

JCTC

Journal of Chemical Theory and Computation

Modeling Induction Phenomena in Intermolecular Interactions with an Ab Initio Force Field

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Received June 26, 2007

Abstract: One possible road toward the development of a polarizable potential energy function relies on the use of distributed polarizabilities derived from the induction energy mapped around the molecule. Whereas such polarizable models are expected to reproduce the signature induction energy with an appreciable accuracy, it is far from clear whether they will perform equally well in the context of intermolecular interactions. To address this issue, while pursuing the ultimate goal of a “plug-and-play”-like approach, polarizability models determined quantum mechanically and consisting of atomic isotropic dipole plus charge-flow polarizabilities were combined with the classical, nonpolarizable Charmm force field. Performance of the models was probed in the challenging test cases of cation- π binding and the association of a divalent calcium ion with water, where induction effects are envisioned to be considerable. Since brute force comparison of the binding energies estimated from the polarizable and the classical Charmm potential energy functions is not justified, the individual electrostatic and induction contributions of the force field were confronted to the corresponding terms of a symmetry-adapted perturbation theory (SAPT) expansion carried out with the 6-311++G(d,p) basis set. While the quantum-mechanical and the molecular-mechanical electrostatic and damped induction contributions agree reasonably well, overall reproduction of the binding energies is plagued by an underestimated repulsion that underlines the necessity of de novo parametrization of the classical 6-12 form of the van der Waals potential. Based on the SAPT expansion, new Lennard-Jones parameters were optimized, which, combined with the remainder of the polarizable force field, yield an improved reproduction of the target binding energies.

Introduction

One of the keys to the success of pairwise additive macromolecular force fields resides in the assumption that in numerical simulations, polarization phenomena can be ac-

counted for in an average sense by means of an appropriately parametrized electrostatic term. Such effective potential energy functions compensate for missing through-space induction effects by inflating artificially the polarity of the constituent molecules.¹ A popular implicit polarization scheme, which has pervaded over the past 20 years, relies upon the observation that at the Hartree–Fock (HF) level of approximation, the split-valence 6-31G(d) basis set exhibits a conspicuous tendency to overestimate systematically gas-phase molecular dipole moments.² In a vast number of instances where explicit polarization phenomena can be

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ignored, additive force fields, in which the electrostatic term consists of point charges either derived from HF/6-31G(*d*) electrostatic potentials or optimized to reproduce the interaction with surrounding water molecules, have proven to describe reasonably well the underlying physical properties of the molecular assemblies.^{3,4} An obvious advantage for turning to an implicit polarization approach is the cost-effectiveness of the numerical simulation, obviating the crucial need for an accurate evaluation of the induced dipole moments, which generally represents an appreciable overhead in the calculation of the potential energy. Given the success of implicit polarization schemes, it is legitimate to call into question the necessity to craft new nonadditive potential energy functions, when additive ones seemingly perform just as well.⁵

Unfortunately, in numerous examples, an exaggerated polarity becomes clearly insufficient to describe adequately the response of the molecular charge distribution to a nonuniform, external electric field—chief among which is the interaction of a very deformable electron cloud with a polarizing charge, instantiated in cation- π complexes.⁶ One of the practical reasons that have hitherto hampered the development of polarizable potential energy functions targeted at numerical simulations is evidently the costly calculation of the induced moments, and the realization that a marginal improvement over conventional, pairwise additive force fields was not necessarily worth the additional computational effort. Yet, the formidable decrease of the computer price/performance ratio over the past decades that benefited the theoretical community by opening new vistas for the numerical simulation of large ensembles of atoms over time scales compatible with the experimentally observed phenomena has also paved the way for the development of more elaborate models for the accurate representation of intermolecular interactions. Convincingly enough, nonpolarizable macromolecular force fields, e.g., Amber,⁴ Charmm,⁷ Gromos,⁸ or Opls-AA,⁹ have proven to behave reasonably well, insofar as biologically relevant molecular assemblies, in which induction effects can be safely ignored, are concerned. As the harnessed computational power allows increasingly larger objects of the cell machinery to be tackled in a routine fashion, the pairwise additive approximation remains; however, an intrinsic limitation to the investigation of biophysical processes where the influence of polarization can no longer be neglected without proper justification. For instance, ions permeating membrane channels have been shown to polarize the conduit through which they diffuse,^{10,11} thereby altering the charge distribution of the residues pertaining to the conduction pathway, and, hence, the interplay of the permeant with its environment.

More than a renaissance, the research area of polarizable force fields has been recently the theater of an increasing activity, where the relative merits and drawbacks of competing approaches are being explored. One of the earliest routes devised for modeling through-space polarization phenomena in numerical simulations consists of parametrizing the induction forces in terms of atomic quantities, which can be subsequently plugged into molecular mechanics calculations. At the conceptual level, this solution supposes that the

electron density response be partitioned into regions of the Cartesian space that correspond to atoms and/or functional groups.¹² It also supposes a truncation of the multipole expansion and a selection of leading terms in the classical expression of the forces exerted between atomic distributions. The popular scheme put forth by Applequist¹³ for the construction of models of distributed polarizabilities is based on a self-consistent determination of atomic parameters which are coupled through screened dipole–dipole interactions. Revisited in the couth version of Thole,¹⁴ this heuristic approach bears, however, a marked component of arbitrariness, making the physical interpretation of the derived atomic quantities somewhat arguable. It has been, nonetheless, utilized on several occasions in the statistical simulations of condensed phases, where induction effects were anticipated to play a significant role. In retrospect, it is not clear whether such a partitioning scheme, reduced to an isotropic description of the polarization effects, would increase dramatically the accuracy of the modeled intermolecular interactions, compared to a well parametrized additive force field. In cation- π complexes, for instance, whereas the use of a nonadditive potential energy function appears to improve the accord with the quantum chemical interaction energies bereft of a basis set superposition error¹⁵ (BSSE), inclusion of the latter ironically suggests that the pairwise additive approximation would perform better.¹⁶ Moreover, the overhead imposed by the self-consistent computation of the induced dipole moments in molecular mechanics simulations brings us back to questioning the necessity of turning to polarizable potential energy functions. Much effort, however, has been invested in recent years not only on the front of partitioning the electron density response into distributed polarizabilities^{17–22} but also on that of their incorporation in numerical simulations at a lesser computational cost.²³

In spite of these remarkable advances, the theoretical community appears to be still facing the Gordian knot of increasing the level of sophistication of the current potential energy functions and, hence, the burden of the force evaluation, at the expense of a more extensive sampling of the configurational space. Promising alternative routes to the spatial partitioning of the electron density response are being explored in the context of biomolecular simulations. Among these routes, the Drude shell²⁴ or dispersion oscillator model relies on a concept devised over a century ago for investigating the charge fluctuation forces in a variety of materials. In a nutshell, it consists of the introduction of massless particles attached to polarizable atoms by means of stiff harmonic springs and bearing a partial charge. It can be shown that the atomic polarizability is a function of both the spring constant and the point charge borne by the so-called Drude particle. In response to an external electric field, the latter is displaced with respect to the atomic core, thereby modifying the molecular charge distribution.^{25,26} Models of fluctuating charges constitute yet another promising formalism^{27–29} in which the point charges are handled as dynamical variables reflected in the corresponding atomic electronegativities. Conceptually, the electron gas surrounding any nucleus, which is shown to have a chemical potential equal to the negative of the atomic electronegativity, spreads across the

entire molecule equalizing the chemical potential at every atomic position. This notion of electronegativity equalization was introduced over 50 years ago by Sanderson³⁰ and provides a convenient framework for modeling the flow of electrons between atoms as a response to variations of the electric field felt by the participating nuclear sites. Whether these approaches aimed at handling induction effects explicitly in numerical simulations describe the spatial anisotropy of the polarizability with an acceptable accuracy remains, however, unclear.

