ORIGINAL PAPER

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AIPAR: ab initio parametrization of intermolecular potentials for computer simulations

Abstract An unambiguous, fully ab initio and automated technique denoted AIPAR ("ab initio parametrization") implemented in the SJBR program has been proposed to yield intermolecular interaction potentials between polar molecules and water. The AIPAR procedure has been applied to several organic molecules covering a wide range of structure and functional groups, namely methanol, acetone (propanone), methanethiol (methyl mercaptan), imidazole (1,3-diazole), oxazole and furan. The AIPAR-derived sets of parameters compare well with the empirical OPLS ones, mainly when the all-atoms model is employed in the OPLS procedure. Monte Carlo simulations were performed for an aqueous solution of methanol and for an equimolar binary mixture methanol–water using the AIPAR and OPLS parameters. The thermodynamic and geometric results obtained with the parameters obtained with the AIPAR procedure compare favorably with the OPLS simulations, even for the binary mixture, demonstrating the precision, robustness and transferability of the parameters obtained with the AIPAR procedure.

Keywords Hydration · Simulation · Ab initio potentials · Monte Carlo · Parametrization

Introduction

Molecular simulations of aqueous solutions of polar solutes are important for rationalization and even prediction of several chemical and biological processes, such as reactions [1–3] and spectroscopy [4, 5]. In order to perform computer simulations of chemical processes in aqueous solutions, it is necessary to determine the solute–solvent and solvent–solvent interaction potentials. This can be accomplished by empirical [6, 7] or ab initio [8, 9] methods, where, usually, a simple analytical functional form of the potentials is fitted to reproduce experimental or calculated data. The OPLS procedure [10] and particularly the TIPnP ($n = 3$–5) family of water potentials is one of the most successful empirical methods for computer simulation, probably, due to its compromise between precision and practicability. As for the ab initio type parametrization (AIPAR), a more elaborated functional form for the potential can be employed as well as a larger number of parameters can be considered because of the large amount of information available. Despite being more flexible and robust, these elaborate functional forms are more demanding when used in large computer simulations. In addition, for the ab initio parametrization it is necessary to establish which solute–water configurations will be used for adjusting the potential parameters. As for any parametrization procedure, the choice of these configurations is one of the determining steps defining the performance and quality of the resulting potential interaction.

As a result, we propose a method that uses a simple potential function (Coulomb plus Lennard-Jones) for the solute–water interactions parametrized from ab initio calculations as well as TIP4P for water–water interactions. The guiding principles for devising this method were: (1) applicable for medium and possibly large polar solute molecules, (2) transferable set of parameters, that can be used with other solvents and solutes, (3) the configurations are generated from the isolated properties of the solute, (4) requires minimum user intervention, preferably fully automated, and (5) free of any arbitrariness. The first concern is the generation of the appropriate configurations for the ab initio calculations of the solute–water interaction energies. For a proper sampling of the phase space, it is important also to consider high-energy configurations, so that we have

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incorporated in the method the ability to generate and use the most stable as well as some high-energy configurations of solute–water. These configurations are obtained unambiguously from the isolated solute molecule based upon electrostatic considerations. Once these configurations are defined, their energies are determined by molecular orbital ab initio calculations, and the solute–water interaction energies are obtained after being corrected for the basis set superposition error (BSSE). These interaction energies are used in a multivariate simplex fitting of the potential function parameters. This whole procedure is denominated Ab Initio Parametrization (AIPAR) and has been implemented in a program called SJBR. This method has been tested for some representative molecules (heterocycles, methanol, methanethiol, propanone) and is compared to the OPLS parameters and computer simulations.

