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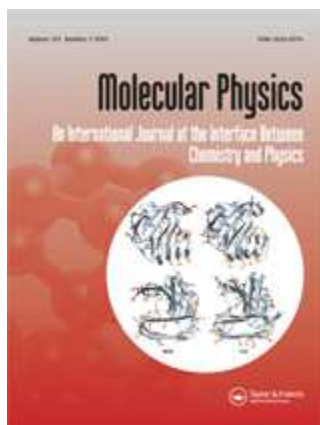
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An ab initio strategy for handling induction phenomena in metal ion complexes

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A strategy that incorporates in the macromolecular, non-polarizable CHARMM force field models of atomic charges and polarizabilities determined from high-level quantum mechanical calculations is probed in the paradigmatic case of metal ion complexes. Although the ab initio polarizable potential energy function is capable of hierarchizing correctly the affinity of a divalent calcium ion for three distinct electron-donor chelating agents, severe inaccuracies in the underlying contributions to the total binding energy, compared to a reference symmetry-adapted perturbation theory (SAPT) expansion, illuminate the incompleteness of the interaction model. The reported calculations suggest that mapping faithfully the signature electrostatic potential and induction energy of the isolated species is a necessary, albeit not sufficient condition to guarantee that intermolecular interactions be described accurately when key physical phenomena are evidently missing from a force field to which explicit induction effects have been introduced. They further suggest that in the present strategy, naive attempts to correct the flawed reproduction of the electrostatic and induction terms of the perturbative expansion — rooted, for instance, in an inappropriate representation of electron-cloud penetration — through *de novo* parametrization of the mathematically questionable “6-12” form of the van der Waals potential, common to many macromolecular force fields, are unavoidably bound to failure.

1. Introduction

Over the past years, the development of polarizable potential energy functions targeted at numerical simulations of molecular systems has focused tremendous effort. As access to massively parallel computer architectures opened new perspectives for the investigation of larger assemblies of atoms over time scales compatible with the experimentally observed phenomena, it was also realized that more elaborate force fields were needed for an accurate description of intermolecular interactions. Although nonpolarizable macromolecular potential energy functions, *e.g.* AMBER [1], CHARMM [2], GROMOS [3], or OPLS-AA [4], have proven to behave reasonably well for biologically relevant molecular systems in which through-space polarization effects can be accounted for in an average sense, the pairwise additive approximation remains an intrinsic limitation for the study of biophysical processes where the induction effects at play cannot be neglected without proper justification. Among these processes, ions permeating a membrane channel have been shown to perturb the charge distribution of those residues lining the pore through which they diffuse, thereby modulating the interplay of the permeant and its surroundings. Similarly, ions embedded in metalloproteins polarize their environment, altering accordingly the charge distribution of the chelating agents [5], which suggests that induction effects may have a pronounced influence on the binding hierarchy of these ions.

A pioneering strategy devised for modeling explicitly through-space induction effects in numerical simulations consists in parameterizing the induction forces in terms of atomic quantities [6]. From a conceptual perspective, this solution assumes that the electron density response can be partitioned into regions of the Cartesian space corresponding to atoms. It further assumes a truncation of the multipole expansion and a selection of leading terms in the classical expression of the forces exerted between atomic distributions. Much effort has been invested in the task of partitioning the electron density response into distributed polarizabilities [7–13]. Transformation of cumbersome, large ensembles of components into finite sets of physically sound, optimally partitioned electric properties [14] (OPEP) constitutes a promising alternative to conventional distributed polarizability analysis. In a nutshell, the strategy embodied in OPEP relies upon a least-squares fit of atomic polarizabilities to the reference quantum-mechanical induction energy mapped around the molecule. Combining isotropic dipole polarizabilities with a zeroth-order charge-flow term between vicinal atoms [15], the anisotropy of induction effects can be essentially recovered, thereby obviating the requirement of an explicit inclusion of anisotropic contributions [16].

An ideal route for the design of polarizable force fields would consist in plugging directly into an existing pairwise additive potential energy function the polarizability parameters determined quantum mechanically. A number of obstacles preclude, however, the direct application of this strategy. First, the electrostatic term of nonpolarizable force fields markedly exaggerates the polarity of the constituent molecules, thereby compensating in an average sense for missing induction effects. In the context of an explicit treatment of polarization phenomena, atomic charges ought to be either scaled down [17], or consistently optimized to be representative of the true gas phase [18]. Furthermore, polarizability parameters are expected to depend inherently on the nature of the environment and, hence, should be adapted accordingly [19]. Here, description of both electrostatic and polarization terms of the potential energy function is consistent with a low-pressure gaseous state. In principle, these contributions should be tailored to reflect the characteristics of the surroundings.

Perhaps most critically, potential energy functions are very complex constructs, the building blocks of which are intimately related. Minute modifications of their parameters can perturb significantly the delicate, almost precarious balance between the different contributions. In addition to the scaling, or the novel derivation of atomic charges, van der Waals parameters ought to be crafted accordingly to mirror the gas phase electrostatics and the explicit inclusion of induction effects. Comparing the relative performances of potential energy functions to which polarizability parameters have been incorporated, yet without appropriate adjustment of the other terms, would obviously be unfair to the original pairwise additive force field. Besides, it should be acknowledged that macromolecular, multi-purpose potential energy functions have not been designed for gas phase calculations.

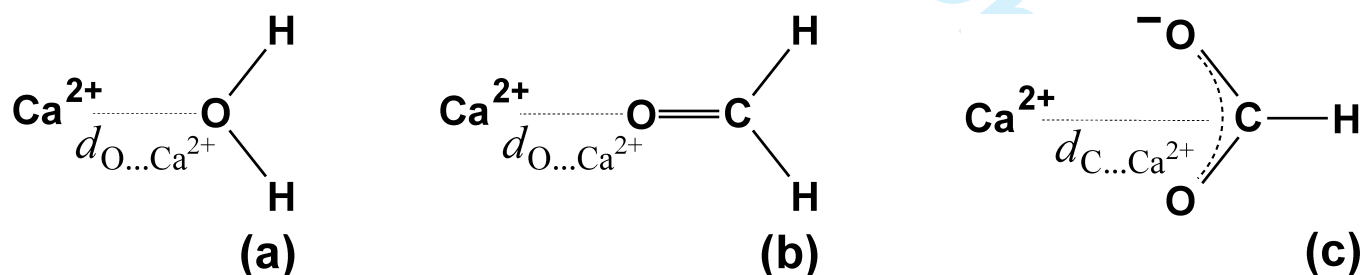


Figure 1: Interaction of a divalent calcium ion with (a) water, (b) formaldehyde, and (c) a formate ion. Approach of the cation towards the three ligands is considered along the \mathcal{C}_2 axis of the latter.

To illustrate the critical role played by polarization phenomena in intermolecular interactions, the complexes formed by a calcium ion and three possible electron-donor chelating agents, namely water, formaldehyde and formate, will be considered (see Figure 1). These test cases represent a paradigm for reproducing

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accurately the hierarchy of binding affinities in less rudimentary, possibly biologically relevant molecular systems — *e.g.* metalloproteins, in which a misdescription of the non-covalent interactions involving the ion may be liable for altering irreversibly the three-dimensional structure of the catalytic site and, hence, its function.

In the following section, the theoretical background is outlined, together with the computational details for the determination of atomic charges and polarizabilities. Relying on the functional utilized in macromolecular force fields like CHARMM [2], *de novo* parametrization of the Lennard-Jones potential is carried out based on symmetry-adapted perturbation theory [20,21] (SAPT) calculations, from which the exact individual contributions to the interaction energy can be readily inferred. Performance of the resulting *ab initio* polarizable force field are subsequently appraised in terms of reproducing the target quantum mechanical interaction energies for the three ionic complexes. Last, concluding remarks are drawn, highlighting the advantages and shortcomings of the proposed parametrization scheme.

