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## Molecular mechanics for zinc complexes with fluctuating atomic charges

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**Abstract** A recently developed force field with fluctuating atomic charges has been parametrized to implement calculations for zinc complexes. The atomic charges are calculated by means of a semi-empirical quantum chemical method (bond polarization theory, BPT). The major goal of this new force field is reliable description of the geometry of zinc complexes and their intermolecular interactions with other molecular systems. It is possible to include all mutual polarizations into the term for the electrostatic interaction using the atomic charges obtained from the BPT. The treatment of the polarization effects including the whole system is one of the most important advantages of this method in respect of alternative combinations of quantum chemical procedures with force fields. If a ranking of complex stabilities is established, polarization effects might significantly change the sequence.

To reduce the number of force-field parameters, a new method was introduced for estimation of the equilibrium length of metal bonds to ligands. The method was tested to describe the structure of a variety of zinc complexes where the structures are known from X-ray investigations. For small molecules, ab initio data were used as references. For the larger complexes, data from semi-empirical calculations were compared with the force field results. Significant deviations are observed for low coordination numbers and for some five-coordi-

nated compounds. The best geometries are obtained for  $[\text{ZnL}_4]^{2+}$  complexes.

For molecular dynamics simulations and conformational searches it is of interest whether the non-bonded approach for the metal ligand system gives stable structures. Therefore, interaction energies of zinc ions with different numbers of water molecules were calculated and compared with results from ab initio calculations. Starting from  $[\text{Zn}(\text{H}_2\text{O})_3]^{2+}$  the results strongly correlate linearly with the ab initio values and relative differences are reproduced satisfactorily.

To test COSMOS on other types of ligand and more complicated systems we decided to apply a method to a number of complexes of pentahydrated  $\text{Zn}^{2+}$  with guanine, adenine, and the guanine–cytosine and adenine–thymine base pairs. Structures corresponding to energy minima are sought by molecular dynamics simulations and subsequent geometry optimization of coordinate snapshots. The interaction energies of these structures are compared with results from ab initio calculations of similar structures. The absolute values obtained with COSMOS are usually too low but the relative stabilities are reproduced in agreement with the ab initio calculations.

Finally the stability of a number of four-coordinated zinc complexes with nitrogen coordination was investigated. We used the energy values to predict the stability of zinc complexes of pseudo-peptide ligands before their synthesis was performed.

**Keywords** Force field · Zinc complexes · Calculation of atomic charges · Electrostatic interactions · Bond distances

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### Introduction

The description of intermolecular interactions by means of potential functions is very important for elucidating how metalloproteins catalyze reactions in cells. Zinc is essential in a number of metalloenzymes, e.g. carbonic anhydrase,

alcohol dehydrogenase, and zinc-finger proteins [1]. Force fields give us the possibility of simulating interactions of large molecular systems with relatively simple potential energy functions. The development of generalized force fields with a reasonable numbers of parameters and high accuracy in modeling several chemical or physical properties would, therefore, be of great advantage.

If interactions of molecules with charged centers, ions or solvents are investigated, the correct description of polarization effects is essential. Many problems in force field calculations arise from the calculation of Coulomb interactions with fixed charges, neglecting all mutual polarizations. These charges are parameters that are adjusted to give correct interaction energies in structures not too far from the equilibrium geometry. In classical force fields (see e.g. CHARMM [2], AMBER [3], GROMOS [4], OPLS [5], and MMFF [6]) atomic charges are exaggerated to account for the energy contributions from polarizations.

The COSMOS (COmputer Simulation of MOlecular Structures) force field [7] presents a method which includes the semi-empirical charge calculation based on bond polarization theory (BPT) [8, 9] into a molecular mechanics force field. The most important advantage of BPT is that the atomic charges depend on the three-dimensional structure of the molecule. The algorithm is fast because no self-consistency cycles are necessary and the matrix that has to be inverted is only of the dimension of the number of atoms.

Recently, several force fields for metal complexes have been developed (and reviewed [10, 11]). In most cases functions with a large number of parameters are used to describe the metal–ligand interactions (see, for instance, YETI [12]). The problem is to determine all these parameters either from experimental data or by quantum chemical calculations. We therefore propose simple general principles that work with a minimum of parameters instead of adding new complicated terms to the force field. Even if this approach leads to larger errors for some special cases, we did not try to eliminate these differences by special terms or parametrizations. Rappé et al. [13] included a parametrization for metal atoms into their “Universal Force Field” (UFF) and discussed the dependence of the bond lengths on bond orders. An explicit dependence was not included in the UFF. Starting with a similar concept, we propose a formula for the calculation of the valences of bonds between metal atoms and ligands.

Because hydrogen bridges are essentially caused by electrostatic interactions, we introduced no specific term for this bond type. If a hydrogen-bond donor and an acceptor are found the van der Waals’ term of the proton and that of the acceptor are switched off. The charge polarization should increase the electrostatic interaction, stabilizing the hydrogen-bond.

In the search for stable complex compounds it seems preferable to treat the metal atom as an ion without the definition of bonds. Vedani and Huhta [12] introduced a compromise between the bonded and non-bonded (elec-

trostatic) approach to simulate changes in the coordination of the metal atom. In the course of a general search for stable complex structures such a non-bonded treatment would be of great advantage. In the case of the non-bonded approach, the problem of the strong electrostatic interactions between metal and ligands has to be solved. Hoops et al. [14] adapted the AMBER force field for metal complexes and fitted the atomic charges to calculated electrostatic potentials (ESP charges). This procedure gives good interaction energies for structures not too far from equilibrium geometries but the ESP charges do not change as the structure changes.

One possibility of obtaining atomic charges within force field calculations is the fluctuating charge (FQ) model based on the empirical electronegativity equalization principle. Recently this FQ model was parametrized in ab initio calculations (Banks et al. [15]) of the electrostatic potential of alanine. The authors integrated their method into the OPLS force field but applications other than polyalanine need new parametrizations.

The most advanced procedure for the calculation of interaction energies in force fields is the SIBFA (sum of interactions between fragments ab initio computed) procedure. This method was successfully applied to several zinc complexes (Gresh and Šponer [16] and Tiraboschi et al. [17]). For calculation of interaction energies of complexes by use of the SIBFA procedure ab initio calculations of the ligands must be performed in advance to derive their charges, dipoles, and polarizabilities.