On account of their overwhelming complexity, compared with the somewhat simpler Drude shell or fluctuating charge models, fully polarizable classical force fields have admittedly not yet come of age to be amenable to numerical simulations of biologically relevant molecular systems over long time-scales. It can be argued, however, that such force fields, if appropriately parametrized, represent the best possible route toward a faithful description of the response electron density upon perturbation by an external electric field.^{31–34} In spite of the additional cost implied, which has limited their use so far to mere proofs of concept, fully polarizable classical force fields are expected to become rapidly a relevant competitor to more approximate schemes.

The caveat “appropriately parametrized” bears some significance in the sense that the prevalent criterion adopted to measure the accuracy of the polarizable models is their propensity to reproduce the induction energy mapped around the molecule. Adopting this philosophy, models truncated to an isotropic point dipole representation, in the spirit of Applequist’s prescription,¹³ may turn out to be inadequate only because they are incomplete. In the present study, the physically sound, rigorous framework of optimally partitioned electric properties^{35,36} (OPEP) is employed for understanding the spatial anisotropy of through-space induction phenomena. In particular, it will be shown that anisotropy can be recovered in models combining isotropic dipole polarizabilities with a zeroth-order charge-flow term between vicinal atoms. To illustrate the critical role played by polarization in intermolecular interactions, two classes of charged complexes will be considered, viz. the cation- π motif resulting from the interaction of benzene with ammonium, and the complexes formed by a calcium ion and a chelating agent, namely water. In the following section, the theoretical formalism is introduced, together with the computational details for the determination of the distributed models of polarizabilities. Next, the performance of the *ab initio* polarizable force field for reproducing the quantum mechanical interaction energies will be examined in the light of symmetry-adapted perturbation theory³⁷ (SAPT) calculations, which supplies benchmark values of the polarization contribution. Finally, concluding remarks will be drawn, emphasizing the issue of transferability of the models in classical macromolecular force fields.

Methods

Over 25 years ago, Cox and Williams³⁸ planted the seed of a method now widely utilized to parametrize the electrostatic term of potential energy functions. In essence, this approach relies on a least-squares fit of atomic charges to the quantum-

mechanical electrostatic potential evaluated around the molecule, reminiscing the idea that the former constitutes the fingerprint of the latter.^{39–41} Following a similar philosophy, a variety of alternative numerical schemes has been put forth to derive models of distributed polarizabilities based on a least-squares fitting procedure to the polarization potential, i.e., the induction energy associated with the presence of a test charge.^{17,20,42} Just like atomic multipole moments can be determined at any given order from the sole knowledge of the reference electrostatic potential, so can atomic polarizabilities, provided that the induction energy has been mapped appropriately around the molecule of interest.⁴³ Yet, whereas the electrostatic potential at any given point in Cartesian space can be obtained readily from the wave function of a single-point quantum-mechanical calculation, induction energy maps are far more cumbersome to determine. Arguably enough, the most straightforward route is a finite-perturbation approach, whereby the molecule interacts with a nonpolarizable charge, q_k , located at point k . The corresponding induction energy can be expressed as

$$\mathcal{U}_{\text{ind},k} = \varepsilon_{\text{tot},k}^{\text{QM}} - \varepsilon_0^{\text{QM}} - q_k V_k^{\text{QM}}(\mathbf{r}_k) \quad (1)$$

Here, $\varepsilon_{\text{tot},k}^{\text{QM}}$ stands for the energy of the molecule in the presence of the point charge, which requires one individual quantum-mechanical calculation for each point k of the grid over which the induction energy is mapped. $\varepsilon_0^{\text{QM}}$ is the energy of the isolated molecule, and $V_k^{\text{QM}}(\mathbf{r}_k)$ is the electrostatic potential generated at point k by the isolated molecule.

Quite obviously, the prerequisite of multiple, independent quantum-mechanical calculations imposed by the need for a detailed, accurate picture of the induction energy around the molecule constitutes the main weakness of the finite-perturbation method. Its overwhelming computational cost, rooted in the necessity to include intramolecular electron correlation and employ a sufficiently large basis set to guarantee the faithful reproduction of the molecular polarizabilities, constitutes a stringent limitation of the approach. Whereas the induction energy can be mapped with an appropriate resolution and spatial extension for small, prototypical molecules, the finite-perturbation method becomes rapidly impractical for larger chemical compounds. Given this computational limitation, alternative routes have been explored for faster, yet reliable evaluation of induction energies, chief among which is an elegant method relying upon a single quantum-mechanical calculation carried out at the coupled-perturbed HF (CPHF) or any higher level of approximation.²¹ A topological analysis of the response charge density is then performed in the spirit of the “atoms in molecules” theory⁴⁴ to derive the components of the distributed polarizabilities, $\alpha_{l k, l' k'}^{s s'} = \alpha_{l k, l' k'}(\mathbf{r}_s, \mathbf{r}_{s'})$, at a given rank $l, l' \leq L$ —where L is the highest rank of the components forming what will henceforth be referred to as the model of topologically partitioned electric properties (TPEP).^{19,45–47} Such a model, which usually consists of a sizable number of terms, can be utilized to regenerate the induction energy resulting from the polarization of the molecule by the nonpolarizable charge q_k :

$$\mathcal{U}_{\text{ind},k} = -\frac{1}{2}q_k^2 \sum_{s,l,m} \sum_{s',l',m'} T_{00,1\kappa}^{ks} \alpha_{l\kappa,l'\kappa'}^{ss'} T_{l'\kappa',00}^{s'k} \quad (2)$$

Here, s and s' denote two polarizable sites of the molecule. $T_{l\kappa,00}^{sk}$ is a matrix element of the electrostatic tensor^{48,49} corresponding to multipole component $\{l,\kappa\}$, which gives at point s the electrostatic potential, or its successive derivatives, created by point charge q_k .