2. Methods

2.1. Theoretical background

Interaction energies, $\Delta\mathcal{U}_{\text{tot}}^{\text{MM}}$, determined from classical polarizable force fields can be expressed as a sum of individual contributions:

$$\Delta\mathcal{U}_{\text{tot}}^{\text{MM}} = \Delta\mathcal{U}_{\text{ele}} + \Delta\mathcal{U}_{\text{ind}} + \Delta\mathcal{U}_{\text{damp}} + \Delta\mathcal{U}_{\text{vdW}} \quad (1)$$

where $\Delta\mathcal{U}_{\text{ele}}$, $\Delta\mathcal{U}_{\text{ind}}$, $\Delta\mathcal{U}_{\text{damp}}$ and $\Delta\mathcal{U}_{\text{vdW}}$ stand for the electrostatic, the induction, the damping and the van der Waals energy terms, respectively. SAPT calculations provide a rigorous partitioning of the total interaction energy, $\Delta\mathcal{U}_{\text{tot}}^{\text{SAPT}}$ into physically meaningful components:

$$\Delta\mathcal{U}_{\text{tot}}^{\text{SAPT}} = \Delta\mathcal{U}_{\text{ele}} + \Delta\mathcal{U}_{\text{ind}} + \Delta\mathcal{U}_{\text{exch}} + \Delta\mathcal{U}_{\text{disp}} + \Delta\mathcal{U}_{\text{exch-ind}} + \Delta\mathcal{U}_{\text{exch-disp}} + \delta\text{HF} \quad (2)$$

Here, $\Delta\mathcal{U}_{\text{exch}}$, $\Delta\mathcal{U}_{\text{disp}}$, $\Delta\mathcal{U}_{\text{exch-ind}}$ and $\Delta\mathcal{U}_{\text{exch-disp}}$ denote the exchange, dispersion, exchange-induction and exchange-dispersion contributions to the interaction energy. δHF embraces induction and exchange-induction higher order terms of the perturbative expansion.

Armed with accurate models of net atomic charges and implicitly interacting distributed polarizabilities [16], the strategy pursued in the present work consists in optimizing the van der Waals part of the classical potential energy function in the light of SAPT calculations [22]. This parametrization scheme implies a number of underlying assumptions requiring particular attention, chief among which the ability of a simplistic Coulomb sum truncated at the monopole level to reproduce faithfully the quantum-mechanical electrostatic contribution $\Delta\mathcal{U}_{\text{ele}}$. Brute incorporation of induction phenomena in molecular mechanical force fields raises additional concerns due to the physically unrealistic forces that can thrust the polarizing charge towards the polarizable center. In principle, the classical and the quantum-mechanical polarization terms are comparable, provided that spatial mapping of the induction energy by the model of atomic polarizabilities has the required precision. The SAPT expansion involves, however, additional contributions that ought to be incorporated in the classical description of $\Delta\mathcal{U}_{\text{tot}}$. Such is the case of the exchange-induction term, $\Delta\mathcal{U}_{\text{exch-ind}}$, which is usually modeled by damping the interaction of the electric field with the polarizable sites, using a surrogate empirical function, $\Delta\mathcal{U}_{\text{damp}}$. Whereas the latter contribution does not compare directly with its SAPT exchange-induction counterpart, it can 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 [22].

Dissecting the classical van der Waals interaction, $\Delta\mathcal{U}_{\text{vdW}}$, into meaningful contributions is unfortunately less straightforward. The questionable form of the Lennard-Jones potential utilized in a variety of macromolecular force fields like AMBER [1], CHARMM [2], GROMOS [3], or OPLS-AA [4], precludes any physical interpretation in terms of true repulsion and dispersion energies. In practice, Lennard-Jones potentials encompass contributions that cannot be captured in either the electrostatic or the polarization terms of the classical description, thus, going beyond the components that can be recovered rigorously from an SAPT expansion — *viz.* the exact dispersion, $\Delta\mathcal{U}_{\text{disp}}$, exchange, $\Delta\mathcal{U}_{\text{exch}}$, and exchange-dispersion, $\Delta\mathcal{U}_{\text{exch-disp}}$, contributions. Noteworthy, a number of classical approaches have been devised to represent the latter sum of contributions, going beyond a mere Lennard-Jones term, among which the SIBFA [23], the ORIENT [24] and the EFP [25] potential. Classical equivalence of the SAPT δHF term is even less obvious, as most of the contributions embraced in the latter do not necessarily appear in the parametrization

of the classical polarizability models. For instance, hyper-polarizability effects are generally neglected by computing the target quantum-mechanical induction energy sufficiently far from the nuclei.

2.2. Computational details

Models of net atomic charges were derived using OPEP [14] from the electrostatic potential computed quantum mechanically at the MP2/6-311++G(*d*, *p*) level of approximation, including inner-shell orbitals [26,27] (see Table I). The grids over which the electrostatic potential created by water, formaldehyde and formate was mapped contained 2,106, 3,079 and 3,056 points, respectively. Models of implicitly interacting distributed polarizabilities were also derived with OPEP, based on maps of induction energies generated using a finite-perturbation approach [28] and the formalism of topologically partitioned electric properties (TPEP) [10,12]. The induction-energy maps of water, formaldehyde and formate were obtained using grids of 3,905, 19,152 and 19,099 points, respectively, at the MP2 level of theory with the Sadlej basis set [29], which has proven to be well suited for the determination of polarizability parameters [28]. The calcium cation was assumed to be nonpolarizable. For all chelating agents considered in this work, preliminary optimization of the molecular geometries was performed at the MP2/6-311++G(2*d*, 2*p*) level, employing the Gaussian98 suite of programs [30].

The inherent anisotropy of induction phenomena can be recovered without the explicit incorporation of anisotropic dipole components in the distributed polarizability models. As can be seen in Table II, zero-order charge-flow polarizabilities and first-order isotropic dipole polarizabilities offer a reasonable compromise between accuracy and tractability.

Electrostatic and polarization models were associated to the CHARMM [2] macromolecular force field for the computation of the classical potential energy surfaces that delineate the interaction of the calcium ion with the three electron donors along their \mathcal{C}_2 axis. Cognizant of the imbalance entailed by the inclusion of induction phenomena in the potential energy function, *de novo* optimization of the constituent Lennard-Jones parameters was carried out using a Levenberg-Marquardt nonlinear fitting algorithm [31]. Assuming that (i) the pure electrostatic component of equation (2) and its classical counterpart coincide, and (ii) the damped induction contribution, *i.e.* $\Delta\mathcal{U}_{\text{ind}} + \Delta\mathcal{U}_{\text{damp}}$, reproduces appropriately the sum of the two SAPT terms, $\Delta\mathcal{U}_{\text{ind}} + \Delta\mathcal{U}_{\text{exch-ind}}$, the van der Waals component of $\Delta\mathcal{U}_{\text{tot}}^{\text{MM}}$ was determined in the form of a “6–

Table I: Models of distributed multipoles and regenerated molecular multipole moments of water, formaldehyde and formate at the MP2/6–311++G(d, p)/MP2/6–311++G(2*d*, 2*p*) level of approximation.

	distributed multipoles		molecular multipoles		MP2/6–311++G(d, p)
Water	Q_{00}^O	−0.782	Q_{10}	−0.869	−0.857
	Q_{00}^H	0.391	Q_{20}	−0.219	−0.274
	RMSD	1.029			
	$\Delta\varepsilon$	51.119			
Formaldehyde	Q_{00}^C	0.429	Q_{10}	−0.949	−0.946
	Q_{00}^H	−0.005	Q_{20}	−0.284	−0.488
	Q_{00}^O	−0.419	Q_{30}	−1.332	0.086
	RMSD	0.432			
	$\Delta\varepsilon$	7.568			
Formate	Q_{00}^C	0.864	Q_{20}	4.456	4.563
	Q_{00}^H	−0.210	Q_{40}	−17.507	−13.313
	Q_{00}^O	−0.827			
	RMSD	0.468			
	$\Delta\varepsilon$	0.283			

RMSD (in 10^{-3} a.u.) between the reference quantum-mechanical electrostatic potential mapped on a grid of points and that regenerated from the model of distributed multipoles; $\Delta\varepsilon$ (in percents) is the corresponding mean error

12'' potential, based on the remaining terms of the perturbative expansion. Last, for comparison purposes, the quantum-mechanical potential energy surface characterizing the three complexes was determined at the MP2/6-311++G(d, p) level of theory, varying the intermolecular distance by increments of 0.1 Å and evaluating the basis set superposition error (BSSE) [32] at each step.