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## Methods – the zinc parametrization for the COSMOS force field

The COSMOS force field [7] was developed from the following ideas:

1. The functional form of the parametrization of the PIMM ( $\pi$ -SCF molecular mechanics) force field [18] (see also Ref. [19]) was introduced for the bond lengths and bond energies of the single bonds of the most common elements C, O, N, S, Cl, F, and H. The same source was used for the description of torsion angles and energies.
2. The bond lengths and energies of conjugated  $\pi$  bonds were calculated from their valences using the parameters of O’Keefe and Brese [20]. For the calculation of the valences of conjugated  $\pi$  bond a formula is proposed that takes into account the surroundings of the two atoms forming the bond.
3. The bond angle term is associated with the deformation of an angle from its equilibrium value, and the valence bond concept of Root et al. [21] was used for calculation of the angular energy.
4. For description of van der Waals interactions the potential functions according to Halgren [22] were used. The electrostatic part of the energy was calculated using atomic charges from the BPT procedure.

These force field components have now been adapted for zinc. The parameter set for the zinc should fulfil the requirements:

1. the number of parameters should be as limited as possible;
2. the parameters of the different energy contributions should be independent; and
3. the force field should be universally useful for common zinc compounds.

The second point should be particularly emphasized, because we work with quantum chemically calculated atomic charges that fluctuate with the change of the molecular structure. This can only be accomplished if the electrostatic energy is independent of the parametrization of the other energy contributions. Only an independent parametrization can guarantee that new parts of the force fields like zinc can be introduced without changing the rest of the force field.

### Bond energy

The metal atoms in coordination compounds can generally form different numbers of complex bonds. In  $\text{Zn}^{2+}$  complexes the coordination number 4 is common but 5 and 6 are also observed. To calculate the equilibrium bond lengths  $r_{ab}^0$  for such a large number of possible cases we propose to extend the valence concept to the case of complex compounds. This concept dates back to Pauling [23] who established a relationship between valence  $v_{ab}$  and bond distance:

$$r_{ab}^0 = R_{ab} - 0.37 \ln v_{ab} \quad (1)$$

A new parametrization of Eq. (1) was reported by O'Keefe and Brese. [24] They proposed a different constant (0.37 instead of the Pauling value 0.35) and developed an empirical relationship between the length of an ideal single bond  $R_{ab}$  ( $v_{ab}=1$ ) and the ionic character of a bond between the atoms a and b. The parameters for the calculation of  $R_{ab}$  were published for most elements of the periodic system [24]. In our calculations only the parameter for the single-bond radius of oxygen was changed from 0.64 to 0.6741 Å, because the Zn–O and C=O bond lengths obtained were too short when the original value was used. The valences of bonds of metal atoms in complexes will regularly be  $<1$ . This can be easily understood if we establish a direct proportionality between the valence and the number of electrons forming the bonds (occupation number). The following formula is introduced for the valence of a  $\sigma$ -bond:

$$v_{ab} = \sqrt{V_a^D / n_a^D} \sqrt{V_b^A / n_b^A} \quad (2)$$

where  $V^A$  is the valence (number of valence electrons) of the metal atom (bond-acceptor A) and  $n$  is the number of bonds. For the metal atoms the number of bonds  $n^A$  is usually equal to the coordination number. In the zinc imidazole complex (II in Fig. 6) we obtain

$$v_{\text{Zn-N}} = \sqrt{\frac{3}{4}} \sqrt{\frac{2}{4}}$$

for the valence of a Zn–N bond. The donors (D) of the bond electrons are the ligand atoms. This bond occupation number  $v_{ab}$  is used to calculate the bond length from Eq. (1). The force constants  $k_{ab}$  are calculated from the default bond value of 700 kcal mol<sup>-1</sup> Å<sup>-1</sup> multiplied by the valence  $v_{ab}$ .

### Angular energy

Root et al. [21] used the relationship between bond angle and hybridization to calculate the equilibrium bond angle. A weight factor describing the preference of the atom pair for a hybridization state and the gross hybridization of the central atom is inserted into the formula used to calculate the hybridization. This hybridization preference is parametrized for each pair of ligand and central atom. This parameter is set to the default value of 1.0 for all Zn–X pairs. In our approach the gross hybridization of Zn depends only on its coordination number  $n$ . We therefore set the gross hybridization to  $sp^{n-1}$  ( $n>1$ ). The hybridization of  $s$  and  $p$  electrons leads to a maximum coordination number of four. For coordination numbers of zinc larger than four the angular energy term is switched off. For higher coordination numbers and space-filling ligands, it is sufficient to consider the electrostatic and van der Waals interactions of the ligands. If the bonded approach is used, the energies of four-coordinated zinc compounds cannot be compared with those of higher coordination numbers because the energy does not vary smoothly with coordination number.

### Van der Waals energy

Within the COSMOS force field we implemented the van der Waals interaction energy functions of Halgren [22]. For the imine nitrogen ( $-\text{N}=\text{C}$ , MM2X type 9) an intermolecular  $R^*$  van der Waals parameter of 3.40 Å was introduced to reproduce the distance of  $\text{Zn}^{2+}$  ion to the imidazole N atoms in  $[\text{Zn}(\text{imidazole})_4]^{2+}$ . Because only the values for  $\text{Zn}^{2+}$  ions were given by Halgren [22] we introduced for bonded zinc an exp-6 potential term with the parametrization from Mayo et al. [25]. They used a well depth parameter of 0.055 kcal mol<sup>-1</sup> and an equilibrium distance of 4.45 Å for Zn. Van der Waals interactions between bonded neighbors and next neighbors are switched off. For all calculations presented here the cut-off radius was set large enough to ensure that all interactions were taken into account.

### Coulomb energy

One special feature of the COSMOS force field is the possibility of calculating new atomic charges in each

step of a molecular mechanics calculation. These charges contain all mutual polarizations and therefore no extra terms are needed to include polarizations into the electrostatic energy. Because atomic charges derived from ab initio calculations depend both on the basis set and on the method of population analysis, it is necessary to define atomic charges that represent the electrostatic energy with sufficient accuracy. The parametrization of the BPT was performed using atomic charges derived from ab initio STO-3G calculations using Mulliken population analysis. But these charges cannot be used in calculations of electrostatic energies. Within the force field calculations these charges are scaled to ESP (electrostatic potential) values (see discussion below). In Ref. [7] the electrostatic part of the interaction energy was compared with results from ab initio calculations of simple molecule pairs and DNA/RNA base pairs and it turned out that this scaling worked surprisingly well.

