# Development and Testing of PFFSol1.1, a New Polarizable Atomic Force Field for Calculation of Molecular Interactions in Implicit Water Environment

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S *Supporting Information*

ABSTRACT: A detailed calculation of protein interactions with explicitly considered water molecules takes enormous time. If water is considered implicitly (as media rather than as molecules), calculations become faster. These calculations are less precise, unless one uses voluminous computations of solvent-accessible areas. Our goal is to obtain parameters for nonbonded atom−atom interactions in implicitly considered water without computation of solvent-accessible areas. Because the "in-vacuum" interactions of atoms are obtained from experimental structures of crystals and enthalpies of their sublimation, the "in-water" interactions must be corrected using solvation free energies obtained from Henry's constants. Thus, we obtained parameters for the in-water van der Waals, electrostatic, and polarized interactions for atoms typical of protein structures. Parameters of covalent interactions were taken from the ENCAD force field and partial charges of atoms from quantum-mechanical calculations. The sought parameters of the in-water nonbonded interactions were optimized to achieve the best description of crystal structures and their sublimation and solvation at the room temperature. With the optimized parameters, the correlation between the calculated and experimental cohesion of molecules in crystals is 98.3% in the in-vacuum case (the supplementary force field PFFSubl1.1) and 95.4% the in-water case (the sought force field PFFSol1.1).
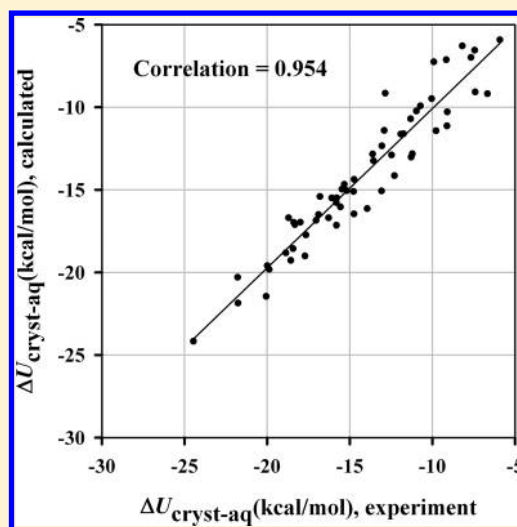
INTRODUCTION

Computer modeling of processes taking part in macromolecules (e.g., proteins) requires very high precision of the used molecular force fields. For example, a recent progress in modeling of protein folding[1−3] has been achieved only after some improvement[2] of potentials of covalent forces; and still, the force fields used now are not quite satisfactory to reproduce folded structures of some larger proteins.[3]

Harold Scheraga, whose 90th birthday is celebrated these days, was one of the first, among other pioneers, who developed and applied molecular force fields to study conformations of proteins and peptides.[4−13]

An accurate calculation of interactions within proteins and in protein−protein and protein−ligand systems must take into account not only forces acting in them but also their interactions with the surrounding water. Currently, with standard force field (FF) potentials,[14−21] the latter requires to compute the interaction of protein (and ligand) with thousands of surrounding waters, as well as that between these water molecules. As compared with calculations which do not consider water explicitly, this alone strongly slows down the computation of protein−ligand binding constants and sites. Moreover, the computation of hydrophobic interactions requires calculating water entropy,

i.e., screening of thousands of configurations of waters for any specified arrangement of protein and ligand.[22,23] This additionally slows down the computation of protein−ligand interaction several hundredfold.

To speed up the computations, the water surrounding a protein is sometimes neglected. However, this can be appropriate only for the internal protein regions having no contacts with water. A more correct approach is to enrich standard (vacuum) potentials with an implicit accounting of water surrounding the protein[24−27] (in particular, by introducing a water-dependent dielectric permittivity). In the implicit solvent models, the total solvation free energy is added to the "in-vacuum" energy. This additional free energy corresponds to a sum of nonpolar and electrostatic contributions. The estimate of the nonpolar contributions is usually based on the water-accessible areas of protein and ligand atoms.[28,29] If not performed by a rather slow thermodynamic integration[22,23] of the free energy changes caused by small changes in configuration and position of non-water molecules (proteins and ligands), this approach requires

calculation of differences between two large values: the free energy of protein−ligand complex in water and the sum of free energies of the separate proteins and ligands in water. These large values are determined only approximately, giving a large error when calculating their small difference. The estimate of the electrostatic contributions is based on a macroscopic continuum electrostatics, which is calculated using either a rather time-consuming solution of the Poisson−Boltzmann equations[30−32] or a faster but less precise generalized Born method.[29,33]

The goal of this work is to introduce a simple polarizable force field (PFF) working in implicit solvent without calculation of the solvent-accessible areas, and to obtain the "in-water" parameters of noncovalent interactions for this PFF. Because the interaction between the solute molecules leads to replacement of their interactions with the solvent atoms by the interactions of atoms of these solute molecules, one may suggest that the in-water potentials of the solute atoms (i.e., the solute atom−atom interactions in the implicit water environment) may have the same functional form as the normal, in-vacuum potentials, but with modified interaction parameters. Of course, this is an approximation, because the solute and the displaced solvent atoms do not have exactly the same positions. But this is a convenient approximation and, in this work, we will check the accuracy of results of this approximation.

The sought in-water parameters of the PFF are calculated from experimental solubility and sublimation enthalpy of molecular crystals with known spatial structures. The crystal structures are mainly taken from the Cambridge Structural Database (CSD);[34] the sublimation data from refs 35 and 36; and the data on solubility in water from refs 35 and 37. Parameters of covalent interactions are taken from the force field ENCAD,[17] which is sufficiently simply and comprehensively described, and partial charges of atoms from quantum-mechanical calculations, as in ref 38.

As a result, we obtained the optimized parameters for the sought FF PFFSol1.1 (Polarizable Force Field from Solubility) to assess interactions between molecules in an implicitly given water environment. In addition, we obtained parameters for the supplementary in-vacuum FF PFFSubl1.1 (Polarizable Force Field from Sublimation), which can be used in the absence of water or for calculations with explicitly given water molecules.

A similar approach has been used by us recently[39] to obtain the optimized parameters for the simplest, *non*-polarized force fields: in-vacuum FFSubl and in-water FFSol. They reproduce the effective cohesion energy of molecules in crystals with an error of about 6% (FFSubl) to 10% (FFSol) and the correlation with experiment of 95.4% (FFSubl) to 92.0% (FFSol),[39] i.e., not worse than the other, much more complicated force fields. However, polarizable force fields introduced in ref 40 and further developed in this paper give smaller errors, 4% (PFFSubl1.1) to 8% (PFFSol1.1), and higher correlations with experiment 98.3% (PFFSubl1.1) to 95.4% (PFFSol1.1).