3. Results and discussion

Metalloproteins represent approximately one third of all known proteins that serve catalytic, regulatory, or structural roles [33]. Yet, modeling of these entities remains a difficult undertaking due to the intrinsic non-

Table II: Models of distributed polarizabilities and regenerated molecular polarizabilities of water, formaldehyde and formate at the MP2/Sadlej//MP2/6–311++G(2d, 2p) level of approximation.

	distributed polarizabilities		molecular polarizabilities		MP2/Sadlej
Water	$\alpha_{00,00}^{\text{OH}}$	−0.808	$\alpha_{10,10}$	10.177	9.751
	$\alpha_{1\kappa,1\kappa'}^{\text{OO}}$	8.180	$\alpha_{11c,11c}$	11.483	10.063
			$\alpha_{11s,11s}$	8.180	9.542
	RMSD	0.127			
	$\Delta\varepsilon$	7.000			
Formaldehyde	$\alpha_{00,00}^{\text{CH}}$	−1.984	$\alpha_{10,10}$	27.934	22.419
	$\alpha_{00,00}^{\text{CO}}$	−2.070	$\alpha_{11c,11c}$	12.220	12.844
	$\alpha_{1\kappa,1\kappa'}^{\text{CC}}$	8.133	$\alpha_{11s,11s}$	24.680	17.966
	$\alpha_{1\kappa,1\kappa'}^{\text{OO}}$	4.087			
	RMSD	0.136			
	$\Delta\varepsilon$	14.228			
Formate	$\alpha_{00,00}^{\text{CH}}$	−2.201	$\alpha_{10,10}$	38.900	36.551
	$\alpha_{00,00}^{\text{CO}}$	−2.104	$\alpha_{1c,1c}$	24.732	24.684
	$\alpha_{1\kappa,1\kappa'}^{\text{CC}}$	10.459	$\alpha_{1c,1c}$	44.321	42.080
	$\alpha_{1\kappa,1\kappa'}^{\text{OO}}$	7.134			
	RMSD	0.265			
	$\Delta\varepsilon$	2.700			

RMSD (in 10^{-3} a.u.) between the reference quantum-mechanical induction energy mapped on a grid of points and that regenerated from the model of distributed polarizabilities; $\Delta\varepsilon$ (in percents) is the corresponding mean error

additive character of the metal-ligand interactions involved. Polarization and charge transfer are known, indeed, to represent significant contributions to the overall interaction energy [34,35]. Standard pairwise additive force fields used to investigate biological systems cannot, however, capture in any effective way the underlying physical complexity of these interactions. So far, common solutions imagined to address this problem consisted either in considering a bonded model of the active site — *i.e.* all metal-ligand interactions are treated as non-dissociable bonds, or to derive *ad hoc* electrostatic atomic charge models of the metal-ligand moieties [36]. Recently Dal Peraro *et al.* have introduced an elegant method to model metalloproteins [5]. Deriving point charges from the *Atoms in Molecules* theory of Bader [37] for differ-

ent proteins, they were able to preserve the integrity of the active site over multi-nanosecond molecular dynamics simulations in a condensed phase. This static approximation of both induction phenomena and charge transfer cannot, however, mimic with a proper accuracy processes involving a modification of the surroundings — *e.g.* insertion, substitution and permutation of a given ligand. Sophisticated potentials including an explicit treatment of these nonadditive interactions have been successfully derived for a variety of metalloproteins [38,34,39–42].

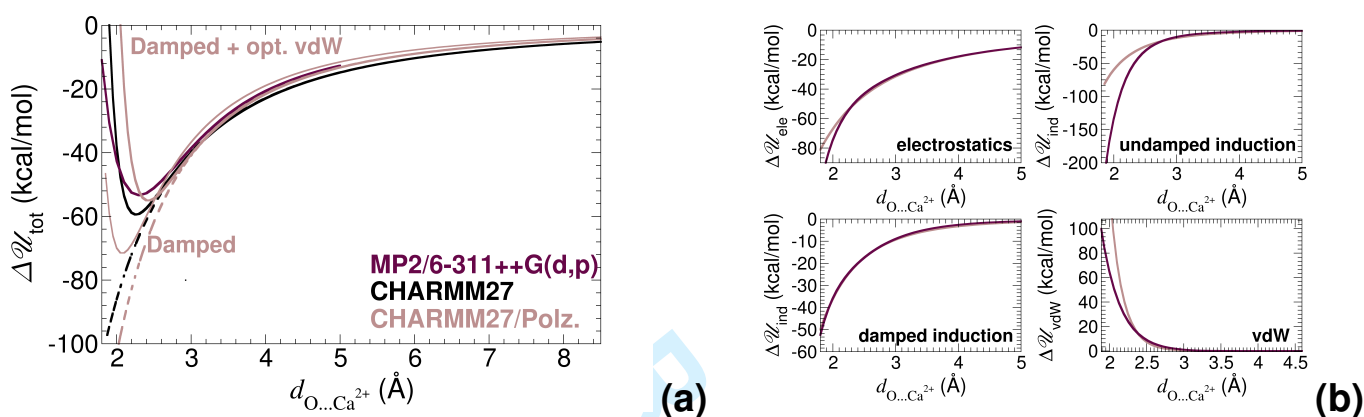


Figure 2: Interaction of a divalent calcium ion with water. (a) Comparison of the binding energies determined from BSSE-corrected MP2/6–311++G(*d*, *p*) calculations (dark solid line), the classical, nonpolarizable CHARMM force field (black lines), and the latter supplemented by a model of distributed 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. (b) Components of the interaction energy, determined from an SAPT expansion using the 6-311++G(*d*, *p*) basis set (dark solid line) and the polarizable potential energy function (light solid line). The undamped induction contribution corresponds to the pure induction term of equations (1) and (2). 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.

Here, a similar route is followed, attempting to plug simple, yet accurate polarizable models into a CHARMM-like potential energy function. The chosen prototypical interactions of a calcium cation with different chelating agents — *viz.* water, formaldehyde and formate are commonly found at the active site of calcium metalloproteins, where water or amino acids like aspartate or glutamate form recurrent motifs in the first coordination shell of the cation [43]. The main focus of the present work is on the ability of the various models to reproduce correctly the hierarchy of interaction energies for a calcium ion and a number of its usual partners at the catalytic site of a metalloprotein. The performance of the derived ab

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initio polarizable force field is further assessed through a comparison of the individual energy contributions with an SAPT expansion of the overall interaction energy.

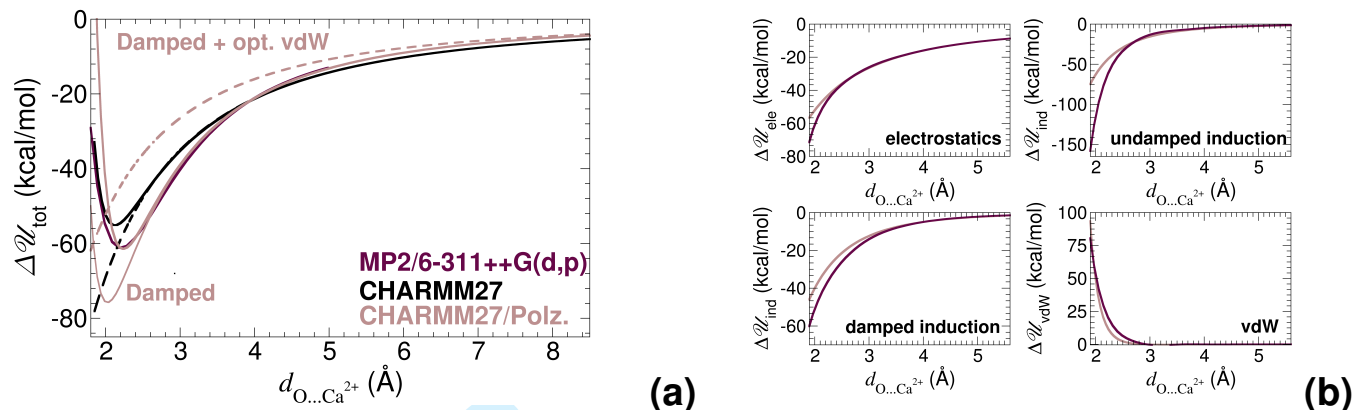


Figure 3: Interaction of a divalent calcium ion with formaldehyde. (a) Comparison of the binding energies determined from BSSE-corrected MP2/6–311++G(*d, p*) calculations (dark solid line), the classical, nonpolarizable CHARMM force field (black lines), and the latter supplemented by a model of distributed 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. (b) Components of the interaction energy, determined from an SAPT expansion using the 6-311++G(*d, p*) basis set (dark solid line) and the polarizable potential energy function (light solid line). The undamped induction contribution corresponds to the pure induction term of equations (1) and (2). 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 potential energy surfaces delineating the interaction of a calcium ion with water, formaldehyde and formate are reported in Figures 2, 3 and 4. Not too surprisingly, the additive pairwise TIP3P model used to describe water overestimates the interaction energy by *ca.* 6 kcal/mol, compared to the reference gas phase MP2/6-311++G(*d, p*) calculation. This discrepancy is rooted in the TIP3P atomic charges, which are artificially inflated to account for the average polarization of a water molecule in the bulk. Direct comparison against the original pairwise additive potential energy function is somewhat unfair, as the latter was obviously not designed for numerical simulations in the gas phase. The immediate environment of a water molecule associated to a cation in the active site of a metalloprotein differs substantially from that of the bulk liquid, which is expected to be mirrored in different polarization states.