One significant refinement within the reformulation of the bond polarization formula, in respect of the former formulation in Ref. [9] is that the dependence of the bond occupation number is explicitly taken into account. All integrals over bond orbitals are multiplied by the occupation numbers  $N$  of the bonds to account for weak complex bonds or conjugated  $\pi$  bonds. We arrive at the following bond polarization formula for the atomic charge on an atom  $a$ :

$$-q_a = \sum_b^{n_a} N_{ab}^\sigma d_{ab}^\sigma + \sum_b^{n_a} (N_{ab}^\pi)^2 A_{ab}^\pi V_{ab}^\pi + \pi - \text{term} \quad (3)$$

(the superscript  $\pi$ -term has the same structure as the  $\sigma$ -term).

The bond polarization energies  $V_{ab}$  are calculated using hybrid atomic orbitals forming the bond between the atoms  $a$  and  $b$  and atomic charges on all other atoms of the system (for the explicit expressions of the  $V_{ab}$  integrals see Ref. [8] and for  $d$ -functions see Ref. [26]). The occupation numbers  $N$  are estimated by using the valence formula (Eq. 1):

$$N_{ab}^\sigma = 2v_{ab} \text{ and } N_{ab}^\pi = 2(v_{ab} - 1) \quad (4)$$

Two parameters per bond must be determined:

1. the polarity of an unpolarized bond  $d_{ab}$ , and
2. the slope  $A_{ab}$  describing the change of the charge with bond polarization.

If all atomic charges of a molecule are known, these parameters can simply be determined from the least-squares solution of an over-determined set of linear equations, because the polarization energies,  $V$ , depend linearly on all other atomic charges. The equations all have the form of Eq. (3).

The parametrization for the elements C, H, O, and N has been given elsewhere [9]. We now include bonds of the elements F, Cl, P, Si, and Zn (Table 1). For parametrization of elements excluding zinc a set of 134 molecules was geometry optimized on the STO-3G HF level using the GAUSSIAN 94 program [27]. For zinc we se-

**Table 1** Parameters<sup>a</sup> for the bond polarization model obtained by a least-squares calibration procedure

Bond	$d_{ab}(\sigma)$	$d_{ab}(\pi)$	$A_{ab}(\sigma)$	$A_{ab}(\pi)$
C-C	–	–	0.6527	0.4082
C-O	0.1350	0.1052	-0.8982	2.3918
C-N	0.0567	0.0567	0.10776	-0.3291
O-H	-0.2098	–	-0.0353	–
C-H	-0.0646	–	0.0592	–
N-H	-0.1630	–	0.3186	–
C-F	0.1480	–	0.5975	–
C-Cl	0.0517	–	0.2319	–
P-O	0.1966	0.2631	0.23389	0.2362
Si-O	0.3445	–	-0.0402	–
Si-C	0.1934	–	0.5090	–
Si-H	0.2643	–	-8.2322	–
Si-Cl	0.3904	–	-1.2413	–
Zn-N	0.3904	–	-3.0530	–
Zn-O	0.5084	–	0.0116	–

<sup>a</sup>For the meaning of the parameters see Eq. (3)

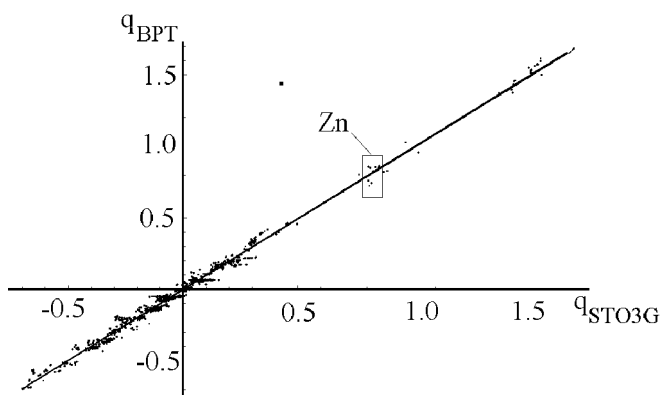
lected the X-ray structures of nine complex compounds from the Cambridge data base. We included only structures with zinc in oxygen or nitrogen coordination and excluded compounds with more than one zinc atom per molecule. The hydrogen positions were geometry-optimized using the COSMOS force field. Single-point STO-3G HF calculations were then performed to obtain the atomic charges for these structures. The resulting parameters for the BPT formula (Eq. 3) that were calculated by the least square procedure are given in Table 1. The polarization parameters  $A_{ab}$  (in atomic units of charge per Hartree) should give an estimate whether or not a bond can be easily polarized. The  $d_{ab}$  parameters (in atomic units of charge) reflects the polarity of an unpolarized bond with an occupation number  $N$  of one. These values are easily understood by regarding the electronegativity difference of the bond partners. A rough estimate for the  $d_{ab}$  parameters can be obtained from the following formula, by using the Pauling electronegativities of the atoms  $a$  and  $b$  [28]:

$$p_{ab} = (0.16 + 0.035|EN_a - EN_b|)(EN_a - EN_b) \quad (5)$$

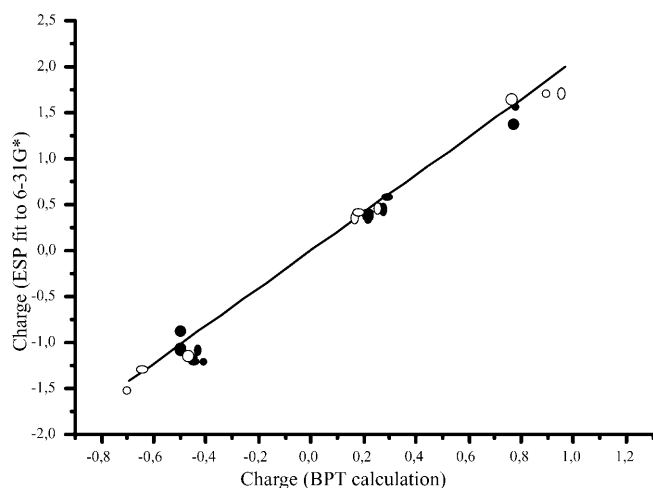
If a molecule contains bonds between elements that have no polarization parameters, the bond polarity is estimated from Eq. (5).