In this contribution, models of distributed polarizabilities will be derived with the OPEP suite of programs³⁵ from maps of induction energies generated using both the finite-perturbation approach and TPEP models.⁴³ In the case of the cation- π interaction of an ammonium ion with benzene, the induction energy was mapped on grids containing, respectively, 1247 and 3192 points, following the first numerical scheme. For the interaction of a calcium cation, assumed to be nonpolarizable, with water, the induction energy was evaluated on a grid consisting of 3905 points. In addition, models of net atomic charges were derived with the Opep code from the electrostatic potential computed quantum mechanically for the different chemical compounds^{39,40} (see Table 1). In all cases, calculations were conducted at the MP2 level of theory with the Sadlej basis set,⁵⁰ which supplies polarizability parameters at a favorable quality/cost ratio. Preliminary optimization of the molecular geometries was performed at the MP2/6-311++G(2d,2p) level of approximation, using Gaussian98⁵¹—MP2/Sadlej computations based on MP2/6-311++G(2d,2p) optimized geometries will be referred to as MP2/Sadlej//MP2/6-311++G(2d,2p). As was demonstrated recently,³⁶ anisotropy of polarization phenomena can be recovered without the explicit introduction of anisotropic components in the distributed polarizability models, which would not only increase the complexity of the latter but also require a more cumbersome treatment of the corresponding induction forces in numerical simulations. Models combining isotropic dipole- and charge-flow polarizabilities have proven to yield a reasonable reproduction of the target induction energies and molecular quantities and will be utilized in the present investigation (see Table 2). These models will be associated with the Charmm⁷ macromolecular force field for the computation of the classical potential energy surfaces delineating the interaction of the ammonium ion with the aromatic ring and that of the calcium ion with water. The quantum-mechanical potential energy surfaces were determined at the MP2/6-311++G(d,p) level of theory, varying the intermolecular distance in 0.1-Å increments and evaluating the BSSE¹⁵ at each step.

For several years, one of the Grail quests for force field developers has been the search for polarizability parameters that could be plugged directly into an existing potential energy function obeying pairwise additivity. It should be remembered, however, that the electrostatic term of the latter exaggerates significantly the polarity of the participating molecules to compensate in an average sense for missing induction effects and, thus, ought to be scaled down accordingly.⁵² Given that this implicit polarization scheme relies essentially on the erratic shortcomings of the basis set utilized to derive the point charge models, only a heuristic

Table 1. Models of Net Atomic Charges and Regenerated Molecular Multipole Moments of Benzene, Ammonium, and Water at the MP2/Sadlej//MP2/6-311++G(2d,2p) Level of Approximation^a

	molecular multipoles				
	point charges		regenerated		MP2/Sadlej
benzene	Q_{00}^C	−0.124	Q_{20}	2.804	2.868
	Q_{00}^H	0.124	Q_{30}	11.131	11.380
	rmsd	0.222			
	$\Delta\epsilon$	22.858			
ammonium	Q_{00}^N	−0.848	Q_{30}	7.446	7.398
	Q_{00}^H	0.462	Q_{40}	6.727	8.071
	rmsd	0.073			
	$\Delta\epsilon$	0.035			
water	Q_{00}^O	−0.672	Q_{10}	−0.747	−0.732
	Q_{00}^H	0.336	Q_{20}	−0.189	−0.231
	rmsd	1.308			
	$\Delta\epsilon$	54.273			

^a The root-mean-square deviation (rmsd) between the electrostatic potentials determined quantum-mechanically and regenerated from the point charge models is expressed in 10^{-3} au. The corresponding mean error, $\Delta\epsilon$, is given in percents.³⁹

Table 2. Models of Distributed Polarizabilities and Regenerated Molecular Polarizabilities of Benzene, Ammonium, and Water at the MP2/Sadlej//MP2/6-311++G(2d,2p) Level of Approximation^a

	molecular polarizabilities				
	distributed polarizabilities		regenerated		MP2/Sadlej
benzene	$\alpha_{00,00}^{CC}$	−1.822	$\alpha_{10,10}$	47.537	45.171
	$\alpha_{00,00}^{CH}$	−0.280	$\alpha_{11c,11c}$	89.089	81.401
	$\alpha_{00,00}^{CC}$	7.953	$\alpha_{11s,11s}$	89.089	81.401
	$\alpha_{1\kappa,1\kappa'}^{CC}$	0.025			
	rmsd	0.025			
	$\Delta\epsilon$	2.737			
ammonium	$\alpha_{1\kappa,1\kappa'}^{NN}$	10.708	$\alpha_{1\kappa,1\kappa'}$	10.708	9.078
	rmsd	0.195			
	$\Delta\epsilon$	16.684			
water	$\alpha_{00,00}^{OH}$	−0.808	$\alpha_{10,10}$	10.177	9.751
	$\alpha_{00,00}^{OO}$	8.180	$\alpha_{11c,11c}$	11.483	10.063
	$\alpha_{1\kappa,1\kappa'}^{OO}$		$\alpha_{11s,11s}$	8.180	9.542
	rmsd	0.127			
	$\Delta\epsilon$	7.000			

^a The root-mean-square deviation (rmsd) between the induction energies determined quantum-mechanically and regenerated from the models of distributed polarizabilities is expressed in 10^{-3} au. The corresponding mean error, $\Delta\epsilon$, is given in percents.²⁰

correction can be applied. A more rational approach consists of determining new sets of atomic charges representative of a true gas phase,⁵³ which is an easy task for a handful of small organic molecules, as is the case in the present investigation, but admittedly constitutes a tedious endeavor for a complete macromolecular force field. There is an additional complication hitherto only marginally discussed: polarizability parameters are anticipated to depend inherently on the characteristics of the environment and, therefore, ought to be adapted correspondingly.^{54–56} In the present work, the description of the electrostatic and the induction contributions of the force field is consistent with a low-pressure gaseous phase, albeit it should be modified to reflect the nature of the surroundings.

Potential energy functions are very complex constructs, the building blocks of which are intimately connected. Subtle modifications of the constituent parameters can perturb significantly the delicate balance between the different terms of the force field. Beyond the scaling, or possibly the new derivation of point charges, van der Waals parameters, in principle, ought to be also adjusted to reflect the gas-phase electrostatics and the explicit inclusion of induction effects. Brute force comparison of force field performances upon plugging polarizability parameters, yet without any tuning of the other terms, would evidently render a biased picture and be somewhat unfair to the original pairwise additive potential energy function. Moreover, macromolecular force fields like Amber,⁴ Charmm,⁷ Gromos, or Opls-AA⁹ have not been designed for numerical simulations in the gas phase. The point that the present work intends to make, however, is a demonstration that the proposed models of distributed polarizabilities yield an accurate reproduction of the induction contribution to the total interaction energies. To achieve this objective, the latter was confronted to reference SAPT2 calculations,^{37,57} with the 6-311++G(*d,p*) basis set, for the selected series of complexes where polarization phenomena are appreciable. In the framework of the SAPT2 approach, the correlated contribution to the interaction energy is nearly equivalent to the supermolecular MP2 correlation energy.