■ METHODS AND MATERIALS

The total FF acting on molecules comprises the energies of noncovalent (U_{noncov}) and covalent (U_{cov}) interactions. In this work, we are interested in U_{noncov}, whereas U_{cov} (not influenced by the media) are taken from the literature, namely from the ENCAD FF.[17]

Polarized Force Field of Noncovalent Interactions. Polarized force fields of noncovalent interactions are taken in a form that is applicable for both in-water and in-vacuum conditions:

$$U_{noncov}\{\mathbf{r}\} = \sum_{(i,j)} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right] + \frac{1}{\varepsilon} \sum_{(i,j)} \frac{q_i q_j}{r_{ij}} - \frac{1}{2} \sum_i \left(\frac{\tilde{\alpha}_i}{\varepsilon^2} \right) \mathbf{D}_i^2 \tag{1}$$

The first two terms are conventional: they correspond to van der Waals (vdW) interactions of atoms and to electrostatic interaction of charges (in both cases, (i,j) are all atom pairs, where atoms i and j are separated by three or more covalent bonds or belong to different molecules[17]). The value $r_{ij} = |\mathbf{r}_j - \mathbf{r}_i|$, where $\mathbf{r}_i$ is the 3D coordinate of atom i. The terms A_{ij}, B_{ij} describe the exchange-repulsion (A) and dispersion (B) counterparts of vdW atom−atom interactions presented in the Lennard-Jones form. All $A_{ij} > 0$ (both in the solvent and in the vacuum): they describe repulsion of atoms i, j; however, the values A_{ij} for the in-water case may differ from those for the in-vacuum case. The terms B_{ij} are always positive in the vacuum:[41] here, they describe attraction of atoms. However, the B_{ij} values strongly depend on the medium; so, in principle, some of the in-water B_{ij} values may be even negative.[42] The value ε is the dielectric permittivity, which, of course, must be different in the in-vacuum and in-water force fields. q_i is the atom's i partial charge (which, in this work, is assumed to be the same in the in-vacuum and in-water force fields).

The last term (which is a kind of extension of the generalized Born method (cf. ref 43) to the corpuscular medium) corresponds to interaction of polarizable atoms (and the implicit solvent cavities that imbed them, in the case of the in-water FF) with electric fields created by the other atoms. $\tilde{\alpha}_i$ is polarizability of atom i (and the corresponding implicit solvent cavity, for the in-water FF) in the given medium, and

$$\mathbf{D}_i = \sum_{j \in (i,j)} \frac{q_j}{r_{ji}^2} \cdot \mathbf{n}_{ji} \tag{2}$$

(where $\mathbf{n}_{ji} = (\mathbf{r}_j - \mathbf{r}_i)/r_{ji}$) is the electric induction produced by the remote charges in the point occupied by the given atom i. If atom i is considered as a sphere with volume v_i and permittivity ε_i in a surrounding medium with the permittivity ε

$$\tilde{\alpha}_i = \frac{\varepsilon}{4\pi} v_i \frac{3(\varepsilon_i - \varepsilon)}{\varepsilon_i + 2\varepsilon} \tag{3}$$

(see ref 44); thus, $\tilde{\alpha}_i > 0$ in the absence of any atomic environment (where $\varepsilon = 1$, while all $\varepsilon_i > 1$), but it can be negative in a medium that has permittivity ε higher than ε_i. In the other words, the last term of eq 1 describes attraction of polarizable atoms *into* the intense electric field in the in-vacuum case, while in the in-water case it describes also repulsion of the implicit atom-imbedding water cavity *from* the intense electric field. Because the values v_i, ε_i, and ε are not known precisely, we use only the values $\alpha_i \equiv (\tilde{\alpha}_i/\varepsilon^2)$ as the single parameters (cf. ref 40) that should be fitted using experimental data.

It should be mentioned that the thus introduced U_{noncov}, which now includes some three-particle interactions, is computed in a time proportional to the only squared number of atoms.

It should be also mentioned that U_{noncov}, being the "energy" in a strict sense of the word for the in-vacuum case only, is rather the "mean-force energy" for the in-water case.[24−26]

Equation 1 describes the main, but not all terms of U_{noncov}; in particular, it describes neither interaction between polarized atoms (which is implicitly included in the permittivity ε), nor many-body vdW interactions,[45] nor many-body interactions of protein and ligand atoms that may arise from integration over various configurations of the solvent. However, a simple form of eq 1 has two important advantages: (i) it has the same form for the in-water and in-vacuum force fields, and (ii) it has relatively few adjustable parameters, which can be fitted using available, not as numerous, experimental data on molecular crystals with known structure and solubility.

The number of adjustable parameter (A_{ij}, B_{ij}, α_i, ε, where $A_{ij} \equiv A_{ji}$, $B_{ij} \equiv B_{ji}$) is equal to $M(M + 1) + M + 1$, where M is the number of types of atoms considered. Actually, their number is even $3M + 1$, because the two-atom values A_{ij}, B_{ij} can be presented as products of single-atom values:[17]

$$A_{ij} \approx A^*_i A^*_j; \qquad B_{ij} \approx B^*_i B^*_j \qquad (4)$$

To speed up computations using molecular force fields, the atom−atom interactions in eqs 1 and 2 are usually (cf. ref 17) cut off at a distance $R_c \approx 10$ Å using functions of the kind

$$1/r^m \Rightarrow f_m(r, R_c) = \begin{cases} 1/r^m - (m+1)/R_c^m \\ \quad + mr/R_c^{m+1} & (\text{at } r \leq R_c) \\ 0 & (\text{at } r > R_c) \end{cases}$$

$$(5)$$

The functions $f_m(r, R_c)$ and their derivatives tend to zero at $r \rightarrow R_c$. The cutoff distance $R_c = 10$ Å is physically appropriate for the very short range vdW interactions, but it seems somewhat too severe to truncate the more long-range Coulomb forces at this distance. The cutoff distance of 20−30 Å seems to be more appropriate for the Coulomb forces, but, in this case, the computations slow down by an order of magnitude or more, because almost all atoms contain some partial charge. Therefore, we keep $R_c = 10$ Å (used in refs 17 and 39) also in this work, the main aim of which is to outline development of a polarizable atomic force field for an implicit water environment; in future, we plan to optimize the R_c values to obtain more accurate force fields.