Figure 1 depicts the correlation of the BPT charges with the values obtained by the STO-3G calculations for the calibration set of molecules. The overall correlation is relatively good but the clustering in the region of small values is an indication that small charge differences between hydrogen atoms are underestimated.

The most favored method for obtaining atomic charges for force field parametrizations is to fit the values to ab initio calculations of electrostatic potentials (ESP charges). Hoops et al. [14] applied this method for the zinc parametrization of the AMBER force field. The authors performed MNDO and ab initio (6-31G\*, STO-3G\*, MINI-4, MIDI-4) calculations for  $[\text{Zn}(\text{H}_2\text{O})(\text{NH}_3)_3]^{2+}$  and



**Fig. 1** Correlation of the atomic charges of 143 molecules calculated with the bond polarization theory BPT with values from ab initio STO-3G calculations. This set of atomic charges was used in the least-square fit to determine the parameters of Table 1



**Fig. 2** Correlation of BPT charges with values of an 6-31G\* ab initio ESP charge analysis (Hoops et al. [14]). (—) linear regression (fixed zero point)  $R=0.992$ , slope 2.05 (●) ESP charges of  $[\text{Zn}(\text{H}_2\text{O})(\text{NH}_3)_3]^{2+}$  and  $[\text{ZnOH}(\text{NH}_3)_3]^+$  (○) NBO analysis of the charge distribution of  $[\text{Zn}(\text{NH}_3)_4]^{2+}$ ,  $\text{Zn}(\text{NH}_2)_2$ ,  $\text{Zn}(\text{OH})_2$  calculated on the 6-311+G\* level

$[\text{ZnOH}(\text{NH}_3)_3]^+$  and analyzed the ESP charges of these compounds. We performed COSMOS force field calculations for the same molecules and correlated the BPT charges to the ESP values for the 6-31G\* basis set. From linear regression analysis (fixed zero point) we obtained a high correlation coefficient ( $R=0.992$ , 31 values) and a slope of 2.050. It should therefore be possible to scale the BPT charges to the more ionic picture of the ESP.

A promising alternative to the Mulliken population analysis is the NBO method (natural bond orbital population analysis [29]) because this method might eliminate the strong basis set dependence of the atomic charges. We therefore compared the BPT charges with values obtained from the NBO analysis of some zinc compounds of Table 2 (Zn–N or Zn–O bonds only:  $[\text{Zn}(\text{NH}_3)_4]^{2+}$ ,  $\text{Zn}(\text{NH}_2)_2$ ,  $\text{Zn}(\text{OH})_2$ ) calculated on the HF 6-311+G\*

**Table 2** The geometry of small molecules – comparison of Zn–X bond lengths from COSMOS force field and ab initio calculations

Molecule	COSMOS-calculated bond length (Å) <sup>a</sup>	ab initio-calculated bond length (Å) <sup>b</sup>	$\Delta\%$
$[\text{Zn}(\text{NH}_3)_4]^{2+}$	2.028	2.0511	1.1
$\text{Zn}(\text{NH}_2)_2$	1.779	1.8201	2.2
$[\text{Zn}(\text{NCS})_4]^{2+}$	1.921	1.9902	3.5
$\text{Zn}(\text{CH}_3)_2$	1.851	1.9571	5.4
$\text{ZnPh}_2$	1.850	1.9142	3.3
$\text{Zn}(\text{OH})_2$	1.736	1.7721	2
$\text{ZnF}_2$	1.618	1.7501	9.1
$\text{Zn}^{2+}\text{F}_7^{2-}$	1.670		4.6
$\text{Zn}(\text{SH})_2$	2.086	2.1791	4.3
$[\text{Zn}(\text{SCN})_4]^{2+}$	2.295	2.4202	5.2

<sup>a</sup> B3LYP/6-311+G(3df,3pd) Bräuer et al. [30]

<sup>b</sup> Antes and Frenking [35]

level (open circles in Fig. 2). The NBO data fit surprisingly well into the ESP correlation ( $R=0.996$  and a slope of 2.041). For the BPT parametrization it is, therefore, sufficient to perform STO-3G calculations and scale the resulting charges to obtain the correct interaction energies. The electrostatic interactions within the force field are calculated from BPT charges by Coulombs law excluding interactions between bonded neighbors.

## Results and discussion

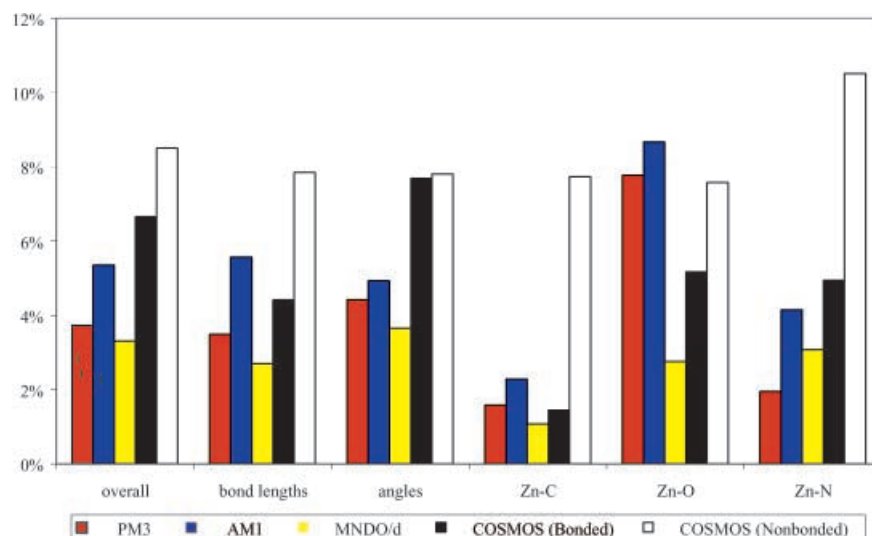
### Geometry calculations of zinc complexes

As a first test of the force field we performed calculations on small zinc compounds where geometry data of accurate ab initio calculations were known. Best results were obtained for four-coordinated zinc compounds (Table 2) where deviations from the ab initio bond length results do not exceed 3.5%. It should be noted that the ionic approach for zinc fluoride gave much better geometry parameters than the bonded approach. Because BPT parametrization for sulfur and Zn–C bonds has not yet been performed, the larger deviations for Zn–S and Zn–C bonds were not investigated in detail.