At this stage, for clarity, the relationship between the convoluted contributions of the empirical potential energy function

$$\Delta \mathcal{U}_{\text{tot}}^{\text{MM}} = \Delta \mathcal{U}_{\text{ele}} + \Delta \mathcal{U}_{\text{ind}} + \Delta \mathcal{U}_{\text{damp}} + \Delta \mathcal{U}_{\text{vdW}} \quad (3)$$

and the different terms of an SAPT calculation

$$\Delta \mathcal{U}_{\text{tot}}^{\text{SAPT}} = \Delta \mathcal{U}_{\text{ele}} + \Delta \mathcal{U}_{\text{ind}} + \Delta \mathcal{U}_{\text{exch}} + \Delta \mathcal{U}_{\text{disp}} + \Delta \mathcal{U}_{\text{exch-ind}} + \Delta \mathcal{U}_{\text{exch-disp}} + \delta \text{HF} \quad (4)$$

ought to be established—here, $\Delta \mathcal{U}_{\text{tot}}$ denotes the total interaction energy obtained either from an empirical force field (MM) or from the SAPT scheme. Aside from the pairwise additive approximation adopted by most macromolecular force fields, the choice to describe nonbonded interactions by means of a rudimentary 6-12 Lennard-Jones potential and a Coulomb sum truncated at the monopole level clouds the assignment of a true physical meaning to these contributions. In particular, physical interpretation of individual force field components is difficult when the corresponding parameters are not fitted independently.⁵⁸ Under most circumstances, assuming that the molecular charge distribution can be represented accurately by net atomic charges, the electrostatic terms, $\Delta \mathcal{U}_{\text{ele}}$, extracted from force-field and SAPT calculations, are generally comparable, granted that penetration effects are negligible.⁵⁹ The same, unfortunately, cannot be said for the so-called van der Waals interactions, $\Delta \mathcal{U}_{\text{vdW}}$. The ad hoc, albeit physically questionable form of the Lennard-Jones potential cannot be interpreted straightforwardly, on a one-to-one basis, in terms of repulsion and dispersion. Lennard-Jones energies, in reality, embrace different terms that can be recovered from an SAPT expansion, namely a dispersion, $\Delta \mathcal{U}_{\text{disp}}$, an exchange, $\Delta \mathcal{U}_{\text{exch}}$, and an exchange-dispersion, $\Delta \mathcal{U}_{\text{exch-disp}}$, contribu-

tion. Direct incorporation of induction phenomena in classical potential energy functions raises additional concerns on account of the physically unrealistic forces that thrust the polarizing charge toward the polarizable center. In principle, the classical and the quantum-mechanical induction contributions are comparable, provided that (i) the induction energy is mapped by the model of distributed polarizabilities with an appropriate accuracy and (ii) contamination from the penetration of the electron clouds is avoided. The SAPT expansion involves, however, other terms, which ought to be modeled in the classical, polarizable force field, chief among which is an exchange-induction term, $\Delta \mathcal{U}_{\text{exch-ind}}$. The latter is supplemented by a collection of third and higher order induction and exchange-induction terms. A common route to the description of the exchange-induction contribution consists of damping the interaction of the electric field with the polarizable sites, employing a surrogate empirical function, $\Delta \mathcal{U}_{\text{damp}}$, which does not necessarily compare to the homologue SAPT component. In the present work, use was made of a damping correction that preserves the traceless feature of the interaction tensor.^{60,61} The equivalence of the SAPT induction and exchange-induction higher order terms⁶²—i.e. δHF , in the classical force field is less obvious, as most of these contributions do not necessarily appear in the parametrization of the polarizability models, viz. hyperpolarizability effects, which are usually neglected by computing the target quantum-mechanical induction energy at grid points lying far enough from the nuclei.

Results and Discussion

Cation- π Interactions. Over the past 20 years, cation- π interactions have progressively emerged as an important component in the subtle balance of noncovalent interactions that determine the three-dimensional structure of proteins.^{6,63} They constitute a major driving force in molecular recognition processes, sufficiently strong to compete with the hydration of charged moieties and promote protein–ligand association in hydrophobic cavities formed by aromatic residues—e.g. the binding of acetylcholine to acetylcholinesterase. From an electrostatic perspective, the leading contribution to cation- π interactions is the favorable charge-quadrupole attraction of the charged species toward the π -electron cloud of the aromatic ring. A pure electrostatic description appears, however, to be generally incomplete to supply a faithful, accurate description of cation- π interactions due to the substantial polarizability of aromatic compounds combined with the polarizing character of the positively charged ion.⁶⁴ Absence of explicit induction effects in classical representations invariably results in underestimated binding constants, compared to reference quantum-mechanical calculations. Tackling polarization phenomena in cation- π complexes has been endeavored at different levels of sophistication, ranging from rudimentary, ad hoc corrections to the classical pairwise additive force field^{63,65} to the explicit incorporation of isotropic polarizability parameters.¹⁶ In retrospect, compared to up-to-date quantum-mechanically determined binding energies, neither route would seem to constitute an optimal solution. Cost-effective short-range corrections to the nonpolarizable potential energy function

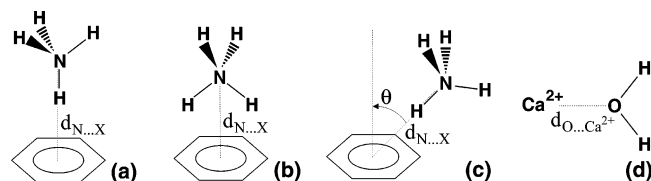


Figure 1. Ammonium-benzene cation- π interaction. (a) Monodentate and (b) bidentate complexes. X refers to the centroid of the aromatic ring. (c) Alternate approach of the cation toward the π -electron cloud of benzene, whereby the N-H chemical bond pointing toward its centroid and the normal to the aromatic plane form a 45° angle. Interaction of a divalent calcium ion with water (d). Approach of the cation toward the donor ligand is considered along the C_2 axis of the latter.

evidently cannot account for multiple cations binding the same π -electron cloud. On the other hand, inasmuch as explicit induction forces are concerned, it is far from clear whether a fully isotropic description of the polarizability is adequate for modeling cation- π interactions correctly. A simple glance at the molecular dipole polarizability of benzene estimated at the MP2/Sadlej level of theory is enough to realize that in-plane deformation of the π -electron cloud by a polarizing charge is considerably larger than it would be in the perpendicular direction (see Table 1).

An analysis of the topologically distributed polarizability model of benzene⁴⁵ reveals that a considerable portion of the in-plane polarizability—viz. typically 75%, can be described as interatomic charge-flow, whereas the out-of-plane component is almost entirely due to atomic dipole-dipole polarizabilities. Although the pattern of the topological charge-flow polarizabilities follows the well-known rules of organic chemistry, with a significant contribution between the para carbon atoms and an opposite sign meta-contribution, it can be expected that a simplified OPEP model, consisting of isotropic atomic polarizabilities borne by carbon atoms and retaining only the ortho-type charge-flow between them, is capable of reproducing the essential features of the charge-density response.

The mono- and the bidentate interactions of an ammonium ion with benzene, whereby, respectively, one and two N-H chemical bonds point toward the centroid of the aromatic ring, is depicted in Figure 1. The potential energy surfaces delineating the cation- π interaction determined using the classical Charmm force field, with and without a polarizability correction, are reported in Figures 2 and 3—see also Table 3. Not too surprisingly, the nonpolarizable potential energy function markedly underestimates the strength of the interaction. Macromolecular force fields are, however, targeted at numerical simulations in condensed phases, thus making any brute force comparison with gas-phase quantum-mechanical calculations somewhat arguable. The binding energies determined with the native Charmm force field should, therefore, be seen as a mere indicator. Accord between the values obtained at the MP2/6-311++G(*d,p*) level of theory and using a polarizable description is somewhat enhanced, but is this comparison necessarily justified?