In contrast, the CHARMM additive pairwise potential underestimates by 6.1 kcal/mol the quantum-

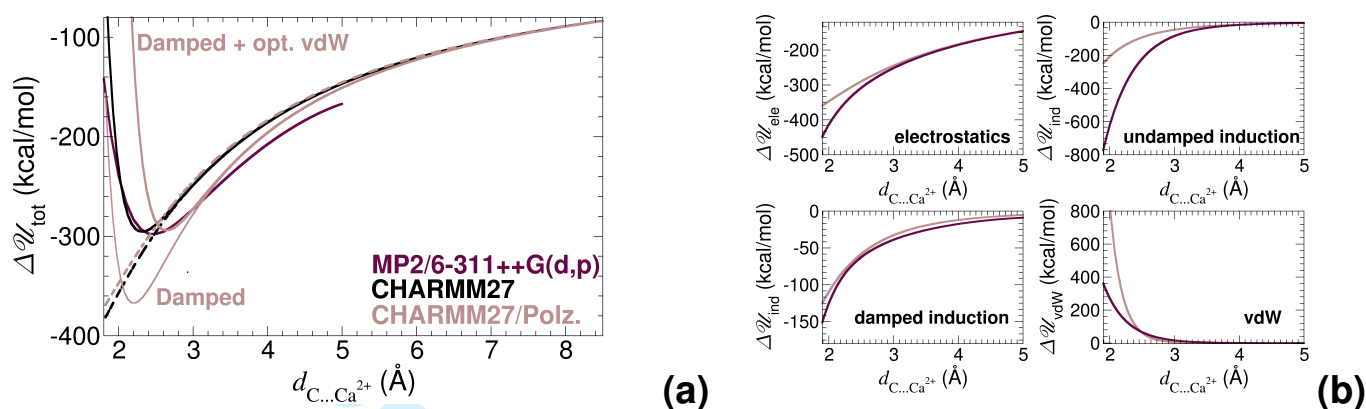


Figure 4: Interaction of a divalent calcium ion with a formate ion. (a) Comparison of the binding energies determined from BSSE-corrected MP2/6–311++G(d, p) calculations (dark solid line), the classical, nonpolarizable CHARMM force field (black lines), and the latter supplemented by a model of distributed 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. (b) Components of the interaction energy, determined from an SAPT expansion using the 6-311++G(d, p) basis set (dark solid line) and the polarizable potential energy function (light solid line). The undamped induction contribution corresponds to the pure induction term of equations (1) and (2). 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. Additional approaches of the divalent calcium toward the chelating agent, along a C—O bond and in the direction perpendicular to the plane of the negatively charged ion, are reported in the supplementary material.

mechanical gas phase interaction energy characterizing the binding of a calcium ion by formaldehyde. In the case of formate, CHARMM performs quite nicely and predicts a binding energy minimum close to the MP2/6-31++G(d, p) reference, albeit slightly shifted towards shorter separations. The MP2 interaction energy estimated for the calcium-formaldehyde complex is about 7.8 kcal/mol lower than the value computed for the calcium–water pair, as highlighted in Table III. On the contrary, the classical, nonpolarizable force field favored the binding of the water to the calcium cation by about 2–3 kcal/mol. As a consequence, the CHARMM model allows carbonyl groups to exchange freely with water, when, in reality, quantum mechanics indicates that this process is highly improbable. It is, therefore, becoming quite clear that CHARMM would hardly preserve the integrity of a catalytic site involving a calcium ion interacting concomitantly with an aspartate or a glutamate residue and water.

The ab initio polarizable potential energy function that utilizes the standard Lennard-Jones parameters

Table III: Comparison of the contributions to the binding energies^a of the complexes formed by Ca²⁺ with water, formaldehyde and formate, determined from an MP2/6-311++G(*d, p*) SAPT expansion and a polarizable potential energy function.

	$\Delta \mathcal{U}_{\text{ele}}$		$\Delta \mathcal{U}_{\text{ind}}^b$		$\Delta \mathcal{U}_{\text{vdW}}^c$			$\Delta \mathcal{U}_{\text{tot}}$		
	SAPT	MM	SAPT	MM	SAPT	MM	δHF^d	MP2 ^e	SAPT	MM ^f
Ca ²⁺ ... H ₂ O	-51.7	-51.8	-22.1	-23.0	19.8	22.7 (3.6)	-0.8	-53.4	-54.7	-52.2 (-64.6)
Ca ²⁺ ... H ₂ CO	-48.4	-45.1	-37.5	-31.3	24.2	15.3 (4.8)	-1.6	-61.2	-63.3	-61.1 (-71.6)
Ca ²⁺ ... HCOO ⁻	-308.7	-290.0	-62.2	-58.3	65.8	62.8 (1.4)	-0.5	-297.8	-305.6	-285.6 (-301.6)

^a All quantities are expressed in kcal/mol, with respect to the quantum-mechanical energy minima of Table IV. ^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 CHARMM 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 CHARMM force field.

of the CHARMM force field glaringly exaggerates the binding energy for all three ion metal complexes — *e.g.* by up to 11.2 kcal/mol in the case of the water-calcium dimer (see Figure 2 and Table III). 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 parameterized chemical moieties with an aqueous environment. Alteration of the electrostatic contribution of the nonpolarizable force field creates an imbalance in the construct, which ought to be corrected by *de novo* optimization of its Lennard-Jones parameters. This rationalizes the disagreement between the profiles of Figures 2, 3 and 4 computed at the MP2/6-311++G(*d, p*) level of approximation and using the CHARMM force field supplemented by atomic polarizabilities.

Design of a new set of Lennard-Jones parameters based on the SAPT expansion yields binding energy profiles in qualitative agreement with the quantum-mechanical references. As can be seen in Table III, the binding energy estimated for the water-calcium ion complex from the ab initio polarizable force field — *viz.* -52.2 kcal/mol, compares nicely with the quantum-mechanical energy minima of Table IV —

viz. -53.4 kcal/mol. An equally remarkable agreement is obtained when the calcium ion is bound to formaldehyde. In the case of the strongest interaction featuring formate, the observed deviation of less than 5% remains satisfactory. It is also noteworthy that the SAPT binding energies overshoot the MP2/6-311++G(d, p) estimates by up to 7.8 kcal/mol in the particular instance of the formate–calcium ion complex. This deviation might be ascribed to the frozen core approximation used in MP2 calculations. The repulsive part of the total binding energy curves computed at the molecular-mechanical level is, however, largely overestimated in view of the quantum-mechanical target. A closer look at the components of the interaction energy in Figures 2, 3 and 4 and in Table III illuminates the origin of this discrepancy.

Table IV: Intermolecular separations^a in the complexes formed by Ca^{2+} with water, formaldehyde and formate, determined from MP2/6–311++G(d, p) potential energy surfaces, the classical CHARMM force field and the ab initio polarizable force field.

	$d_{X\dots Y}$		
	QM	CHARMM	CHARMM + polz.
$\text{Ca}^{2+} \cdots \text{H}_2\text{O}$	2.3	2.3	2.4
$\text{Ca}^{2+} \cdots \text{H}_2\text{CO}$	2.2	2.1	2.2
$\text{Ca}^{2+} \cdots \text{HCOO}^-$	2.5	2.3	2.6

^a All quantities are expressed in Å.

The electrostatic contributions estimated from an SAPT expansion and from a model of simple atomic charges coincide both at the equilibrium geometry and at longer separation distances for all three metal ion complexes. At the quantum-mechanical minimum of the binding energy reported in Table IV, the predicted molecular-mechanical electrostatic energy of -51.8 kcal/mol matches perfectly the SAPT value of -51.7 kcal/mol for the water–calcium ion dimer. In contrast, a deviation of less than 7 % is observed between the contributions from the polarizable models and the SAPT reference for formaldehyde and formate (see Table III). At shorter intermolecular separations, the agreement deteriorates, the SAPT electrostatic contributions becoming more attractive than the classical model as the intermolecular distance decreases. This deviation is believed to be rooted in charge penetration effects that a classical formulation of the charge interactions clearly cannot capture [44,45] without an appropriate treatment. These effects arise when two interacting chemical moieties are brought at a close enough distance, such that their respective charge den-

sities overlap. The nuclei on one molecule are no longer shielded by the electron density, and, hence, is expected to undergo a greater attraction for the electron density of the other compound. One possible road to account for electron-cloud penetration effects consists in introducing an appropriate correction function into the classical formulation of the interaction of two or more multipole expansions [46,47].