Methodology

The crux of the AIPAR approach is the generation of the solute–water configurations to be used in the fitting of the interaction potential. In this section we describe how these configurations are unambiguously generated from the solute electrostatic potential, the fitting procedure and the Monte Carlo simulation of some aqueous solutions.

solute–water configurations

From classical electrostatics [11], we know that the electrostatic interaction energy, E_{elect}, is proportional to the electrostatic potential, $\Phi(r)$, namely, $E_{\text{elect}} = q\Phi(r)$, with q the probe charge. Also, the dipole interaction energy between a vector dipole, μ, and an electric field, $\mathbf{E}$, is given by $E_{\text{dip}} = -\mathbf{E} \cdot \mu = \nabla \Phi(r) \cdot \mu$. As a result, the solute–water configurations were chosen as follows [12]: (1) a large cube is constructed such that it encloses the solute and hundreds of water molecules; (2) an uniform grid of points separated by 0.1 nm is generated within the cube and the points within the molecular surface of the solute are disregarded (the solute molecular surface is defined by the spheres centered on each atom of the solute molecule, with the following radii: C = 0.27 nm, N = 0.27 nm, O = 0.27 nm, S = 0.27 nm and H = 0.20 nm); (3) the electrostatic potential, $\Phi(r)$, at each point within the cube is computed from the wavefunction; (4) the largest hundred absolute values of the electrostatic potential were used to place the oxygen atom of the water molecule, thus defining the positions of the water molecules; (5) the electric field $\mathbf{E}$ at each point is approximated by finite difference between the neighboring points and the dipole moment of the water molecule is aligned to the electric field, thus defining the orientations of the water molecules; and (6) finally, the dihedral angle that will complete the definition of the water molecule with respect to the solute is chosen pseudo-randomly, that is, the same seed is used for the random

number generator algorithm for all configurations, thus allowing that low as well as slightly higher interaction energy configurations to be sampled. It should be noted that even though the largest hundred absolute values of the electrostatic potential are selected, they usually are not local extremes on the surface, so that the electric field is non-zero.

Potential function

The solute–water interaction potential is described by three contributions: repulsion, London and coulombic forces, which are modeled by the Lennard-Jones plus Coulomb functions. Thus, the pair-wise interaction potential takes the well-known form,

$$u(r_{ij}) = \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right] + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \tag{1}$$

where, q_i are the charges, A_{ij} and B_{ij} are pair-parameters obtained from the combination rules, $A_{ij} = (A_i A_j)^{1/2}$ and $B_{ij} = (B_i B_j)^{1/2}$, and the site-parameters $A_i = 4\varepsilon_i \sigma_i^{12}$ and $B_i = 4\varepsilon_i \sigma_i^{6}$ can be expressed in terms of the Lennard-Jones parameters ϵ_i and σ_i for each site i, r_{ij} is the distance between sites i and j and ϵ_0 is the electric constant.

Molecular orbital calculations

All ab initio molecular calculations, namely, solute molecular structure, solute electrostatic potential, solute fitted atomic charges and solute–water pair interaction energies, were performed at the MP2/6-31G* level [13] with the Gaussian 94 program [14]. Ab initio calculations were performed for each configuration generated by the previous approach for one solute molecule in the presence of one water molecule. The solute–water pair interaction energies were calculated as the difference between the total energy of the solute–water pair and the total energies of the solute and the water molecules in the presence of the basis set of their counterpart, the so-called counterpoise method [15] for correcting the BSSE. The molecular structure of the solute is the same as one obtained with the MP2/6-31G* method for the isolated molecule and that of the water molecule is the one used in the TIP4P model [10], namely, bond distance O–H = 0.09572 nm and bond angle H–O–H = 104.52°.

The parametrization procedure

The solute atomic charges were determined by the CHELPG fitting procedure [16] for every solute atom (all-atoms parametrization) or for all heavy atoms (united-atoms parametrization), by adding the hydrogen charges to the heavy atom attached to them. The atomic charges for the water molecule were the same as defined by the

TIP4P model, namely, $q(H) = 0.52\,e$ and $q(M) = -1.04\,e$. For each solute–water configuration the Coulomb energy was calculated with these atomic charges, and subtracted from the calculated ab initio interaction energy. This generates the non-coulombic contribution to the interaction potential, which is then used to adjust the Lennard-Jones parameters (ϵ_i and σ_i) with a multivariate simplex algorithm. The initial guess for the ϵ and σ parameters were average OPLS values.