It is becoming quite clear from eqs 3 and 4 that the ability of the polarizable force field to reproduce the reference

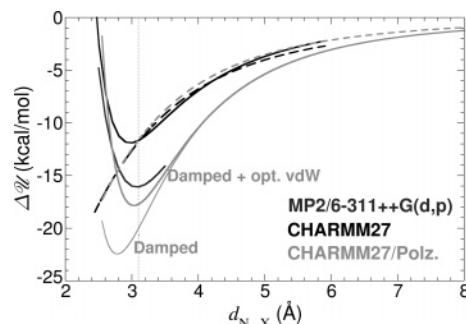


Figure 2. Monodentate motif of the ammonium-benzene cation- π interaction. X refers to the centroid of the aromatic ring. Shown is a comparison of the binding energies determined from BSSE-corrected MP2/6-311++G(*d,p*) calculations (dark solid line), the classical, nonpolarizable Charmm force field (black lines), and the latter supplemented by a model of distributed polarizabilities (light lines), with and without de novo optimization of the participating Lennard-Jones parameters. The electrostatic contribution to the binding energy is depicted as dashed lines. The vertical dotted line marks the position of the quantum-mechanical energy minimum.

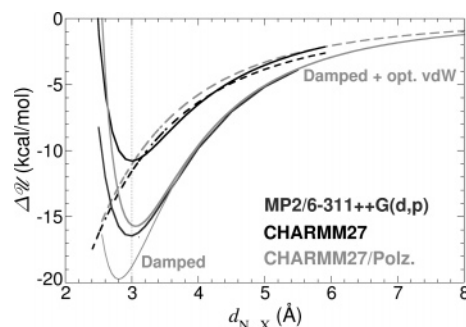


Figure 3. Bidentate motif of the ammonium-benzene cation- π interaction. X refers to the centroid of the aromatic ring. Shown is a comparison of the binding energies determined from BSSE-corrected MP2/6-311++G(*d,p*) calculations (dark solid line), the classical, nonpolarizable Charmm force field (black lines), and the latter supplemented by a model of distributed polarizabilities (light lines), with and without de novo optimization of the participating Lennard-Jones parameters. The electrostatic contribution to the binding energy is depicted as dashed lines. The vertical dotted line marks the position of the quantum-mechanical energy minimum.

quantum-mechanical binding energies should be appraised on the basis of the individual components, rather than as a whole. In Figures 2 and 3, the electrostatic terms inferred from the potential energy function and from the SAPT expansion are compared at various values of the reaction coordinate, for both the mono- and the bidentate motifs. As can be seen in Table 4, at the minimum of the binding energy, the SAPT electrostatic contribution of the monodentate complex matches exactly the molecular mechanics estimate, viz. -11.6 kcal/mol. This remarkable agreement might be due to the fact that point charges determined using the Sadlej basis set tend to overestimate the multipolar part of the electrostatic potential, compared to MP2 reference calculations with large, triple- ζ basis sets supplemented by diffuse functions.⁶⁶ Unfortunately, the accord is less satisfac-

Table 3. Intermolecular Separations^a in the Mono- and Bidentate Forms of the Ammonium-Benzene Complex and in the Complex Formed by Ca²⁺ with Water, Determined from MP2/6-311++G(*d,p*) Potential Energy Surfaces, the Classical Charmm Force Field, and the Ab Initio Polarizable Force Field

	$d_{X...Y}$		
	QM	Charmm	polarizable force field ^b
monodentate	3.1	3.0	3.1
bidentate	3.0	3.0	3.1
Ca ²⁺ ...H ₂ O	2.3	2.3	2.4

^a All quantities are expressed in Å. ^b Polarizable force field with a new optimization of the participating Lennard-Jones parameters.

tory for the bidentate motif, the point charge model underestimating the target electrostatic energy by 1.3 kcal/mol. Does it mean that a simple set of net atomic charges is insufficient to capture the subtle electrostatic effects arising from distinct orientational preferences of the cation? This issue can be readily addressed by solving a system of nonlinear equations satisfying the SAPT electrostatic energies for the two complexes, and the unknowns of which are the charges borne by the constituent atoms of the latter. The only way a single set of point charges can discriminate between the mono- and the bidentate motifs is by assigning a charge of -0.135 to the carbon atoms of benzene, comparable to that derived from the MP2/Sadlej wave function, and a physically unrealistic charge of 0.722 to the nitrogen atom of ammonium. Coercing artificially the cation to localize its charge onto the central nitrogen atom deteriorates dramatically the reproduction of the electrostatic potential, thus, calling into question the relevance of such a representation. It would, therefore, appear that a presumptive physically sound model may not be necessarily capable of discriminating between two forms of the same complex. Even though the higher order moments of both benzene and ammonium are described quite accurately by atom-centered point charges, as suggested by Table 1, it is far from clear whether a monopole approximation is legitimate to model the present cation- π interactions, which evidently constitute a challenging test case.

Table 4. Comparison of the Contributions to the Binding Energies^a of the Mono- and Bidentate Forms of the Ammonium-Benzene Complex and the Complex Formed by Ca²⁺ with Water, Determined from an SAPT2/6-311++G(*d,p*) Expansion and a Polarizable Potential Energy Function

	$\Delta\mathcal{H}_{\text{ele}}$		$\Delta\mathcal{H}_{\text{ind}}^b$		$\Delta\mathcal{H}_{\text{vdW}}^c$		δHF^d	$\Delta\mathcal{H}_{\text{tot}}$		
	SAPT	MM	SAPT	MM	SAPT	MM		MP2 ^e	SAPT	MM ^f
monodentate	-11.6	-11.6	-9.0	-7.9	6.4	1.8	-2.0	-16.1	-16.2	-17.7
						(-0.5)				(-20.0)
bidentate	-13.1	-11.8	-9.1	-8.6	8.3	4.7	-2.5	-16.5	-16.4	-15.7
						(1.1)				(-19.3)
Ca ²⁺ ...H ₂ O	-51.7	-44.5	-22.1	-23.0	19.8	20.3	-0.8	-53.4	-54.7	-47.2
						(3.6)				(-63.9)

^a All quantities are expressed in kcal/mol, with respect to the reference quantum-mechanical energy minima of Table 3. ^b The SAPT value includes the pure induction and the exchange-induction contributions. The MM model consists of the pure induction term, supplemented by a damping correction. ^c The SAPT value corresponds to the sum of the exchange, the dispersion, and the exchange-dispersion contributions. The MM value is simply the Lennard-Jones component of the force field. ^d This contribution encompasses the third and higher order induction and exchange-induction terms of the SAPT expansion. It is clearly absent in the MM description. ^e BSSE-corrected MP2/6-311++G(*d,p*) interaction energies. ^f The values in bold were determined after de novo optimization of the Lennard-Jones parameters. The values in parentheses correspond to estimates obtained with the standard Lennard-Jones parameters of the force field.