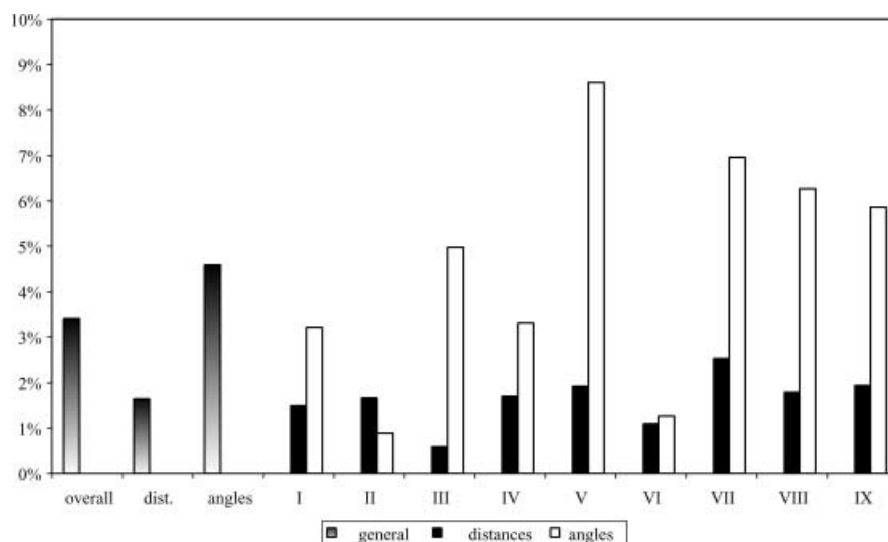
Bräuer et al. [30] published the results of geometry optimizations for a series of zinc complexes using the semi-empirical methods PM3, AM1, and MNDO/d. For comparison, we performed force field calculations for the same set of molecules. The results for the zinc bond length and angles of these compounds (denoted A...P as in Ref. [30]) are presented in Fig. 3. All calculations were performed for both bonded and non-bonded zinc. For MD simulations and conformational search the non-bonded or ionic approach is of great interest.

Problems arise for five-coordinated complexes, because one bond is usually distinctly longer than the other four. The coordination can better be designated as (4+1) (cf. Vedani et al. [31]). If all five bonds are included in the Zn coordination, the differences between bond lengths are averaged because of Eq. (2). If four regular bonds

**Fig. 3** Deviation (%) from experimental values of calculated zinc distances and bond angles of complex compounds. Values from semi-empirical calculations are compared with results from COSMOS force field calculations using the bonded and the non-bonded approach for zinc



**Fig. 4** Deviations (%) of calculated zinc bond distances and angles from experimental values. The values were obtained for four-coordinated zinc complexes with nitrogen (for I-V see Fig. 6) or oxygen coordination using the COSMOS force field (bonded approach). The experimental structures are imported from the Cambridge Database (index I-V see Table 3, index: VI-YASGEE, VII-JURIVB, VIII-FOMKEX, IX-FOMKOH)



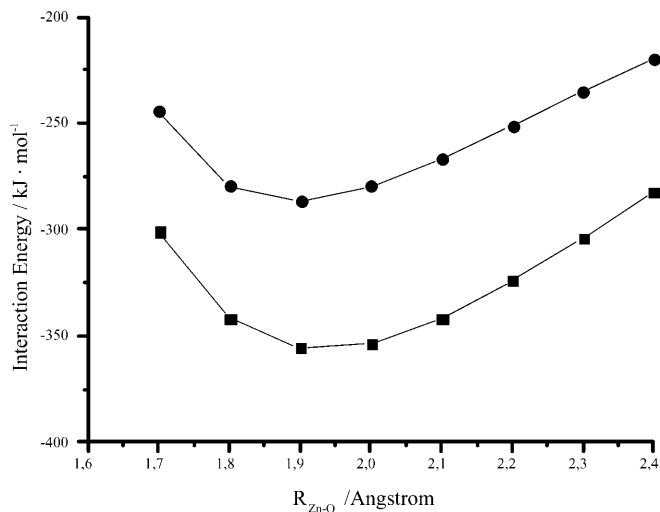
and one weak electrostatic interaction are assumed, the bond to this 5th partner becomes too long. Examples of this effect are complexes with an extra water bonded to zinc or nitrate ions in the zinc surroundings (compounds B and L in Ref. [30]). The position of weak dipolar ligands, e.g. water, cannot be predicted correctly disregarding the influence of crystal lattice. Problems also arise for complexes with two zinc atoms in close vicinity (compound H). We obtained stable complexes even in the non-bonded approach but some of the geometry parameters deviate from the crystal structure by approximately 30%. Taken all together, the errors in the force field calculations are in the same range as errors in semi-empirical methods. The main source of the deviations comes from the complexes containing two zinc atoms. For Zn-N and Zn-C distances, the non-bonded approach gives rise to larger deviations from experiment.

We also performed force field calculations for tetra-coordinated zinc complexes using the bonded approach and compared these results with experimental structures

from the Cambridge Database. This set of molecules was selected to model the ligand sphere of zinc in metallo-proteins as close as possible. The results of the comparison for the zinc bond lengths and angles for these structures are summarized in Fig. 4. The deviation of the zinc bond lengths from experimental values is <2% and the angles deviate by approximately 5%.

#### Electrostatic stabilization of complexes and predictions of relative stabilities

One central question of complex chemistry is whether or not a ligand can form a stable complex. If a new ligand is to be synthesized, one should be able to predict the stability of possible complexes. As a measure of the stability we used the interaction energy calculated as difference between the optimized complex and the optimized monomers or ligands. This value can only be obtained for the non-bonded case. On the other hand, the non-bonded is



**Fig. 5** Dependence of the interaction energy on the zinc–water distance for the system  $[\text{Zn}(\text{H}_2\text{O})]^{2+}$ . (■) – Energy values from an ab initio energy decomposition [29] (●) – scaled non-bonded energy (electrostatic interactions are calculated from BPT charges)

approach is well suited for MD simulations and in the search for stable conformers that form complexes. In all calculations, the BPT charges are scaled to ESP type charges (see Fig. 2) with a scaling factor of 2.050.