As a result, the FF considered can be represented as

$$U_{noncov}\{\mathbf{r}\} = \sum_{(i,j)} [A_{ij} f_{12}(r_{ij}, R_c) - B_{ij} f_6(r_{ij}, R_c)]$$
$$+ \frac{1}{\varepsilon} \sum_{(i,j)} q_i q_j f_1(r_{ij}, R_c) - \frac{1}{2} \sum_i \alpha_i \mathbf{D}_i^2$$

$$(6)$$

where

$$\mathbf{D}_i = \sum_{j \in (i,j)} q_j f_2(r_{ji}, R_c) \cdot \mathbf{n}_{ji}$$

$$(7)$$

Unlike other works on FFs, where potentials are truncated after the final optimizing of the FF parameters (cf. ref 17), we will optimize the FF parameters (for the in-vacuum PFFSubl1.1 and in-water PFFSol1.1 separately) just for the truncated (at $R_c = 10$ Å) interactions, as specified by eqs 6 and 7. This must increase the resulting accuracy of the truncated FFs that will be used on practice.

Type of Atom. The type of atom that determines its properties in various interactions depends not only on its chemical kind, but also on its covalent surrounding. The typing of atoms for noncovalent interactions used here is accepted from the ENCAD FF;[17] it is shown in Table 1. (Here, we

Table 1. Types of Nonionized Atoms Used To Describe Noncovalent Interactions[a]

no.	type of atom	description of atom
1	H	nonpolar hydrogen
2	D	polar hydrogen
3	C	carbon $\rangle$C$\langle$ in sp^3 hybridization
4	A	carbon −C$\langle$ in sp^2 hybridization
5	O	oxygen O= in C=O group and −O− in rings
6	V	oxygen −O− in all groups, except for water and rings
7	W	oxygen −O− in water molecule
8	N	nitrogen: trivalent (including in −N$\langle$ in aromatic rings) and pentavalent
9	L	nitrogen N$\langle$ in aromatic rings
10	S	sulfur −S− in all groups

[a]In this work, we considered only molecular crystals composed of uncharged molecules; therefore, atoms of charged groups (like O in COO$^-$ group or N in NH$^+$, NH$_2^+$, and NH$_3^+$ groups) are not considered here.

confined ourselves to the atoms met in both proteins and in molecular crystals; a more detailed typing of atoms for noncovalent and covalent interactions are listed in Table A1.1, Supplement A1; see http://phys.protres.ru/resources/FFS/A1en.doc.)

Partial Charges. Partial charges of atoms are calculated using a quantum mechanical approach RESP (restricted electrostatic potential)[19,38,46] providing for an optimal pattern of spatial distribution of electrostatic potential around a molecule. A quantum mechanical optimization of the molecule's electron density was performed (starting from its crystal structure) using the PC GAMESS/Firefly QC program[47] (which is partially based on the GAMESS (US) code[48]) using the set of basis functions HF/6-31G* (see ref 47), recommended in ref 19. Having obtained an optimal electron configuration of the molecule, the charges of its electron clouds were ascribed to the nuclei of its atoms using the *resp* program from the Antechamber 1.27 package.[49]

Energy of Covalent Interactions. The energy of covalent interactions, U_{cov}, was used in the form and parametrization accepted in the ENCAD force field[17] for both the in-water and in-vacuum cases (see Tables A1.2−A1.5 in Supplement A1, http://phys.protres.ru/resources/FFS/A1en.doc). When the ENCAD parameters were insufficient for describing the molecules considered in this work, the missing parameters were added by similarity to the available ENCAD parameters, taking into account the equilibrium values of the bond lengths and angles from crystals available in CSD.[34] U_{cov} takes into account elastic deformation (depending on the involved atoms) of covalent bonds, covalent angles, dihedral angles, and (for the case when three atoms are bound to the fourth, central one) the angles of deviation of the "boundary" atoms from the plane formed by the remaining two covalent bonds.

Experimental Data Necessary for Computing In-Vacuum and In-Water Potentials. The values of the FF parameters (for both in-water and in-vacuum PFFs) were

4648

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optimized to provide the best description of the corresponding experimental data:

(a) the experimentally determined solubility of molecular crystals in water (for PFFSol1.1) and cohesion of the crystal molecules (for the in-vacuum PFFSubl1.1);

(b) the observed crystal geometry, including geometric parameters of crystal lattice and spatial structures and positions of molecules in crystal (for both PFFs).

Free energy of solution of the crystal molecules in water is formed of the enthalpy of their sublimation (i.e., transition from crystal to vapor) and the change in the mean force potential acting on molecule in water (as compared with that in vapor, which is practically zero).

The sublimation enthalpy of 1 mol of molecules is $\Delta H_{\text{subl}} = H_{\text{vap}} - H_{\text{cryst}}$, where $H_{\text{vap}} \equiv E_{\text{vap}} + PV_{\text{vap}}$ and $H_{\text{cryst}} \equiv E_{\text{cryst}} + PV_{\text{cryst}}$ are the enthalpies of 1 mol of molecules in saturated vapor and crystal, respectively. E_{vap}, E_{cryst} and V_{vap}, V_{cryst} are the corresponding energies and volumes, and P is pressure of saturated vapor. PV_{cryst} is close to zero, since $PV_{\text{vap}} \approx RT$ at low pressure (where R is gas constant and T is absolute temperature of vapor) and $V_{\text{cryst}} \ll V_{\text{vap}}$; thus, the difference between energies of molecules in crystal and vapor (calculated per mole) is

$$E_{\text{cryst}} - E_{\text{vap}} \approx -\Delta H_{\text{subl}} + RT \quad (8)$$

If the concentration of molecules dissolved in water, c_{aq}, is in equilibrium with $c_{\text{vap}} = 1/V_{\text{vap}}$, the concentration of the same molecules in vapor, then the mean force potential that additionally (as compared with the situation in vapor) acts on 1 mol of molecules in water is $\Delta\Phi_{\text{aq-vap}} = -RT \ln(c_{\text{aq}}/c_{\text{vap}})$. Note that $c_{\text{aq}}/c_{\text{vap}}$ at $c \to 0$ is the Henry's law constant $k_{\text{H,cc}}$ (related to a more frequently used Henry's constant $k_{\text{H,pc}} = \lim_{c \to 0}(P_{\text{vap}}/c_{\text{aq}})$ by the relation $k_{\text{H,cc}} = RT/k_{\text{H,pc}}$).[37] Thus, the difference between potential energies of molecules in crystal and aqueous solution is

$$\Delta\Phi_{\text{cryst-aq}} = E_{\text{cryst}} - E_{\text{vap}} - \Delta\Phi_{\text{aq-vap}}$$
$$\approx -\Delta H_{\text{subl}} + RT + RT \ln(k_{\text{H,cc}}) \quad (9)$$