Considering the polarization term of the interaction energy in Figures 2, 3 and 4, the *pure* induction contribution, $\Delta\mathcal{U}_{\text{ind}}$, to the SAPT expansion is considerably stronger than the value derived from distributed polarizability models. At the equilibrium geometry, $\Delta\mathcal{U}_{\text{ind}}$ inferred from the SAPT expansion is almost an order of magnitude larger than the classical estimate, and even larger at shorter distances. As has been shown previously [48], $\Delta\mathcal{U}_{\text{ind}}$ in SAPT calculations is excessively large on account of Coulomb singularities in the interaction operator. This shortcoming has already been highlighted by Claverie in related perturbational approaches [49]. These singularities also yield very large positive estimates of the exchange-induction term, $\Delta\mathcal{U}_{\text{exch-ind}}$. Assignment of a physical meaning to these individual contributions, therefore, constitutes a daunting task. As put forth by Misquitta and Stone [50], the vocabulary *SAPT induction energy* denotes the sum of the two contributions, $\Delta\mathcal{U}_{\text{ind}}$ and $\Delta\mathcal{U}_{\text{exch-ind}}$. For polar molecules, nonlinear or many-body, induction and exchange-induction contributions are often large and cannot be neglected. These third- and higher-order induction and exchange-induction terms are referred to as δHF in the SAPT expansion. They do not appear explicitly in the molecular-mechanical derivation of the interaction energy. Misquitta and Stone [50] have, however, shown that the higher-order energies could be partially recovered through an appropriate damping function associated to a polarizable model. Admittedly, the damping function adopted in this work [51,52] has not been designed to account for these higher-order effects. It may be contended, however, that a comparison of the induction energies computed from the damped classical polarizable model with the total induction of the SAPT calculation supplemented by δHF is legitimate.

As can be observed in Figure 2 and Table III, an almost perfect agreement for the water-calcium ion complex at any separation distances is attained. In the case of formaldehyde depicted in Figure 3, the induction energy computed from the ab initio polarizable force field departs from the reference SAPT expansion for distances shorter than 3.6 Å. This discrepancy probably stems from the limited ability of the distributed polarizability model to reproduce correctly the molecular polarizability tensor. Moreover, the damping function developed by Jensen *et al.* [51] has been derived from a series of molecules only remotely related to the formaldehyde-calcium ion complex, thereby suggesting the need to design a better appropriate damping function, or, at the very least, an improved parametrization thereof. In the challenging

example of formate associated to the calcium ion shown in Figure 4, the induction energy obtained from the damped polarizable model matches satisfactorily the estimate of the SAPT calculation. Yet, the classical curve is slightly shifted, compared to the SAPT profile. As can be seen in Table III, this discrepancy on the order of a few kcal/mol is in line with the 9.2 kcal/mol deviation observed between the total energy of interaction computed at the SAPT and at the MP2/6-311++G(*d,p*) level. It is also noteworthy that in this study the calcium ion has been considered non-polarizable. However weak, the polarizability of the cation should be included if an extremely precise interaction energy is sought.

The van der Waals contribution is expressed in the SAPT expansion as the sum of exchange, dispersion, and exchange-dispersion terms whereas it is described by means of a Lennard-Jones potential in the present ab initio polarizable force field. For metal ion complexes, brute-force comparison of the two descriptions delineated in see Figures 2, 3 and 4 reveals that the ab initio polarizable force field strongly exaggerates the repulsive part of the SAPT reference curve. This illustrates the incapacity of a rudimentary “6-12” potential to reproduce simultaneously the repulsive and the attractive contributions to the SAPT van der Waals energy, thus, calling for the development of alternate mathematical forms of this potential. Such a strategy has been successfully endeavored by Piquemal *et al.* in the case of divalent cations interacting with the sophisticated polarizable AMOEBA water model [53]. The use of the function devised by Halgren [54] to represent the van der Waals interactions, together with an *ad hoc* parametrization of the Thole damping function [55] proved to reproduce accurately the overall interaction energy in these metal ion complexes.

4. Conclusion

In the present contribution, an ab initio strategy based on accurate quantum mechanical calculations is introduced for handling induction phenomena in metal ion complexes. The proposed polarizable force field combines potential derived net atomic charges with atom-centered charge-flow plus isotropic dipole polarizabilities determined numerically from induction energy maps. Investigation of the complexes formed by a calcium ion and three different electron-donor chelating agents, *viz.* water, formaldehyde and formate, suggests, however, that concomitant reproduction of the electrostatic potential and the polarization energy of the isolated chemical species, does not guarantee an accurate description of intermolecular interactions upon association. The results reported here emphasize that *electrostatic and induction models* ought to

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be distinguished from *interaction models*. Precise description of the target electric properties embodied in low standard deviations with respect to the reference observables for the isolated species does not necessarily imply that the classical electrostatic and induction contributions to the interaction energy match their quantum-mechanical counterparts inferred from an SAPT expansion. As exemplified here, the naive choice of turning to a functional common to many non-polarizable macromolecular force fields, with minimal alteration of the latter for the sake of adaptability, suffers from severe shortcomings, as physically meaningful terms are missing in the proposed description where induction effects are introduced explicitly. Chief amongst these missing contributions are the short-range penetration of electron clouds, anticipated to counterbalance the repulsive behavior witnessed at small distances separating the ion from the chelating agent — *e.g.* formate probably constitutes the most striking illustration of this shortcoming. Not too surprisingly, penetration effects are also present in the induction term. Mathematical surrogate functions aimed at damping the interaction of the electric field with the participating polarizable sites generally prove to be suboptimal at short separations — *i.e.* where the consequences of electron-cloud penetration are expected to be pronounced. Furthermore, *ad hoc* damping functions are seldom designed to account for higher-order induction and exchange-induction contributions, which are embraced in the so-called δHF term of the perturbative expansion. It still remains that, however perfectible, damping functions represent a reasonable compromise to recover physically meaningful induction component of the classical interaction energy. Most importantly, the form of the energy profile that encompasses the SAPT exchange, dispersion and exchange-dispersion contributions cannot be modeled in a satisfactory fashion by means of the mathematically questionable “6-12” form of a simplistic Lennard-Jones potential. If the attractive part of the curve is favored in the course of the nonlinear fitting procedure, its repulsive part will then inevitably be poorly described, and *vice versa*. By and large, a strategy that consists in assigning to the van der Waals term of the macromolecular force field the challenging role of compensating the flaws of all other individual contributions has necessarily stringent limitations. The ability of the proposed strategy to hierarchize correctly at the minimum of the interaction energy the binding affinity of a divalent calcium ion towards three distinct electron donors, nevertheless, provides very encouraging results, underlining the strength of *ab initio* polarizable energy functions for handling accurately induction phenomena. The shortcomings brought to light in the course of this investigation provide new guidelines for the improvement of the interaction models, paving the way for the development of increasingly accurate polarizable force fields and opening new vistas for the realistic description of the catalytic site of metalloproteins with the guarantee to preserve its structure over long time scales.

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Supplementary Material:

An ab initio strategy for handling induction phenomena in metal ion complexes

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Anisotropy of the interaction

To illustrate the ability of the proposed strategy to model the anisotropy of the interaction, binding of the divalent calcium cation to the formate ion was investigated, considering the two additional approaches depicted in Figure 1. Ion pairing was examined as a function of the distance separating Ca^{2+} from the central carbon atom of the anion (i) following a monodentate chelation pattern, and, (ii) in the direction orthogonal to the plane of the latter.



Figure 1: Interaction of a divalent calcium cation with a formate anion. Approach of the former towards the latter is considered **(a)** following a monodentate chelation motif, and **(b)** along the axis perpendicular to the plane of the anion.

The individual contributions to the overall interaction energy obtained from a symmetry-adapted perturbation theory (SAPT) expansion and from the proposed ab initio polarizable force field are compared in Figure 2. As had been observed previously when binding proceeds along the \mathcal{C}_2 axis of the anion, the classical and the reference, quantum-mechanical calculations agree reasonably well for the two additional arrangements, thereby emphasizing the ability of the polarizable potential to model with an appreciable accuracy the anisotropy of the interaction reflected in the computed binding energies.