For zinc we first compared our results for the  $[\text{Zn}(\text{H}_2\text{O})]^{2+}$  system with those from the ab initio calculations of N. Gresh et al. [32] The authors used the frozen-core approximation and added polarization functions to the valence basis set. In their calculations the geometry of the water was fixed to standard values in all cases. In Fig. 5 the dependence of interaction energy on the distance between zinc and water is compared results from with ab initio calculations (the geometry of the water molecule was kept fixed with  $R_{\text{OH}}=0.9575 \text{ \AA}$  and angle  $\text{H-O-H}=104.51^\circ$ ). The form of the energy curve and the position of the minimum obtained from COSMOS are highly similar to the ab initio results but not the absolute values of the interaction energies (Table 3). The equilibrium distance of  $1.92 \text{ \AA}$  is much shorter than the Zn–O van der Waals minimum distance and the interaction energy is mainly the difference between a relatively large attractive electrostatic term and a strongly repulsive van der Waals contribution.

The results of the interaction energy calculations of the other water complexes are given in Table 3. As ex-

pected, the energy for the linear  $[\text{Zn}(\text{H}_2\text{O})_2]^{2+}$  complex is larger by a factor two than for a single water molecule. If more water is added to the coordination sphere of zinc the water contributions no longer add up because of the mutual repulsion of the ligands. The energies were compared with results from the correlated ab initio calculations of Lee et al. [33]. At low coordination numbers the deviation is larger because of the short Zn–O distances. Starting from  $[\text{Zn}(\text{H}_2\text{O})_3]^{2+}$  the results correlate strongly linearly with the ab initio values and relative differences are reproduced satisfactorily. For  $\text{Zn}[(\text{H}_2\text{O})_6]^{2+}$  the difference between the ab initio value and the COSMOS value is in the order of the difference between a correlated and uncorrelated ab initio calculation.

To test COSMOS on other types of ligands and more complicated systems we decided to apply our method to several complexes of pentahydrated  $\text{Zn}^{2+}$  with guanine, adenine, and the guanine–cytosine and adenine–thymine base pairs. Gresh and Šponer [16] performed ab initio and SIBFA calculations for these systems. For guanine and adenine we performed molecular dynamics runs of 100 000 steps (step width 0.5 fs, 273 K). The systems were surrounded by a periodic box to avoid loss of water molecules. Every 100 steps a coordinate snapshot was taken and these snapshots were geometry-optimized (without periodic box) to search for the most stable structures. The results are given in Table 4.

*$[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  with guanine.* In all geometry optimizations we obtained three structures that differed only in the position of the water hydrogens. The most stable form (see Fig. 6) is essentially the same as the structure (b) in Ref. [16]. The distances to the water oxygen atoms are slightly too short ( $1.971\text{--}1.976 \text{ \AA}$  compared with  $2.06\text{--}2.13 \text{ \AA}$ ).

*$[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  with adenine.* In addition to structure (a) in Ref. [16] a more stable structure was found with the zinc out of the adenine plane opposite to the  $\text{NH}_2$  nitrogen. For structure (a) we obtain nearly the same energy as for the uncorrelated calculation.

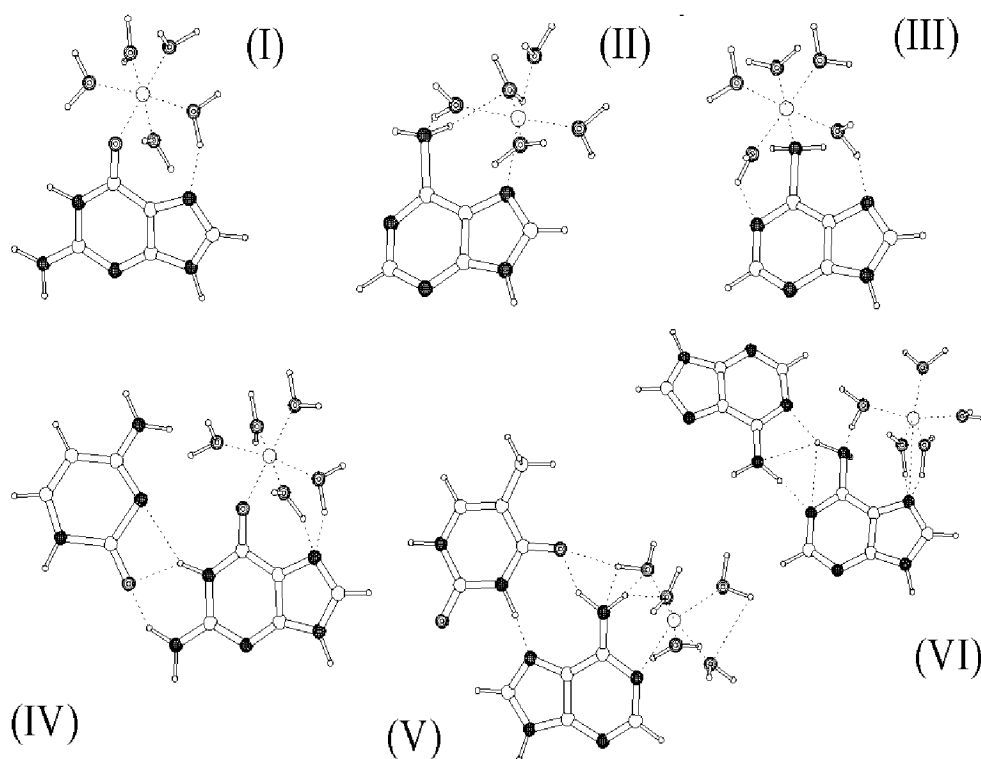
*$[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  with guanine–cytosine.* The MD simulations produced, after geometry optimization, a multitude of possible energy minima; it is outside the scope of this paper to discuss these minima. The most stable structures were stacks of base pairs as shown within the stereo picture pair (Fig. 7). To compare the energies we

**Table 3** COSMOS interaction energies and equilibrium Zn–O distances of zinc–water complexes compared with ab initio interaction energies