In a classical approximation, the energies E_{cryst} and E_{vap} are formed of (a) potential energies of the main states of the molecule in crystal and gas (U_{cryst} and U_{vap}; note that intermolecular interactions contribute to U_{cryst} and do not to U_{vap}), (b) potential energies of the excited (nonquantum) degrees of freedom of the molecule in the corresponding phases, and (c) kinetic energies of all these degrees of freedom. The contribution of kinetic energy to the difference between E_{cryst} and E_{vap} is zero in the classical approximation, where all nonquantum degrees of freedom (note that they are the same for the molecule in gas and in crystal) are excited and have the kinetic energy $RT/2$. However, the potential energies of excited degrees of freedom differ, because the movements in all the free (in gas) degrees of freedom turn (in crystal) into vibrations. The potential energy of a free motion is zero, but it amounts to $\approx RT/2$ for a hindered (by the potential barrier with a height of $\geq RT$) motion. A molecule in gas has, as a whole, n_0 free translational and rotational degrees of freedom ($n_0 = 3$ for monatomic, $n_0 = 5$ for diatomic and all one-dimensional, $n_0 = 6$ for all remaining molecules that are considered in this work). In addition, it has in gas n_{rot} free internal rotations. Thus, the additional potential energy of the excited degrees of freedom of the molecule in crystal is by $(n_0 + n_{\text{rot}})RT/2$ larger than in gas,

i.e., $U_{\text{cryst}} - U_{\text{vap}} = E_{\text{cryst}} - E_{\text{vap}} - (n_0 + n_{\text{rot}})RT/2$. Consequently, the difference between potential energies of the main states of 1 mol of molecules in crystal and gas is

$$\Delta U_{\text{cryst-vap}} \equiv U_{\text{cryst}} - U_{\text{vap}}$$
$$\approx -\Delta H_{\text{subl}} + RT(1 - (n_0 + n_{\text{rot}})/2) \quad (10)$$

whereas the difference between the mean-force "potential energies" of the main states of 1 mol of molecules in crystal and water is

$$\Delta U_{\text{cryst-aq}} \approx -\Delta H_{\text{subl}} + RT(1 - (n_0 + n_{\text{rot}})/2)$$
$$+ RT \ln(k_{\text{H,cc}}) \quad (11)$$

Unlike the $\Delta\Phi_{\text{cryst-aq}}$ values, described by eq 9, the values $\Delta U_{\text{cryst-aq}}$ and $\Delta U_{\text{cryst-vap}}$, pertaining to the main states only, do not include the potential energy associated with thermal oscillations.

In this work, we consider only simple crystals composed of one type molecules for which (a) the crystal structure obtained at room temperature and pressure is available in CSD or other sources, and (b) the values ΔH_{subl} and $k_{\text{H,cc}}$ are either known at a "normal" temperature $T_0 = 298$ K or calculable from available tabular thermodynamic data; see refs 35−37. ($T_0 = 298$ K was chosen because the majority of tabular data refer to 25 °C; however, for the substances melting at $T_{\text{melt}} < T_0$, the value $\Delta H_{\text{subl}}(T_0)$ can be calculated using literature data by extrapolating from $\Delta H_{\text{subl}}(T_{\text{melt}})$; for details of these calculations see ref 36.) Besides, the selected molecules should be (a) not very flexible (to avoid significant intramolecular noncovalent interactions in gas and solution) and (b) not associated/dissociated in solution and/or gas. Finally, 58 molecules (listed in the Supporting Information, Table S1) were chosen for this work.

A more comprehensive description of these molecules with figures, thermodynamic parameters, and computation details is given in Additional Supplement A2; see http://phys.protres.ru/resources/FFS/A2.pdf.

It is noteworthy that the correlation between the in-vacuum $\Delta U_{\text{cryst-vap}}$ and the in-water $\Delta U_{\text{cryst-aq}}$ is rather weak (Figure 1).

Crystal Geometry. Parameters of crystal lattice are described by the vectors **a**, **b**, **c** (in Cartesian coordinates with unit vectors $\mathbf{e}_1$, $\mathbf{e}_2$, and $\mathbf{e}_3$: $\mathbf{a} = a_1\mathbf{e}_1$; $\mathbf{b} = b_1\mathbf{e}_1 + b_2\mathbf{e}_2$; $\mathbf{c} = c_1\mathbf{e}_1 + c_2\mathbf{e}_2 + c_3\mathbf{e}_3$; thus, $B = (a_1;b_1,b_2;c_1,c_2,c_3)$ is a generalized 6D vector, describing the crystal lattice). Here, the lattice vectors observed in crystal has $\mathbf{a}_{\text{cr}} = a_{1,\text{cr}}\mathbf{e}_1$; $\mathbf{b}_{\text{cr}} = b_{1,\text{cr}}\mathbf{e}_1 + b_{2,\text{cr}}\mathbf{e}_2$; $\mathbf{c}_{\text{cr}} = c_{1,\text{cr}}\mathbf{e}_1 + c_{2,\text{cr}}\mathbf{e}_2 + c_{3,\text{cr}}\mathbf{e}_3$, and the calculated equilibrium lattice vector has $\mathbf{a}_{\text{eq}} = a_{1,\text{eq}}\mathbf{e}_1$; $\mathbf{b}_{\text{eq}} = b_{1,\text{eq}}\mathbf{e}_1 + b_{2,\text{eq}}\mathbf{e}_2$; $\mathbf{c}_{\text{eq}} = c_{1,\text{eq}}\mathbf{e}_1 + c_{2,\text{eq}}\mathbf{e}_2 + c_{3,\text{eq}}\mathbf{e}_3$. Since the used crystallography data correspond to a room pressure (which is too low to deform the lattice), the equilibrium parameters are calculated at a zero pressure.