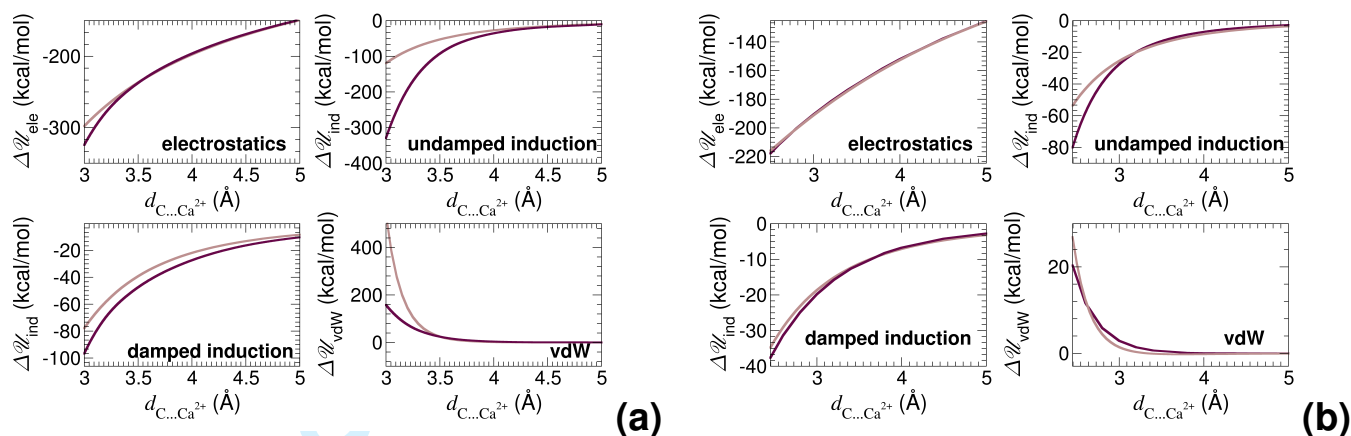
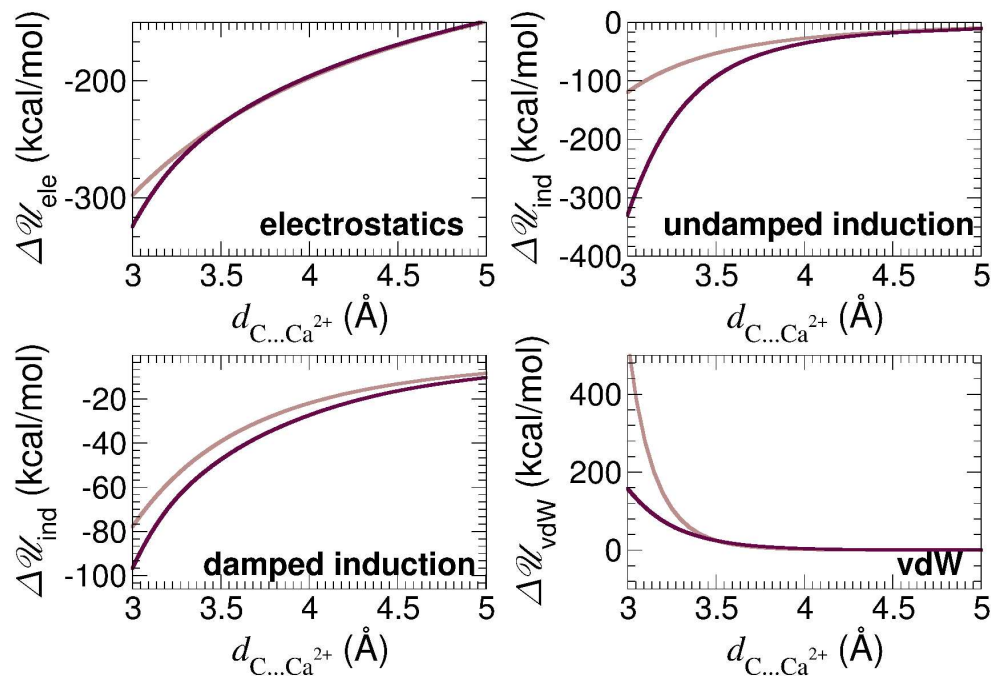
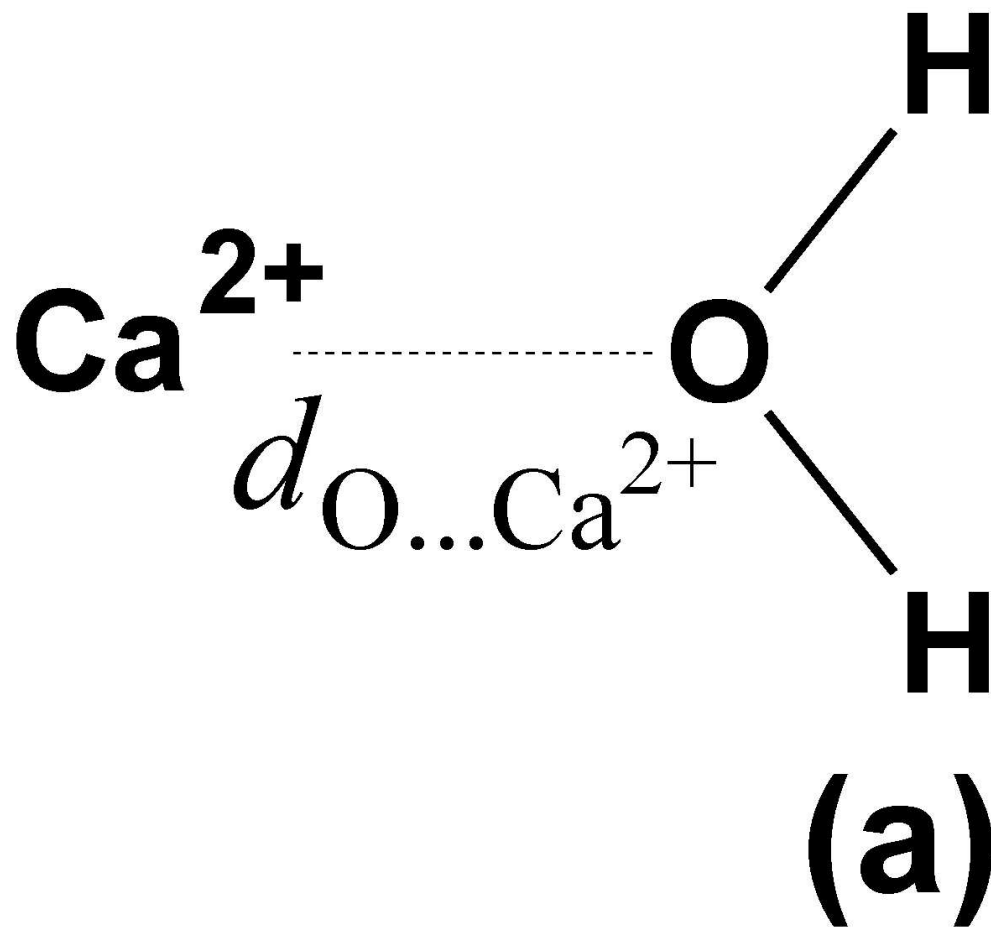


Figure 2: Interaction of a divalent calcium ion with a formate ion **(a)** following a monodentate chelation motif and **(b)** along the direction perpendicular to the plane of the anion. Components of the interaction energy determined from an SAPT expansion using the 6-311++G(*d*, *p*) basis set (dark solid line) and the polarizable potential energy function (light solid line). The undamped induction contribution corresponds to the pure induction term of equations (1) and (2). 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 embraces 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.