	COSMOS interaction energy ( $\text{kJ mol}^{-1}$ )	COSMOS Zn–O equilibrium distance ( $\text{\AA}$ )	ab initio <sup>a</sup> interaction energy ( $\text{kJ mol}^{-1}$ )	ab initio <sup>a</sup> Zn–O equilibrium distance ( $\text{\AA}$ )
$[\text{Zn}(\text{H}_2\text{O})]^{2+}$	–266.8	1.907	–398.9	1.894
$[\text{Zn}(\text{H}_2\text{O})_2]^{2+}$	–539.6	1.912	–754.7	1.901
$[\text{Zn}(\text{H}_2\text{O})_3]^{2+}$	–769.1	1.921	–995.4	1.957
$[\text{Zn}(\text{H}_2\text{O})_4]^{2+}$	–995.4	1.932	–1184.6	2.010
$[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$	–1184.6	1.960 <sup>b</sup>	–1303.5	2.061 <sup>b</sup>
$[\text{Zn}(\text{H}_2\text{O})_6]^{2+}$	–1361.3	1.982	–1427.4	2.136

<sup>a</sup> Lee et al. [33], HF/TZ2P geometry optimization and MP2/TZ2P energy calculations  
<sup>b</sup> Mean value

**Fig. 6** Structures of complexes of  $[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  with guanine (I), adenine (II, III), and the guanine–cytosine (IV), adenine–thymine (V), and adenine–adenine (VI) base pairs (see Table 4)



**Table 4** Interaction energies and geometry parameters of complexes of  $[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  with guanine, adenine, and the guanine–cytosine, adenine–thymine, and adenine–adenine base pairs (the structures are given in Fig. 6)

$[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$ complex with:	COSMOS interaction energy (kJ mol <sup>-1</sup> )	COSMOS Zn–O and Zn–N distances (Å)	ab initio calculation	SIBFA <sup>b</sup> Zn–O and Zn–N distances (Å)
Guanine (I)	–1464.8	Zn–OH <sub>2</sub> : 1.971...1.976; Zn–O=G: 2.032	Structure (b): –1537.9 <sup>a</sup> ; –1688.2 (MP2)	Zn–OH <sub>2</sub> : 2.06...2.18; Zn–O=G: 2.06
Adenine (II)	–1335.4	Zn–OH <sub>2</sub> : 1.953...1.997; Zn–N(7): 2.171	Structure (a): –1343.7 <sup>a</sup> ; –1541.3 (MP2)	Zn–OH <sub>2</sub> : 2.11...2.13; Zn–N(7): 2.06
Adenine (III)	Minimum (II) –1412.2	Zn–OH <sub>2</sub> : 1.977...1.986; Zn–NH <sub>2</sub> : 2.104		
Guanine–Cytosine (IV)	–1667.0	Zn–OH <sub>2</sub> : 1.956...1.983; Zn–O=G: 2.00	Structure (c): –1794.6 <sup>b</sup>	Zn–OH <sub>2</sub> : 2.04...2.13; Zn–O=G: 1.92
Adenine–Thymine (V)	–1405.3	Zn–OH <sub>2</sub> : 1.990...2.011; Zn–N(7): 2.100	–1538.4 <sup>b</sup>	Zn–OH <sub>2</sub> : 2.12...2.14; Zn–N(7): 2.00
Adenine–Adenine (VI)	–1375.3	Zn–OH <sub>2</sub> : 1.944...1.972; Zn–N(7): 2.889	–1497.4 <sup>b</sup>	Zn–OH <sub>2</sub> : 2.12...2.14; Zn–N(7): 2.00

<sup>a</sup> CEP 4–31G+(2d) calculation of Gresh and Šponer [16] without BSSE, geometry optimized using SIBFA, MP2 values with the same basis set

<sup>b</sup> HF-6–13G\* Gresh and Šponer [16]

therefore constructed a planar model that was near to structure (a) in Ref. [16]. Geometry optimization gave a non-planar structure with one water molecule intermediate between the basis (Fig. 6).

$[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  with adenine–thymine. The geometry optimization of planar models gave basically the same structure as in Ref. [16]. The non planarity of the NH<sub>2</sub> group produced an relatively large gain within the interaction en-

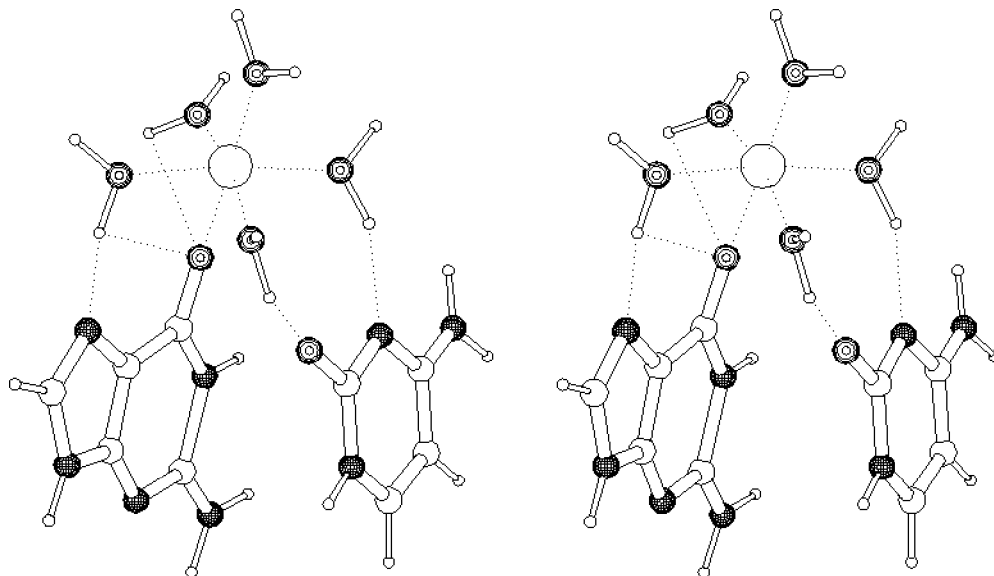
ergy. A problem are the positions of the hydrogen atoms of the water molecules producing many possible minima.

$[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  with adenine–adenine. This base pair posed basically the same problems as the adenine–thymine base pair. Additionally the geometry optimization gave a very long Zn–N distance.