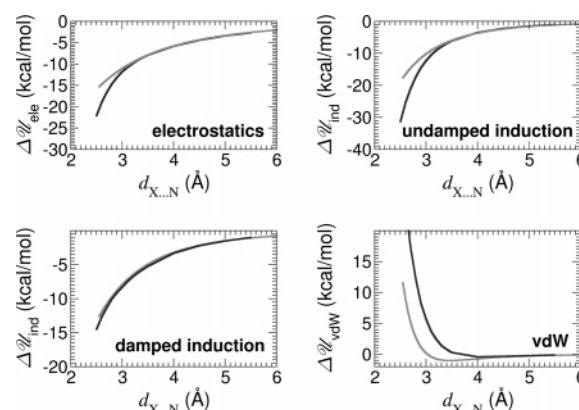


Figure 4. Components of the cation- π interaction energy, determined for the bidentate motif from an MP2/6-311++G(*d,p*) SAPT expansion (dark solid line) and the polarizable potential energy function (light solid line). The undamped induction contribution corresponds to the pure induction term of eqs 3 and 4. At the quantum-mechanical level, the damped induction contribution consists of a sum of induction and exchange-induction terms. At the molecular-mechanical level, it stands for the pure induction component corrected by a damping function. The van der Waals contribution encompasses at the quantum-mechanical level the dispersion, the exchange, and the exchange-dispersion terms of the SAPT expansion. In the classical description, it coincides with the Lennard-Jones potential.

The second term of the SAPT expansion corresponds to the pure induction energy, which, as has been discussed previously, should, in principle, coincide with the contribution arising from the model of distributed polarizabilities. A glimpse at Figure 4, however, indicates otherwise. At short separations of the cation from the π -electron cloud, the polarizable force field underestimates the target SAPT term markedly. At the minimum of the binding energy for the bidentate motif, this discrepancy is still equal to ca. 3.4 kcal/mol. The two profiles delineating the quantum mechanical and the classical distance dependence of $\Delta\mathcal{H}_{\text{ind}}$, nevertheless, rapidly merge only 0.3 Å beyond the minimum, suggesting that the long-range behavior of the polarizable model is correct. It is tempting to invoke the incompleteness of the

latter to rationalize the observed short-range divergence of the induction energy. In particular, as reported in Table 2, the present models consist of distributed isotropic dipole and charge-flow polarizabilities, and, hence, ignore short-range, higher-order terms. To which extent do they contribute to the faithful description of intermolecular interactions remains unclear. Equally unclear is the influence of charge flows between non-neighboring atoms, which are envisioned to be at play in the well-known Kekule model of benzene.

The disagreement between the *pure* induction energies determined quantum mechanically and by means of the distributed polarizability models, however, casts doubt on the physical interpretation of $\Delta\mathcal{U}_{\text{ind}}$ at short distances. For instance, the classical representation of distributed polarizabilities does not account for any possible overlap of the electron clouds that would damp the electric field felt by the polarizable sites. Yet, the introduction of a damping correction in the interaction tensor raises conceptual difficulties. As an example, the formalism put forth by Thole yields an interaction tensor that is no longer traceless, contrary to the unaltered tensor. More importantly, the damping function proposed by Thole is not continuous, which can be critical at short intermolecular distances. Although, strictly speaking, the ad hoc damping correction, $\Delta\mathcal{U}_{\text{damp}}$, cannot be compared directly with the SAPT exchange-induction term, $\Delta\mathcal{U}_{\text{exch-ind}}$, it may be contended that the sum of $\Delta\mathcal{U}_{\text{ind}}$ and $\Delta\mathcal{U}_{\text{damp}}$, in the classical description can be related to the sum of $\Delta\mathcal{U}_{\text{ind}}$ and $\Delta\mathcal{U}_{\text{exch-ind}}$, at the quantum-mechanical level. This is illustrated in the components of Figure 4, which highlight the coincidence of the damped induction profiles over the entire range of cation- π distances explored on the potential energy surface and show that below 3 Å, the undamped induction is considerably stronger than the value derived from the distributed polarizability model. This behavior might be related to the instability of the SAPT induction energy reflecting a divergence of the polarization series. This overestimation is corrected by the exchange-induction term,⁶⁷ justifying that the comparison should be done between the damped classical induction energy, on the one hand, and the sum of induction and exchange-induction energies, on the other. Quantitatively, Table 4 reveals that the agreement between the polarizable models and the quantum-mechanical calculations varies from 0.5 to 1.1 kcal/mol for the bidentate and the monodentate complexes, respectively. Interestingly enough, in the light of a Kitaura-Morokuma energy decomposition⁶⁸ performed at the HF/6-311+G(*d,p*) level of theory for the mono- and the bidentate motifs of the ammonium-benzene complex, a contribution embracing polarization and charge-transfer terms of -9.0 to -9.3 kcal/mol was found.⁶⁹ It should be reminded, however, that in a perturbation expansion of the total interaction energy, the charge-transfer term is a short-range part of the induction contribution.⁷⁰

The exact role played by van der Waals interactions in the binding energies is somewhat more difficult to apprehend. As has been emphasized previously, what is generically referred to as the van der Waals contribution can be expressed in the SAPT expansion as the sum of exchange, dispersion, and exchange-dispersion terms. The meaning of

van der Waals interactions in a molecular-mechanical description is far more ambiguous, as it embraces in a heuristic, ad hoc function everything from the nonbonded contribution that is neither electrostatic nor induction-related. Assigning a physical meaning to this function and to its individual terms, therefore, constitutes a daunting task. At the beginning of this section, the arbitrariness and the unfair nature of a gross assessment of the Charmm force field to reproduce quantum-mechanical binding energies of cation- π complexes has been underlined. Equally arbitrary is the direct comparison of the binding energies determined quantum mechanically and employing a polarizable and a nonpolarizable force field. The reason is self-explanatory: The van der Waals part of the classical Charmm potential energy function has been optimized for a given set of net atomic charges, assumed to reflect the interaction of the parametrized chemical moieties with an aqueous environment.^{7,71} Alteration of the electrostatic contribution to the empirical force field by using point charges appropriate for gas-phase simulations creates an imbalance in the construct, that ought to be corrected by a new optimization of the Lennard-Jones parameters. This rationalizes the noteworthy disagreement between the profiles of Figures 2 and 3 computed at the MP2/6-311++G(*d,p*) level of approximation and using the Charmm force field supplemented by atomic polarizabilities. A rapid glance at the van der Waals contributions gathered in Table 4 and Figure 4 suffices to appraise the paramount importance of a proper parametrization of these interactions. At the minimum of the binding energy, the molecular-mechanical interaction energy based on Charmm Lennard-Jones parameters underestimates the repulsion of the nuclei by an amount of 6.9–7.2 kcal/mol for the monodentate and the bidentate complex, respectively. This lack of repulsion between the polarizing cation and the π -electron cloud is illustrated in Figures 2 and 3, where the position of the energy minima is shifted relative to the quantum-mechanical estimates. Interestingly enough, Figure 4 also reveals that the van der Waals profiles obtained from an SAPT expansion and from the classical description have distinct shapes. Whereas the former decays rapidly and exhibits a marginal, shallow minimum around 4 Å, the latter is much smoother, with a pronounced minimum near 3.5 Å. Novel parametrization of the Lennard-Jones interaction potential is, in principle, feasible, based on the wealth of data supplied by the SAPT expansion computed over the entire reaction pathway. Given the geometries of the bidentate cation- π complex and the components of the binding energy at various separations depicted in Figure 4, updated Lennard-Jones parameters can be fitted numerically to the sum of the dispersion, the exchange, and the exchange-dispersion terms of eq 4.