Spatial structures of the molecules of the central lattice cell (000) are specified by the set of coordinates of their atoms, $\{\mathbf{r}\}_{000}$. Then the atomic coordinates in the cell $\{m_1; m_2; m_3\}$ are $\{\mathbf{r}\}_{m1m2m3} = \{\mathbf{r}\}_{000} + m_1\mathbf{a} + m_2\mathbf{b} + m_3\mathbf{c}$, where **a**, **b**, and **c** are the lattice vectors. Correspondingly, the observed and calculated atomic coordinates are $\{\mathbf{r}_{\text{cr}}\}_{m1m2m3} = \{\mathbf{r}_{\text{cr}}\}_{000} + m_1\mathbf{a}_{\text{cr}} + m_2\mathbf{b}_{\text{cr}} + m_3\mathbf{c}_{\text{cr}}$ and $\{\mathbf{r}_{\text{eq}}\}_{m1m2m3} = \{\mathbf{r}_{\text{eq}}\}_{000} + m_1\mathbf{a}_{\text{eq}} + m_2\mathbf{b}_{\text{eq}} + m_3\mathbf{c}_{\text{eq}}$, respectively.

Optimization of Potentials of Noncovalent Interactions. Parameters of the required FF (ε; A_m^*, B_m^*, α_m, where $m = 1, ..., M$ are the atom types, see Table 1) were obtained by
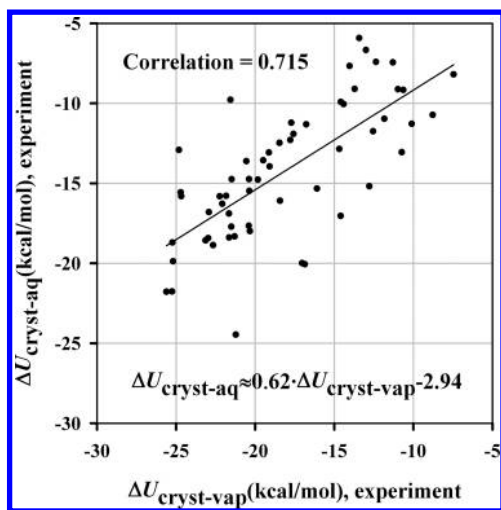
Figure 1. Correlation between the potential energy difference of the main states of molecules in crystal and gas ($\Delta U_{\text{cryst-vap}}$) and the mean-force "potential energy" difference of the main states of molecules in crystal and water ($\Delta U_{\text{cryst-aq}}$).

minimizing the discrepancies between the experimental and calculated (i.e., equilibrium for the given FF) values. In this process, the following characteristics are taken into account for each crystal k:

(a) Normalized square difference of the experimental, $\Delta U_{\text{exp}}^{(k)}$, and calculated, $\Delta U_{\text{calc}}^{(k)}$, energy (or mean-force energy, for the in-water case) of formation of crystal k from 1 mol of separate molecules:

$$[\Delta_1^{(k)}]^2 = [\Delta U_{\text{calc}}^{(k)}(\{\mathbf{r}\}, \{\mathbf{r}^{(\text{free})}\}) - \Delta U_{\text{exp}}^{(k)}]^2 / [\Delta U_{\text{exp}}^{(k)}]^2 \tag{12}$$

For the in-vacuum potentials, $\Delta U_{\text{exp}}^{(k)} = \Delta U_{\text{cryst-vap}}$; for in-water potentials, $\Delta U_{\text{exp}}^{(k)} = \Delta U_{\text{cryst-aq}}$ (for crystal k); see above the calculation of $\Delta U_{\text{cryst-vap}}$ and $\Delta U_{\text{cryst-aq}}$. The value

$$\Delta U_{\text{calc}}^{(k)}(\{\mathbf{r}\}, \{\mathbf{r}^{(\text{free})}\}) = U_{\text{cryst}}^{(k)}\{\mathbf{r}\} - U_{\text{free}}^{(k)}\{\mathbf{r}^{(\text{free})}\} \tag{13}$$

was calculated for the given (in-water or in-vacuum) FF using the coordinates $\mathbf{r}$ of the atoms in crystal k and the coordinates $\mathbf{r}^{(\text{free})}$ of the atoms of a free molecule sublimated from this crystal.

(b) The mean square difference between crystallographic ($\mathbf{a}_{\text{cr}}^{(k)}$, etc.) and calculated ($\mathbf{a}_{\text{eq}}^{(k)}$, etc.) lattice vectors of crystal k, normalized to the mean diameter of atom $\delta = 3$ Å:

$$[\Delta_2^{(k)}]^2 = [[(\mathbf{a}_{\text{cr}}^{(k)} - \mathbf{a}_{\text{eq}}^{(k)})^2 + (\mathbf{b}_{\text{cr}}^{(k)} - \mathbf{b}_{\text{eq}}^{(k)})^2 \\ + (\mathbf{c}_{\text{cr}}^{(k)} - \mathbf{c}_{\text{eq}}^{(k)})^2]/3]/\delta^2 \tag{14}$$

where $\mathbf{a}_{\text{cr}}^{(k)}$, $\mathbf{a}_{\text{eq}}^{(k)}$, $\mathbf{b}_{\text{cr}}^{(k)}$, and $\mathbf{b}_{\text{eq}}^{(k)}$ are coplanar and $\mathbf{a}_{\text{cr}}^{(k)}$ and $\mathbf{a}_{\text{cr}}^{(k)}$ parallel.

(c) The mean square difference between crystallographic and calculated coordinates of all $N_{\text{cell}}^{(k)}$ atoms of the crystal cell, normalized to the mean diameter of atom $\delta = 3$ Å:

$$[\Delta_3^{(k)}]^2 = \left[\sum_{i=1}^{N_{\text{cell}}^{(k)}} (\mathbf{r}_{\text{cr}}^{(i,k)} - \mathbf{r}_{\text{eq}}^{(i,k)})^2 / N_{\text{cell}}^{(k)} \right]/\delta^2 \tag{15}$$

For given FF and coordinates $\{\mathbf{r}\}_{000}$ of atoms in the crystal cell, the energy (or mean-force energy, for the in-water case) of molecule in crystal

$$U_{\text{cryst}}\{\mathbf{r}\} = [[U_{\text{cov}}\{\mathbf{r}\}_{000} + U_{\text{noncov}}\{\mathbf{r}\}_{000}] \\ + 1/2 \sum_{m_1,m_2,m_3}^{m_1^2+m_2^2+m_3^2 \geq 1} [U_{\text{noncov}}^{\text{intercell}} \\ (\{\mathbf{r}\}_{000}; m_1\mathbf{a} + m_2\mathbf{b} + m_3\mathbf{c})]]/Z \tag{16}$$

was obtained by dividing the sum of all interactions within one crystal k lattice cell (000) plus half-sum of all noncovalent interactions of the atoms of this cell with the atoms of other cells (shifted from the atoms of (000) according to vectors $\mathbf{a}$, $\mathbf{b}$, and $\mathbf{c}$ and located in the range R_c from them) by the number of molecules in the crystal cell, Z.