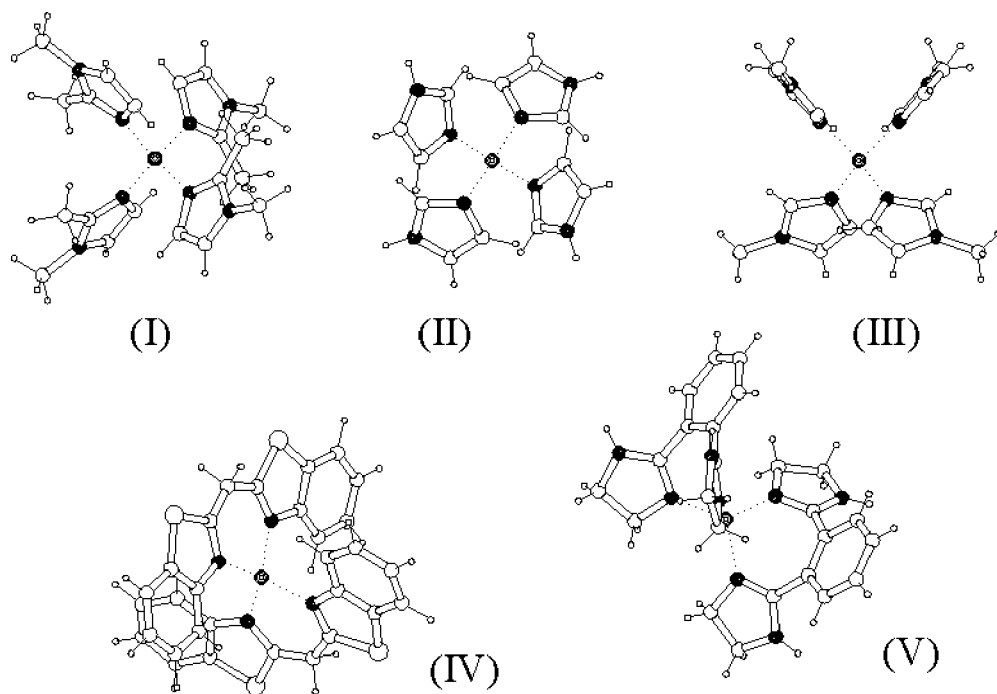
One aim of our work is the prediction of stable structures of synthetic peptide complexes of Zn<sup>2+</sup>. We select-



**Fig. 7** Stereo view of a guanine–cytosine complex of  $[\text{Zn}(\text{H}_2\text{O})_5]^{2+}$  obtained as an energy minimum from a molecular dynamics simulation



**Fig. 8** Structures of four-coordinated zinc complexes with nitrogen coordination from the Cambridge Database used in Table 5 and Fig. 4



ed five complexes with known structures from X-ray investigations (Cambridge Database) where one zinc is bound to four nitrogen atoms. After adding missing hydrogen atoms we optimized the complexes as isolated charged molecules and calculated the interaction energies as the difference between the optimized complex and the optimized ligands (Table 5 and Fig. 8). In all cases COSMOS geometry optimization caused only minor changes in the geometry (Table 5) and the complexes proved to be electrostatically stable. The Zn–N distances in these complexes were always near to 2.0 Å and this value was used to adjust the  $-\text{N}=\text{C}$  parameter of the intermolecular van der Waals potential. Using the BPT

charge calculation it is now possible to study the contribution from the polarization of the ligands by the central metal atom (Table 5). We calculated the atomic charges of the ligands with zero charged zinc atoms and compared the resulting interaction energies with values including polarization. These contributions turned out to be quite different (from  $-42$  to  $-159$   $\text{kJ mol}^{-1}$ ) and this term should not be neglected if the ligand contains  $\pi$ -bonds. Especially if relative differences are discussed the contributions from the polarization are essential to establish a ranking with respect to the stability.

We used the energy values from Table 4 to predict the stability of zinc complexes of ligands before their syn-

**Table 5** Non-bonded zinc–ligand intermolecular interaction energies of complexes with nitrogen coordination ( $\text{kJ mol}^{-1}$ ). The zinc was treated as  $\text{Zn}^{2+}$  ion

Reference ligand <sup>a</sup>	COSMOS interaction energies ( $\text{kJ mol}^{-1}$ )	Contribution <sup>b</sup> from polarization
(I) 1,2-Dimethylimidazole	–882.3	–88
(II) Imidazole	–718.7	–24
(III) <i>N</i> -Methylimidazole	–801.5	–37
(IV) bis-2,2'-(Benzthiazolyl)methane	–952.3	–169
(V) O-bis-2,2'-(4,5 Dihydroimidazolyl)benzene	–799.4	–19

<sup>a</sup> The Roman numbers refer to the labels in Fig. 8. The nomenclature is from the Cambridge data base: (I) FUJGUM, (II) IMZNPC, (III) TEFOE, (IV) JOWID, (V) YASGAA

<sup>b</sup> Ligand charges calculated without  $\text{Zn}^{2+}$  ion (see text)

thesis was performed. From a number of candidates the ligand Bz-His-N(CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>)Gly-His was selected and we predicted the existence of a stable zinc complex and this prediction was successfully confirmed by Greiner et al. [34] who synthesized the ligand and confirmed the complex formation.

## Conclusions

The force field described is a powerful tool for calculating the structures of zinc complexes. Differences between calculated and experimental bond lengths for tetra-coordinated zinc are <2% and approximately 4% for other coordination numbers. This is accomplished mainly by use of a formula to calculate the valence of bonds in complex compounds.

Interaction energies of  $\text{Zn}^{2+}$  complexes with oxygen or nitrogen coordination are comparable with ab initio results on the uncorrelated level. With this force field it is possible to perform MD simulations with periodic boundary conditions and recalculate all atomic charges at every step of the simulation.

The core of the new force field is the semi-empirical charge calculation using the bond polarization theory BPT. Within the framework of this theory two parameters per bond type are needed to calculate the atomic charges from bond polarization integrals. This method provides a fast method for calculation of atomic charges. All polarizations can be included in the electrostatic energy of the force field. The model gives a good approach for the inclusion of polarization effects of charged centers in a molecular system, and the influence of a solution or a lattice to a molecular system for the calculation of the coulomb term. A typical calculation of a molecular system with 2000–3000 atoms including all net atomic charges takes approximately 2 min on a standard PC. Because the procedure scales quadratically with the number of atoms calculations for even larger systems are possible.

*Footnote.* The authors will gladly provide free force field software which includes all routines of the force field and for BPT atomic charge calculations.

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