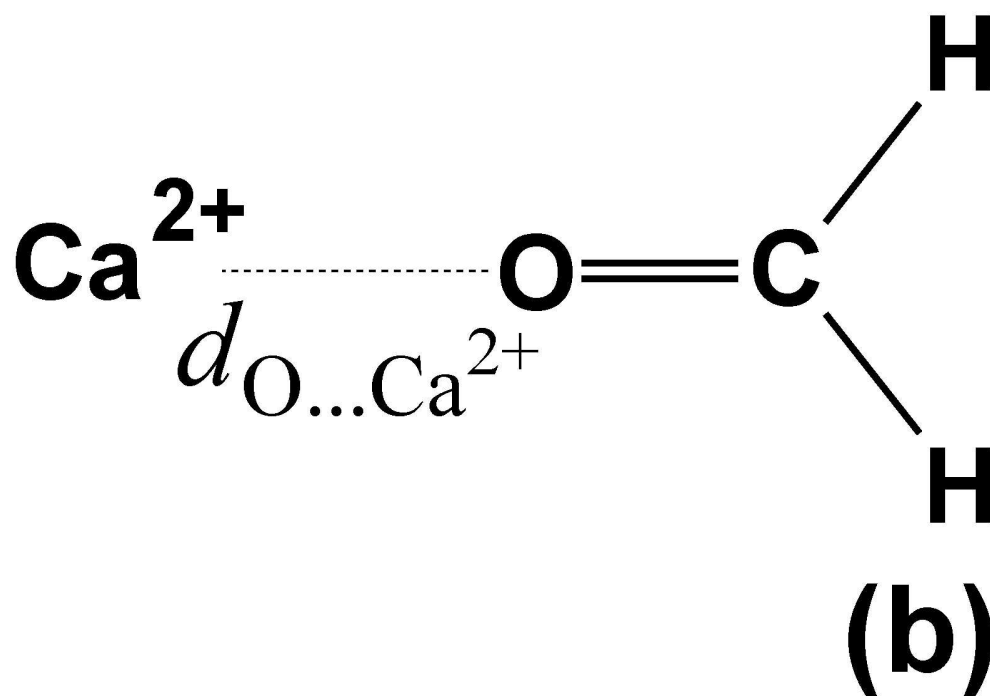




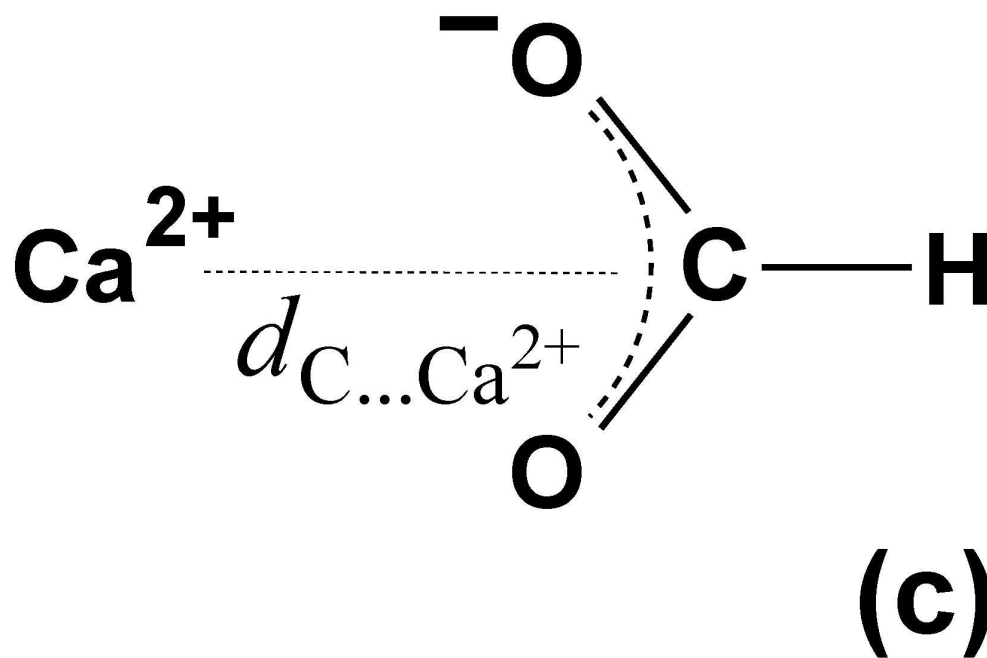
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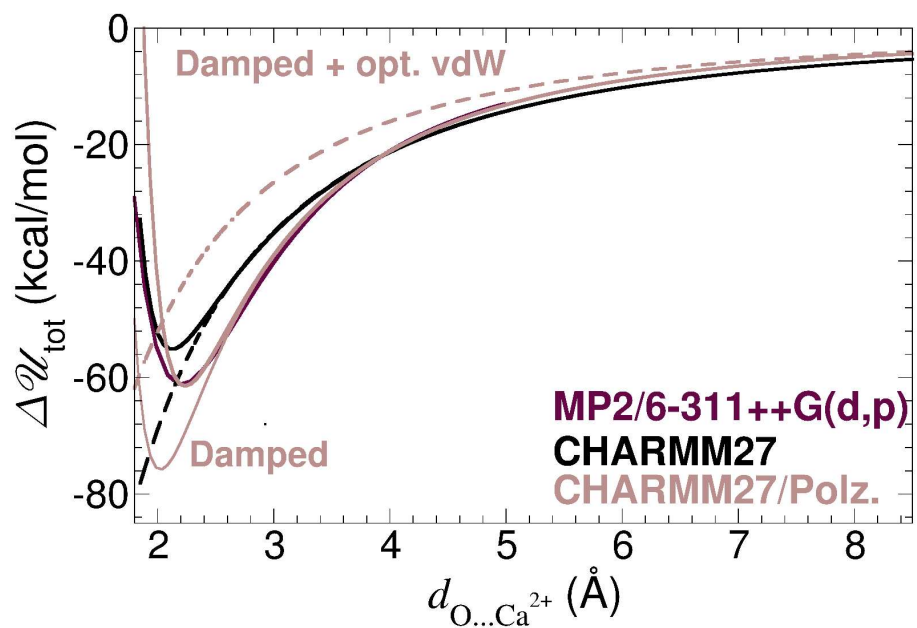
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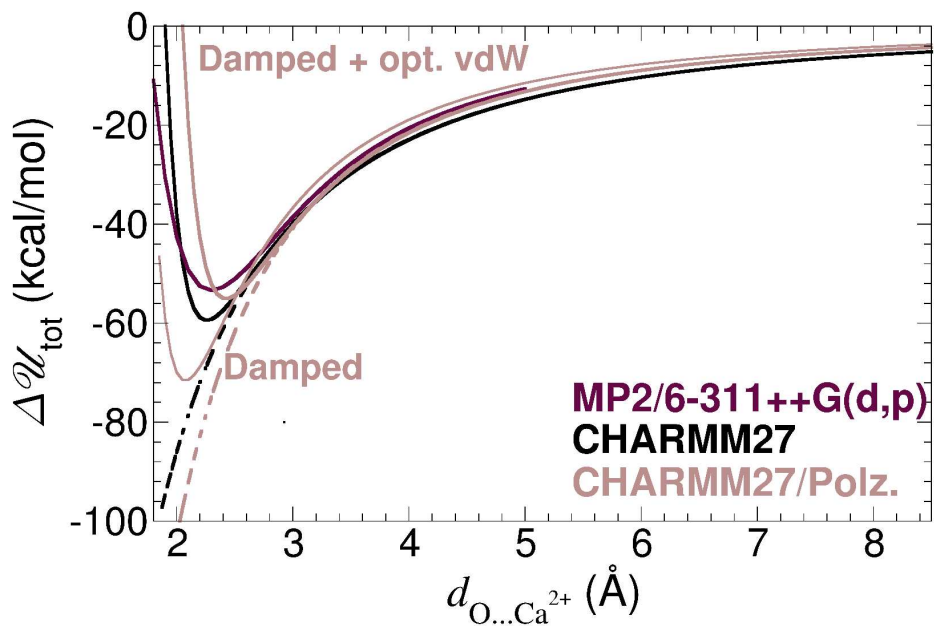


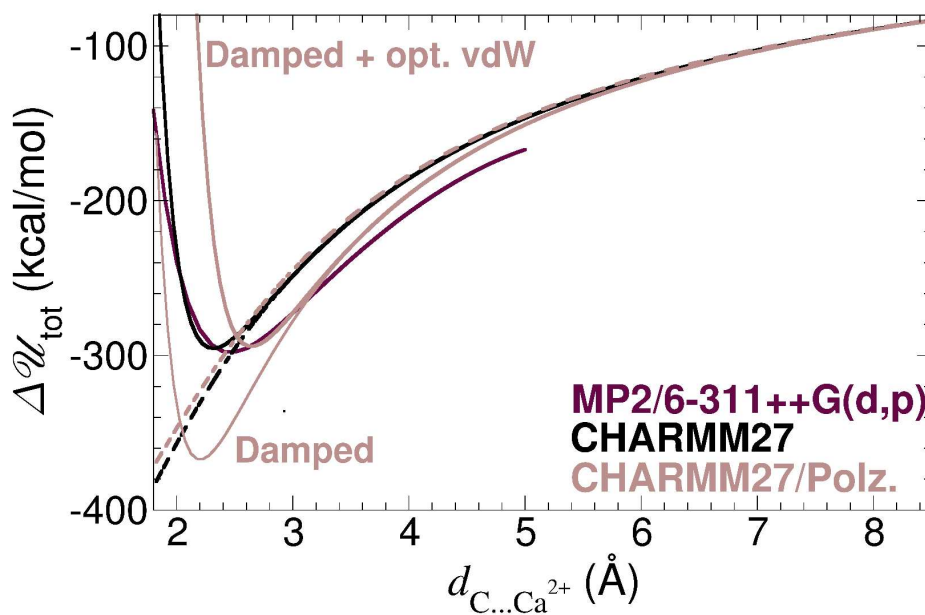
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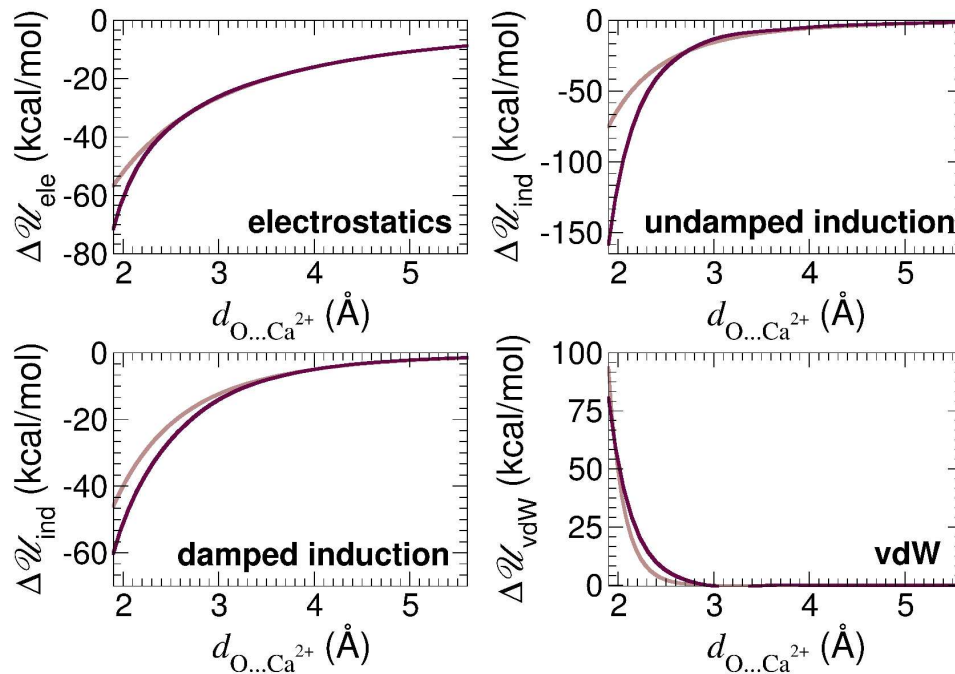