As for the energy (or mean-force energy, for the in-water case) of a free molecule, the coordinates of whose atoms are specified by the vectors $\{\mathbf{r}^{(\text{free})}\}$ (which may be distinct from the vectors $\{\mathbf{r}\}$, specifying the coordinates of the molecule in crystal), it is calculated as

$$U_{\text{free}}\{\mathbf{r}^{(\text{free})}\} = U_{\text{cov}}\{\mathbf{r}^{(\text{free})}\} + U_{\text{noncov}}\{\mathbf{r}^{(\text{free})}\} \tag{17}$$

Thus, the total discrepancy function is determined by the sum of discrepancies averaged over all K considered crystals:

$$\Delta^2 = \overline{\Delta_1^2} + \overline{\Delta_2^2} + \overline{\Delta_3^2} \\ = \frac{1}{K} \sum_{k=1}^{K} [\Delta_1^{(k)}]^2 + \frac{1}{K} \sum_{k=1}^{K} [\Delta_2^{(k)}]^2 + \frac{1}{K} \sum_{k=1}^{K} [\Delta_3^{(k)}]^2 \tag{18}$$

The optimal FF parameters (ε; A_i^*, B_i^*, α_i; $i,j = 1, ..., M$) were obtained by minimizing the discrepancy function Δ^2.

As the volume of the optimizing parameters is huge, the optimization comprises two stages:

(1) We optimized the values ε and A_i^*, B_i^* ($i,j = 1, ..., M$) as described in ref 39. This procedure includes a complete energy minimization of structures of crystals and separate ("free") molecules for each used set of the FF parameters. With optimization, in the result of this procedure, "precomputed" FF parameters, the "precomputed" equilibrium lattice vectors $\mathbf{a}_{\text{eq}}$, $\mathbf{b}_{\text{eq}}$, $\mathbf{c}_{\text{eq}}$ and atomic coordinates $\{\mathbf{r}_{\text{eq}}\}_{000}$ were obtained with the average (over the 58 used molecules) root-mean-square deviation of 0.2–0.3 Å from the experimental $\mathbf{a}_{\text{cr}}$, $\mathbf{b}_{\text{cr}}$, $\mathbf{c}_{\text{cr}}$, $\{\mathbf{r}_{\text{cr}}\}_{000}$ (see refs 39 and 40).

(2) Having fixed the obtained precomputed values A_i^*, B_i^* ($i = 1, ..., M$) and, for each molecule, $\mathbf{a}_{\text{eq}}$, $\mathbf{b}_{\text{eq}}$, $\mathbf{c}_{\text{eq}}$, $\{\mathbf{r}_{\text{eq}}\}_{000}$, $\{\mathbf{r}_{\text{eq}}^{(\text{free})}\}$ (and thus $U_{\text{cov}}\{\mathbf{r}\}$, $U_{\text{cov}}\{\mathbf{r}^{(\text{free})}\}$), we considered $U_{\text{noncov}}\{\mathbf{r}\}$ (as well as $U_{\text{noncov}}\{\mathbf{r}^{(\text{free})}\}$) in a form

$$\beta \cdot \sum_{(i,j)} [A_{ij}f_{12}(r_{ij}, R_c) - B_{ij}f_6(r_{ij}, R_c)] \\ + \frac{1}{\varepsilon} \cdot \sum_{(i,j)} q_i q_j f_1(r_{ij}, R_c) - \frac{1}{2} \\ \times \sum_i \alpha_i \Big[\sum_{j \in (i,j)} q_j f_2(r_{ji}, R_c) \cdot \mathbf{n}_{ji} \Big]^2 \tag{19}$$

which is a linear form in respect to the undetermined multipliers β, $1/\varepsilon$, and α_i ($i = 1, ..., M$). The discrepancies

$[\Delta_1^{(k)}]^2$ are now quadratic forms in respect to the undetermined multipliers, as well as the discrepancy $\overline{\Delta_1^2} = (1/K)\sum_{k=1}^{K}[\Delta_1^{(k)}]^2$. The quadratic form allows its unambiguous analytical minimization in respect to these undetermined multipliers β, $1/\varepsilon$, $\alpha_1,...,\alpha_M$ at the background of the already precomputed values $A_1^*,... A_M^*$, $B_1^*,... B_M^*$ values (and vectors $\mathbf{a}_{eq}$, $\mathbf{b}_{eq}$, $\mathbf{c}_{eq}$, $\{\mathbf{r}_{eq}\}_{000}\{\mathbf{r}_{eq}^{(free)}\}$ for each molecule, which give $U_{cov}\{\mathbf{r}\}$ and $U_{cov}\{\mathbf{r}^{(free)}\}$ for them).

In this way, we obtain the final values of all the optimized force field parameters: $1/\varepsilon$, $A_i^* = \sqrt{\beta\cdot(A_i^*)}_{precomputed}$, $B_i^* = \sqrt{\beta\cdot(B_i^*)}_{precomputed}$, α_i ($i = 1, ..., M$).

■ RESULTS AND DISCUSSION

Calculation and Testing of Potentials of the Auxiliary In-Vacuum Force Field PFFSubl1.1. This is the first step of our study. We start with the precomputed (using FFSubl; see ref 39) values A_i^*, B_i^* ($i = 1, ..., M$) and, for each molecule, $\mathbf{a}_{eq}$, $\mathbf{b}_{eq}$, $\mathbf{c}_{eq}\{\mathbf{r}_{eq}\}_{000}\{\mathbf{r}_{eq}^{(free)}\}$ (it is noteworthy that the precomputed vectors $\{\mathbf{r}_{eq}\}_{000}$, $\mathbf{a}_{eq}$, $\mathbf{b}_{eq}$, $\mathbf{c}_{eq}$ describe the crystallographic coordinates with the accuracy of 0.2−0.3 Å, see ref 39). Then, we optimized the undetermined multipliers β, $1/\varepsilon$, and α_i ($i = 1, ..., M$) in U_{noncov} given by eq 19, so as to minimize the discrepancy $\overline{\Delta_1^2} = \sum_{k=1}^{K}[\Delta_1^{(k)}]^2/K$. Thus, we obtain the final values of all the optimized PFFSubl1.1 parameters $1/\varepsilon$, $A_i^* = \sqrt{\beta\cdot(A_i^*)}_{precomputed}$, $B_i^* = \sqrt{\beta\cdot(B_i^*)}_{precomputed}$, α_i ($i = 1,..., M$).