Even though the electrostatic, the induction, and the van der Waals contributions were mimicked optimally by the classical polarizable force field, one could still argue that any attempt to match exactly the quantum-mechanical binding energies is doomed from the onset on account of neglected terms in the potential energy function. These terms, which are referred to as δHF in the SAPT expansion 4, are third and higher order induction and exchange-induction contributions. They are evidently absent from the classical

description of the cation- π interaction, as any possible contamination through hyperpolarizability effects of the induction energy has been carefully probed in the fitting procedure of the polarizability parameters.⁷² As can be seen in Table 4, the δ HF component represents about 10–15% of the total interaction energy and, hence, cannot be ignored in cation- π complexes. This issue, which has been seldom tackled hitherto, further calls into question the promising agreement reached in previous endeavors to model the energetics of such intricate molecular systems.^{16,63,65} Granted that hyperpolarizability effects cannot be easily incorporated in the models of distributed polarizabilities without modulating more or less severely the accurate reproduction of the quantum-mechanical induction energy, one possible route to account for the higher order—i.e. nonlinear or many-body, induction and exchange-induction contributions embodied in the δ HF term consists of considering the latter in the de novo parametrization of the Lennard-Jones potential. New parameters were optimized following this route and combined to the pure electrostatic and damped induction contributions of the classical force field. The markedly improved accord between the quantum- and the molecular-mechanical estimates of the binding energies is highlighted in Figures 2 and 3. Since the new Lennard-Jones parameters were fitted to the SAPT expansion performed on the bidentate complex, it is not completely surprising that the agreement is somewhat better for the latter than for the monodentate motif. As indicated in Table 4, accuracy in the reproduction of the target quantum-mechanical binding energy for the bidentate complex, within 0.7 kcal/mol, is unprecedented. The discrepancy between the quantum-mechanical and the molecular-mechanical values is, however, somewhat more pronounced for the monodentate complex, viz. 1.6 kcal/mol. Remarkably enough, the newly optimized 6-12 potential causes the position of the molecular-mechanical energy minimum to shift, virtually matching that of the corresponding MP2/6-311++G(*d,p*) profiles—see Table 3. Yet, in spite of these improvements, the hierarchy of the associated states of benzene with ammonium still cannot be fully recovered, the monodentate complex emerging 2 kcal/mol below the bidentate complex, when, in principle, their binding energies should be roughly equal. This difference is believed to be rooted in a subtle imbalance between electrostatic and induction contributions that the present polarizable force field cannot capture entirely.

Although the minimum of the binding energy of cation- π complexes generally corresponds to a directional interaction of the polarizing species pointing perpendicularly toward the aromatic ring, approach of the ion may proceed with a different azimuth.⁶³ It has been seen so far that the polarizable models proposed herein have proven to reproduce the quantum-mechanical binding energies reasonably well. To probe the transferability⁷³ of the molecular-mechanical potential energy function to other interaction motifs, the 45° approach of ammonium toward benzene was explored (see Figures 1 and 5). In this orientation, on account of steric hindrances, the cation is necessarily coerced to adopt a monodentate-like binding mode. At the MP2/6-311++G(*d,p*) level of theory, the association energy corresponding

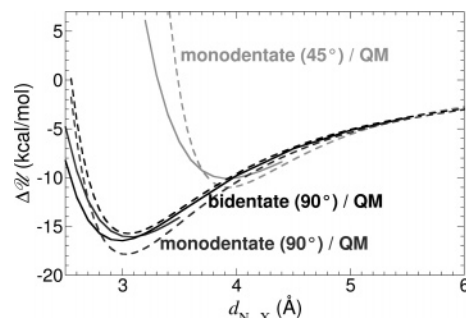


Figure 5. Comparison of the monodentate and the bidentate motifs of the ammonium-benzene complex with an alternate approach of the cation toward the π -electron cloud of benzene, whereby the N–H chemical bond pointing toward its centroid and the normal to the aromatic plane form a 45° angle. Quantum- and molecular-mechanical energies are shown in solid and dashed lines, respectively.

to this approach is about 6.4 kcal/mol higher than the most stable bidentate complex. In glaring contrast with both the bidentate and the monodentate motifs, where the electrostatic component is always stronger than the damped induction term, here, the electrostatic energy is appreciably weaker, which is anticipated to stem from a modulation of the attractive charge-quadrupole interaction by the modified orientation of the cation with respect to the π -electron cloud. As illustrated in Figures 2 and 3, the polarizable force field matches the quantum-mechanical binding energy within 0.9 kcal/mol, which not only is encouraging but also suggests that the classical model is able to capture the anisotropy of induction phenomena.

Interaction of a Calcium Ion with Water. Armed with a consistent strategy for modeling induction phenomena in intermolecular interactions, we now delve into a different class of complexes, wherein polarization effects have been shown to be equally sizable. The C_2 association depicted in Figure 1 of a divalent calcium ion with water was examined at the molecular-mechanical level, using the additive pairwise Charmm force field and an ab initio polarizable force field, and quantum mechanically, at the MP2/6-311++G(*d, p*) level of approximation. From the onset, it can be observed in Figure 6 that the binding energy of the calcium-water complex is reasonably reproduced with or without explicit polarization. Employing the standard Lennard-Jones parameters of the Charmm potential energy function, attraction is clearly exaggerated, highlighted in Table 4, the van der Waals contribution being underestimated by about 16.2 kcal/mol. It is also noteworthy that, compared with the sum of SAPT dispersion, exchange, and exchange-dispersion terms, the position of the shallow minimum of the classical van der Waals profile is shifted about 0.8 Å toward shorter cation-ligand separations (see Figure 7). It is remarkable that the de novo optimization of the molecular-mechanical 6-12 potential based on the SAPT expansion leads to a virtually flawless reproduction of the target quantum-mechanical van der Waals term. The damped induction contribution is also recovered within chemical accuracy. Yet, the ab initio polarizable potential energy function underestimates by 7.2 kcal/mol the total binding energy. A closer look at the

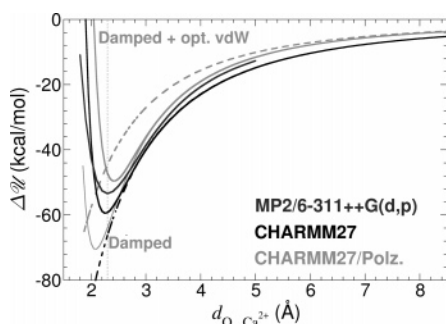


Figure 6. Interaction of a divalent calcium ion with water. Comparison of the binding energies determined from BSSE-corrected MP2/6-311++G(d,p) calculations (dark solid line), the classical, nonpolarizable Charmm force field (black lines), and the latter supplemented by a model of distributed polarizabilities (light lines), with and without de novo optimization of the participating Lennard-Jones parameters. The electrostatic contribution to the binding energy is depicted as dashed lines. The vertical dotted line marks the position of the quantum-mechanical energy minimum.

