground-state electron density in the absence of a perturbing field. Hence, parameters for the density response are uncorrelated with parameters used to represent the static charge distribution. In this way, improvement of force field models by inclusion of additional polarization terms does not require reparametrization of existing static terms. For very large macromolecules, expansion of the energy can be taken about molecular fragments (for instance individual amino acids or DNA nucleotide units), thus allowing distinct chemical groups to be linked together in the same spirit as conventional macromolecular simulation force fields.

It is known that for linear and planar molecules, chemical potential equalization methods that use ''spherical-atom'' representations (more properly termed in the present formalism ''spherical atom-centered basis functions'') cannot describe polarization out of line or out of plane. It has been suggested that implementation of a Drude oscillator model into the standard chemical potential equalization method can be used to circumvent this difficulty.[47] The Drude model uses a harmonic force constant that allows the electronic charge cloud to be displaced from the nuclear center. Similar models have been employed in molecular dynamics simulations of water using distributed charge sites and treating the polarization as a explicit degree of freedom.[48] In the present generalized CPE formalism, dipole (or higher multipole) polarization is a natural consequence of using basis functions with suitable symmetry. The method has the additional advantage that since density basis functions are employed, there is no difficulty associated with divergence of the energy resulting from interactions of point charges and dipoles at close distances.

It should be pointed out that the present model has been

introduced specifically as an empirical model for polarization and charge transfer, derived from density-functional theory. The use of basis functions for the linear density response illustrates that one should be careful in interpreting the parameters of this model as having any well defined ''atomic'' character, since there has been no effort here to rigorously define an atom in a molecule. If such an interpretation is sought, for example, in the analysis of wave functions from electronic structure calculations, one must adopt a rigorous definition of an atom in a molecule,[3] and employ appropriate constraints. Such work has been explored extensively by Cioslowski.[25]

It is noteworthy to make a few comments on the parametrization of the proposed CPE model, and on future directions of research in this area. The main purpose of the present work was to derive a generalized formulation of chemical potential equalization, propose a semiempirical model that employs density basis functions, and demonstrate that this model is sufficient to reproduce induced dipole moments and chemical potentials obtained from LDA calculations. For this purpose, the CPE parameters were fit to LDA results for isolated molecules in the presence of applied fields. These parameters were observed to be transferable to intermolecular interactions as demonstrated in the case of water dimers. However, the fitting procedure adopted here may not be in itself appropriate to derive a force field based on the generalized CPE method. Such a procedure requires parameters to be essentially decoupled so that they may be transferable between like chemical fragments in a large molecule. We note that most of the parameters obtained by fitting to induced dipole moments are correlated and often degenerate; that is, more than one set of parameters is able to give essentially the same fit to the induced dipole moments. This does not imply a limitation in the CPE method, only that the fitting procedure employed is not well conditioned and, hence, insufficient to fully extract all the physical information contained in the model. The development of a more rigorous procedure whereby a complete set of transferable parameters can be obtained has important implications to the field of molecular simulation, and is currently underway by the authors. The method would allow, for instance, a library of biomolecular functional groups to be linked together to form macromolecules.

VII. CONCLUSION

A formulation of chemical potential equalization has been presented, and cast in a form that can be solved using basis functions for the linear density response. The main advances that allow extension of the method to molecular simulations are summarized as follows.

(i) Expansion of the energy is taken about the exact ground-state molecular or fragment density instead of the neutral atom densities; hence it recovers the exact charge distribution in the absence of a perturbing field. This has the advantage that the method can be integrated with conventional empirical point charge and dipole parameters for representation of the static ground-state potential.

(ii) Variational flexibility is provided by modeling the density response in terms of basis functions. This has the advantage that even linear and planar molecules and chemical groups can have correct local anisotropic polarizabilities.

(iii) A simple semiempirical form for the hardness matrix is suggested that allows non-Coulombic contributions to be modeled by an overlap term. Efficient analytical evaluation of the hardness matrix is efficiently accomplished with Gaussian basis functions.

Numerical application at two basis-set levels demonstrates that the CPE method can accurately reproduce induced dipole moments and chemical potentials derived from LDA density-functional calculations. In certain instances, such as the case of linear and planar molecules, inclusion of basis functions with dipolar character is essential. The CPE formulation presented here forms the foundation for future work to model polarization and charge transfer effects in molecular simulations.

ACKNOWLEDGMENTS

The authors would like to thank W. Mortier, R. Nalewajski, and B. Baekelandt for stimulating discussions. D. M. York is a National Science Foundation postdoctoral fellow jointly funded by the North Carolina Supercomputing Center, MCNC, and the National Science Foundation. W. Yang is an Alfred P. Sloan Fellow. This work has been supported by the National Science Foundation and the North Carolina Supercomputing Center.

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