Table 2 presents the obtained atomic parameters of the PFFSubl1.1, optimized at the set of crystal structures and sublimation energies of the 58 used molecules.

Table 2. Set of Atomic Parameters of Nonionized Atoms for the In-Vacuum Force Field PFFSubl1.1[a]

type of atom	A^*_i (Å^6 (kcal/mol)$^{1/2}$)	B^*_i (Å^3 (kcal/mol)$^{1/2}$)	α_i (Å^3)
H	103.53	6.53	1.34
D	0.27	0.87	0.73
C	993.8	21.26	4.63
A	1213.64	25.95	−0.93
O	192.30	14.46	−0.66
V	396.63	17.26	−0.44
W	667.96	33.18	−3.37
N	1224.75	33.29	1.18
L	801.04	34.48	0.47
S	1717.78	51.39	−36.42
dielectric permittivity		$\varepsilon = 1.673$	
$\langle \lvert\Delta U_{calc}^{(k)} - \Delta U_{exp}^{(k)}\rvert / \lvert\Delta U_{exp}^{(k)}\rvert\rangle$[b]		4.18%	

[a]The optimized value of β (used to compute A^*_i, B^*_i from the precomputed[39] in-vacuum ones) is 0.953 27. [b]Mean relative energy deviation for 58 molecules.

It is noteworthy that the obtained ε value optimized for the vacuum ↔ crystal transition is in between the ε values for the vacuum (1) and molecular crystals (where $\varepsilon \approx 3-4$, see refs 35 and 50).

Table 2 also presents the mean relative deviation of the computed from the experimental cohesion energies, while Figure 2 shows the correlation of these energies. One can see that the computed by PFFSubl1.1 values are in good concordance with the experimental ones.

It is useful to compare the obtained results with those obtained by the other FFs. This comparison was done with force fields CFF II (also adjusted to crystal structures),[51]
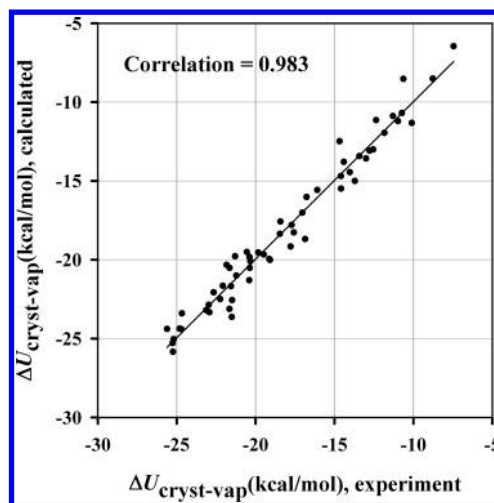

Figure 2. Correlation of the experimental and calculated cohesion energies for the in-vacuum force field PFFSubl1.1 applied to all 58 studied molecular crystals formed from sublimated molecules.

QMPFF3 (adjusted to quantum-mechanical calculations of simple molecules and tested on crystals)[52] and nonpolarized FFSubl;[39] see Table 3.

Table 3. Mean Relative Energy Deviation between Computed and Experimental Cohesion Energies, $\langle\lvert\Delta U_{calc}^{(k)} - \Delta U_{exp}^{(k)}\rvert/\lvert\Delta U_{exp}^{(k)}\rvert\rangle$, for the Crystals Used in Calculations with the Compared Fields

compared force fields	no. of common crystals used in the compared works	rel mean diff between computed and exptl cohesion energies ΔU (%)
CFF II (ref 51)	7	6.7
PFFSubl1.1		2.2
QMPFF3 (ref 52)	30	7.5
PFFSubl1.1		3.4
FFSubl (ref 39)	58	6.3
PFFSubl1.1		4.2

One can see that PFFSubl1.1 better reproduces the cohesion energies than CFF II and QMPFF3. This can be due to a more careful procedure of potential adjustment used in this work that (following ref 39) minimizes the deformation of crystals by the applied FF, but it can be also due to a somewhat more crude estimate of the experimental cohesion energies used in refs 51 and 52. However, one can see also that the polarized PFFSubl1.1 gives only a little better results than the nonpolarized FFSubl.

Calculation of Potentials of the In-Water Force Field PFFSol1.1. This is the main goal of our study. We start with the precomputed (using FFSol; see ref 39.) values A_i^*, B_i^* ($i = 1, ..., M$) and, for each molecule, $\mathbf{a}_{eq}$, $\mathbf{b}_{eq}$, $\mathbf{c}_{eq}\{\mathbf{r}_{eq}\}_{000}\{\mathbf{r}_{eq}^{(free)}\}$. Then, we optimized the undetermined multipliers β, $1/\varepsilon$, and α_i ($i = 1, ..., M$) in $U_{noncov}\{\mathbf{r}\}$ given by eq 19, so as to minimize the discrepancy $\overline{\Delta_1^2} = \sum_{k=1}^{K}[\Delta_1^{(k)}]^2/K$. As a result, we obtain the final values of all the optimized PFFSol1.1 parameters $1/\varepsilon$, $A_i^* = \sqrt{\beta\cdot(A_i^*)}_{precomputed}$, $B_i^* = \sqrt{\beta\cdot(B_i^*)}_{precomputed}$, α_i ($i = 1,..., M$).

Table 4 presents the obtained atomic parameters of the PFFSol1.1, optimized at the set of crystal structures and sublimation + solvation energies of the 58 molecules used.

Table 4. Set of Atomic Parameters of Nonionized Atoms for the In-Water Force Field PFFSol1.1[a]

type of atom	A^*_i (Å^6 (kcal/mol)$^{1/2}$)	B^*_i (Å^3 (kcal/mol)$^{1/2}$)	α_i (Å^3)
H	103.52	7.33	−0.82
D	0.23	0.33	−1.26
C	1292.50	22.46	−9.04
A	1164.66	24.02	−3.64
O	163.49	9.93	3.16
V	729.02	28.12	2.81
W	400.85	24.68	3.01
N	1320.71	36.56	−1.00
L	393.31	17.44	10.89
S	2031.39	47.21	−34.76
dielectric permittivity		$\varepsilon = 4.603$	
$\langle |\Delta U^{(k)}_{calc} - \Delta U^{(k)}_{exp}| / |\Delta U^{(k)}_{exp}| \rangle$[b]		8.36%	

[a]The optimized value of β (used to compute A^*_i, B^*_i from the precomputed[39] in-water ones) is 1.016 93. [b]Mean relative energy deviation for 58 molecules.