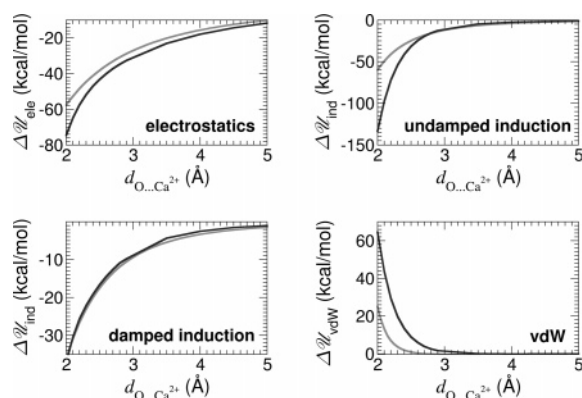


Figure 7. Components of the interaction energy determined for the calcium-water complex from an MP2/6-311++G(d,p) SAPT expansion (dark solid line) and the polarizable potential energy function (light solid line). The undamped induction contribution corresponds to the pure induction term of eqs 3 and 4. At the quantum-mechanical level, the damped induction contribution consists of a sum of induction and exchange-induction terms. At the molecular-mechanical level, it stands for the pure induction component corrected by a damping function. The van der Waals contribution encompasses at the quantum-mechanical level the dispersion, the exchange, and the exchange-dispersion terms of the SAPT expansion. In the classical description, it coincides with the Lennard-Jones potential.

components of the latter reveals that this discrepancy is likely to be rooted in a flawed molecular-mechanical description of the electrostatic contribution, about 7.2 kcal/mol lower than its SAPT counterpart. Remembering that three-point charge models of water are unable to mimic the large atomic quadrupole borne by the central oxygen atom and generally yield errors in the reproduction of the molecular electrostatic potential on the order of 50% (see Table 1), this result is not completely unexpected. Again, we are faced with a stringent test case that underscores the limitations of atom-centered point charge models and urges us to explore the

possibilities of extending them by the inclusion of higher order multipole expansion effects. In an attempt to address this issue, Piquemal et al. have recently delved into the interaction of a calcium ion with the more sophisticated Amoeba⁷⁴ water model.⁷⁵

Paradoxically, replacing the gas-phase MP2/Sadlej charges by those of the TIP3P model of water, i.e., by -0.834 on the oxygen atom, increases dramatically the classical electrostatic contribution from -44.5 to -55.3 kcal/mol, hence improving the overall accord on the total binding energy. The adverb “paradoxically” is utilized here on purpose: it is not really surprising that by boosting the polarity of the water molecule, the absence of higher-order moments is compensated in an artificial fashion, concealing the incompleteness of the point charge model. The true paradox lies in the impression that an error in the parametrization of the electrostatic potential, viz. an incomplete model truncated to the monopole term of the multipole expansion, can be somehow corrected by another error, viz. the use of a charge distribution representative of a condensed phase rather than a low-pressure gaseous state.

Conclusion

The theoretical grounds that underlie the development of an ab initio polarizable force field are reported in this contribution. The key ingredient of the proposed potential energy function is a model of implicitly interacting polarizabilities derived numerically from the induction energy mapped around a molecule. Employing a combination of atom-centered isotropic dipole plus charge-flow polarizabilities, the anisotropy of induction phenomena is essentially recovered, thereby obviating the need for the explicit incorporation of cumbersome anisotropic dipole polarizabilities.³⁶ One might wonder, however, whether the faithful reproduction of the induction energy, the dielectric fingerprint of the molecule, necessarily guarantees an accurate description of intermolecular interactions. To tackle this question, use was made of the pairwise additive Charmm force field, in which models of distributed polarizabilities were plugged. Yet, seamless introduction in a “plug-and-play” fashion of explicit polarization phenomena rapidly proved to be an elusive goal, as newly added contributions to the potential energy perturb the delicate, almost precarious balance of the original, nonpolarizable force field. As a result, direct comparison of the unaltered and the polarizable potential energy functions, in the absence of appropriate correction, is inherently biased. Equally biased is the assessment of these force fields based on gas-phase, high-level quantum-mechanical determinations of potential energy surfaces. What distinguishes, however, the ab initio polarizable force field from its pairwise additive version lies in its physically sound contributions that can be readily compared to the successive terms of an SAPT expansion. In the context of gas-phase quantum-mechanical calculations, the electrostatic component of the polarizable force field is expected to match its SAPT homologue, provided that the electrostatic potential around the molecule is properly described by the distribution of net atomic charges, and penetration of the electron clouds can be safely neglected.^{34,59} As has been shown in the present work, the

pure induction term of the force field supplemented by a damping correction to account for possible overlaps of the participating electron clouds is also expected to coincide with the sum of the induction and the exchange-induction contributions of the SAPT expansion. Evidently enough, altering only partially the nonbonded section of the pairwise additive Charmm force field is inconsistent. This is reflected by an exaggeratedly weak repulsion of the atoms, which can only be corrected through de novo optimization of the constituent Lennard-Jones parameters. The difficulty to develop a balanced polarizable potential energy function, capable of reproducing gas-phase, quantum-mechanical energetics within chemical accuracy, is further magnified by the necessity to take into account higher order terms of the SAPT expansion, which have no real equivalence in the classical description. Case in point—the third and higher-order induction and exchange-induction contributions to the binding energy of the ammonium-benzene complex can be as large as -2.5 kcal/mol, hence, suggesting that derivation of a polarizable force field sufficiently precise for modeling cation- π interactions may easily turn out to be a fateful venture. Such higher order contributions cannot be ignored and ought to be taken into account in the new parametrization of the 6-12 Lennard-Jones potential. Adopting this strategy, which, in the present case, constitutes a proof of concept for gas-phase complexes, the binding energies determined for the monodentate and the bidentate interaction of ammonium with benzene matched reasonably well the MP2/6-311++G(d,p) estimates, albeit hierarchy of the two states is inverted. These results provide a cogent illustration of the difficulties faced by the theoretician when modeling the subtle balance of electrostatic, induction, and van der Waals contributions that drive cation- π interactions—arguably one of the most challenging cases for assessing the performance of a polarizable force field. In this sense, interaction of a calcium ion with water constitutes a somewhat lesser challenge. Since this interaction is predominantly governed by electrostatic and, to a lesser extent, by induction contributions, suboptimal description of the van der Waals term is less critical than in cation- π complexes. This example raises also the question as to whether simple point charge models will ever be satisfactory or if higher atomic multipoles ought to be included as well. It still remains that de novo parametrization of the Lennard-Jones potential is the key to an improved agreement with the quantum-mechanical binding energies. Either for cation- π interactions or association of a divalent cation with a donor ligand, the very encouraging results reported here underline the strength of ab initio polarizable force fields for handling accurately induction phenomena. The strategy developed represents a significant step forward in the race for modeling explicitly polarization effects in molecular systems, opening exciting new vistas for numerical simulations of condensed phases.

Acknowledgment. Georg Jansen is gratefully acknowledged for stimulating discussions. The authors thank Krzysztof Szalewicz for supplying the SAPT code. They are indebted to the Crvhp, Vandœuvre-les-Nancy, France, and to the Centre de Supercomputació de Catalunya (CESCA) Barcelona, Spain, for provision of generous amounts of

computational time. This work was supported by the IngeMol project of the Agence National pour la Recherche, by a joint CNRS/UIUC collaborative grant, and by the Spanish Ministerio de Educación y Ciencia (grant CTQ2005-08797-C02-01/BQU). K.S. is supported by the Humboldt Foundation.

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CT700156A