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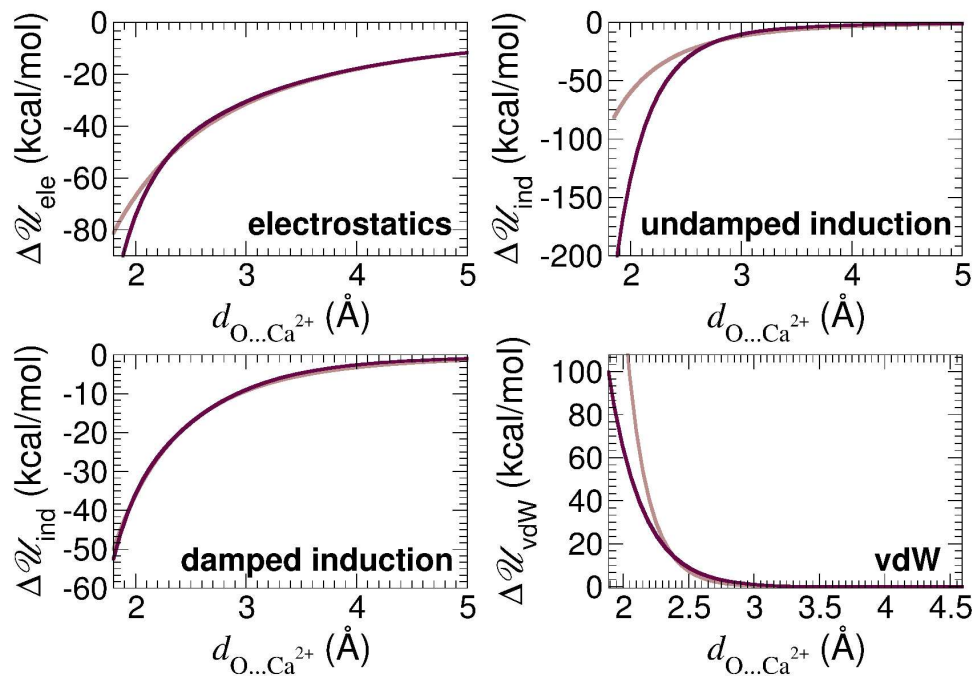


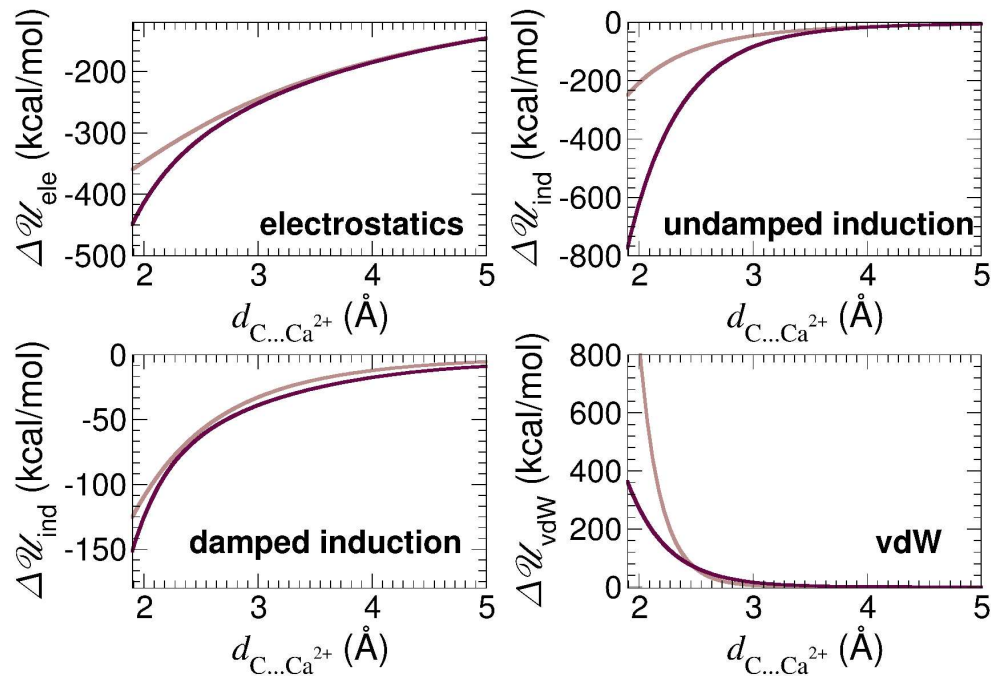




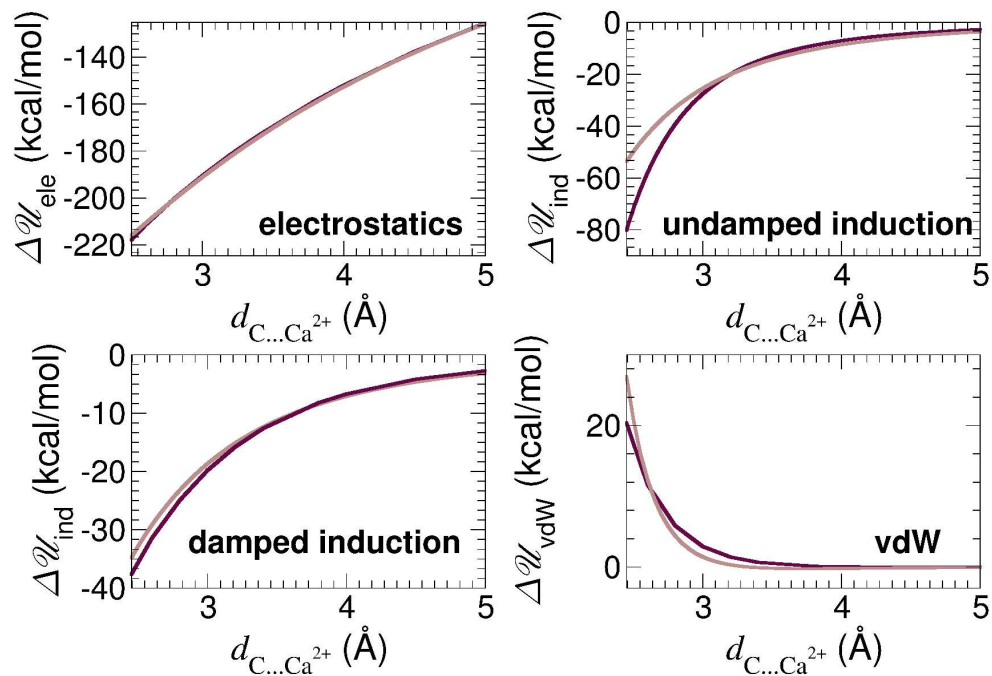


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