Table 4 presents also the mean relative deviation of the computed from the experimental cohesion energies, while Figure 3 shows the correlation of these energies.
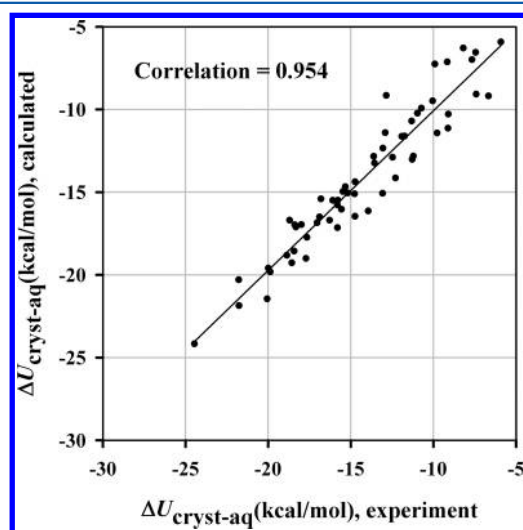
Figure 3. Correlation of the experimental and calculated cohesion energies for the in-water force field PFFSol1.1 applied to all 58 studied molecular crystals formed from water-dissolved molecules.

One can see that the values computed by PFFSol1.1 for the in-water cohesion are in good concordance with the experimental values obtained from the crystal dissociation in water. The correlation for the PFFSol1.1 is only a little worse than that obtained from the in-vacuum FF PFFSubl1.1 for the in-vacuum cohesion, although the correlation between the in-water and in-vacuum cohesion energies is rather poor (see Figure 1).

It is noteworthy that the obtained ε value optimized for the water ↔ crystal transition is in between the ε values for water (≈ 80) and molecular crystals (where $\varepsilon \approx 3-4$, see refs 35 and 50), but closer to the crystals.

Comparison of Tables 2 and 4 (summarized in Table 5) shows that parameters of PFFSol1.1 are different from the parameters of PFFSubl1.1 mainly in the following respects: (1) as it can be expected, the ε value in the in-water PFFSol1.1 is much greater than in the in-vacuum PFFSubl1.1; (2) the values

Table 5. Ratio of the In-Vacuum (PFFSubl1.1) and In-Water (PFFSol1.1) Parameters

type of atom	A_i^*(in-vacuum)/ A_i^*(in-water)	B_i^*(in-vacuum)/ B_i^*(in-water)	α_i(in-vacuum)/ α_i(in-water)
H	1.000	0.891	−1.634
D	1.174	2.636	−0.579
C	0.769	0.947	−0.512
A	1.042	1.080	0.255
O	1.176	1.456	−0.209
V	0.544	0.614	−0.157
W	1.666	1.344	−1.120
N	0.927	0.911	−1.180
L	2.037	1.977	0.043
S	0.846	1.089	1.048
mean	1.118	1.294	−0.404
std dev	0.439	0.604	0.783
std dev/mean	0.392	0.466	−1.935
ε(in-vacuum)/ ε(in-water)		0.363	

B^*, responsible for vdW attraction of polar hydrogens (D) are much smaller in the PFFSol1.1 than in the PFFSubl1.1; (3) the values A^* and B^*, responsible for vdW repulsion and attraction of nitrogens in aromatic rings (L) are much smaller in the PFFSol1.1 than in the PFFSubl1.1; (4) as expected, the atomic polarizabilities α usually have opposite signs in the in-water PFFSol1.1 and in-vacuum PFFSubl1.1, because they describe attraction of polarizable atoms *into* the intense electric field in the in-vacuum case and repulsion of the implicit atom-imbedding water cavity *from* the intense electric field in the in-water case.

It should be noted that the polarized force fields PFFSol1.1 and PFFSubl1.1 developed in this work perform better than the earlier (using the same set of experimental data) developed[39] nonpolarized force fields FFSol and FFSubl: the correlation of computed and experimental cohesion energies for the in-vacuum FFSubl and PFFSubl1.1 is 0.954 and 0.983, respectively, and for the in-water FFSol and PFFSol1.1 it is 0.920 and 0.954, respectively.

For the final control, we performed the same, as above, optimization of the potential parameters using two "half-sets" of the molecules listed in Table S1 (in the Supporting Information), and applied the potentials obtained from the first half-set to calculate the cohesion energies for this *and* another half-set, and vica versa (cf. ref 39). In both cases, these calculated cohesion energies correlate with experiment at the level 94−97% for PFFSubl1.1 and 90−94% for PFFSol1.1, which shows that the obtained potentials are transferable from one set of molecules to the other. However, the examination of potentials obtained from the half-sets for identical atoms revealed that their A_i^* (as well as B_i^*) values can differ by $\sim\pm 20\%$ and sometimes more, while deviations for α_i values can be even greater. Together with a good reproduction of cohesion energies by the half-set-derived parameters of the force fields PFFSubl1.1 and PFFSol1.1, this shows that both these force fields are more or less confluent (which especially concerns the polarizability terms): they allow a spectrum of equally good solutions.

■ CONCLUSIONS

It would be only natural to expect that the in-water PFFSol1.1, which considers water surrounding in a crude implicit approximation, will give a considerably worse approximation to the

experimental cohesion energies ΔU_{exp} in water than the stricter in-vacuum PFFSubl1.1. However, a comparison of the last lines of Tables 2 and 4 shows that PFFSol1.1 and PFFSubl1.1 demonstrate approximately equal and high accuracy. This corroborates our suggestion that the in-water potentials (i.e., potentials of the atom−atom interactions in the implicit water environment) may have the same functional form (given by eq 1) as the normal, in-vacuum potentials, but with modified interaction parameters.

The potentials of noncovalent interactions obtained in this study for the in-vacuum interactions work satisfactory (at the level and even better than potentials of the other modern force fields), but, which is more important, we obtained fundamentally novel (and well-working) potentials of the in-water force field PFFSol1.1 that describe interactions of atoms in the implicitly given water environment.

It should be noted, however, that all the obtained here potentials of noncovalent interactions have been obtained on the basis of the given (by the FF ENCAD)[17] potentials of covalent forces. If the covalent forces would be taken from some other FF, the potentials of noncovalent interactions should be recalculated, and this work gives an algorithm of such a recalculation. It is noteworthy that this algorithm is applicable to both inclusion of polarization potentials in the currently nonpolarizable force fields and to inclusion of new terms (such as many-atom vdW interactions[45]) in the current force fields.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
List of the main crystallographic and thermodynamic data for 58 molecules used for optimization of in-vacuum and in-water potentials of noncovalent interactions at 25 °C and other relevant details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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