The SJBR program

The AIPAR procedure has been implemented in the SJBR program [17] written in standard FORTRAN77. The AGOA [12] program was used to generate the solute–water configurations from the electrostatic potential represented in a cubic grid. It should be noted that all files used in the SJBR program are written in formatted ascii, which are readable by the user, so that the execution of the program can be followed and/or intervened upon. In addition, the routines can be easily modified to interface with other ab initio programs besides Gaussian 94 and also to allow forms for the non-coulombic function other than the Lennard-Jones.

Monte Carlo simulations

Monte Carlo (MC) simulations have been performed for the methanol–water system. In one MC simulation, the methanol molecule was used as a solute (one molecule) within a box with 300 TIP4P water molecules. The other MC simulation consisted of a binary methanol–water solution described by a cubic box containing 125 methanol and 125 TIP4P water molecules. All MC simulations employed the standard Metropolis algorithm for liquid simulation [18] implemented in the DIADORIM program [19, 20] at 25 °C and 1 atm in an isothermical–isobarical (NPT) ensemble with trial box volume changes at every 1,000 MC configurations, that is, particle trial moves. Starting from previously equilibrated boxes, 2×10^6 MC configurations were performed for equilibration, followed by 24×10^6 (methanol as solute) and 16×10^6 (binary methanol–water solution) MC configurations for averaging.

Results and discussion

The results for the methanol molecule in water are presented and discussed in greater detail. For the other molecules only some particularities will be stressed, since they followed the same trends. Figure 1 represents the superimposed configurations obtained with the SJBR program (AGOA procedure) for water around the methanol molecule.

It should be noted that this approach, the AGOA procedure, for generating solute–water configurations is automated and unambiguous, providing structures that
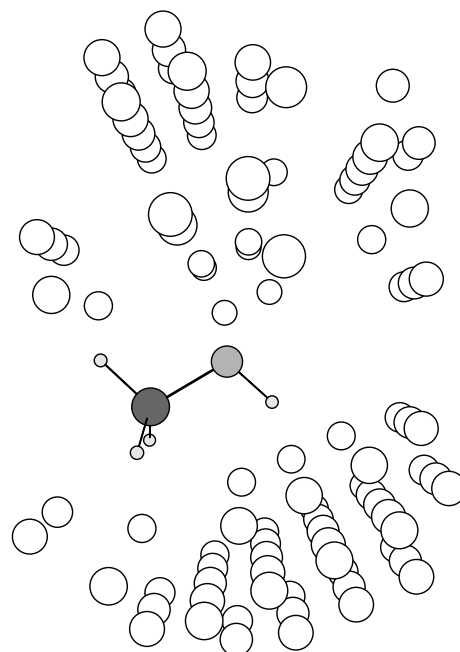

Fig. 1 Superimposed configurations of water (without the hydrogen atoms) around the methanol molecule obtained with the AGOA procedure

can be used to compute energies for fitting of the solute–water interactions. In addition, it is based only upon the electrostatic potential of the isolated solute molecule, which can be obtained at several theoretical levels including semiempirical ones. This approach has been successfully tested for generating configurations of the β-carboline molecule surrounded by water molecules. [12]

The non-coulombic energy for each configuration in Fig. 1 is presented in Fig. 2 with and without the counterpoise correction (CC) for the basis set superposition error (BSSE).

In addition to the known importance of the BSSE correction for describing intermolecular interactions, in the particular case of Fig. 2 it is also clear the importance of the BSSE correction for obtaining a smooth, systematic and quasi-symmetric dependence of the non-coulombic energies with respect to the solute–water configuration. The quasi-symmetric feature is relevant since it shows that the AIPAR procedure yields a slightly larger number of stabilizing non-coulombic energies than destabilizing ones. These BSSE corrected non-coulombic energies are then used to fit the Lennard-Jones parameters of the methanol molecule and the results for the united-atoms (CH_3) model are presented in Table 1 with the OPLS parameters [21] for comparison.

It can be observed that the charge distribution is almost the same for both models, reflecting the good quality of the set of charges obtained from ESP fitting (CHELPG). The σ and ϵ parameters are also in good agreement with the trends reproduced by the AIPAR procedure. In particular, the larger σ parameter for the
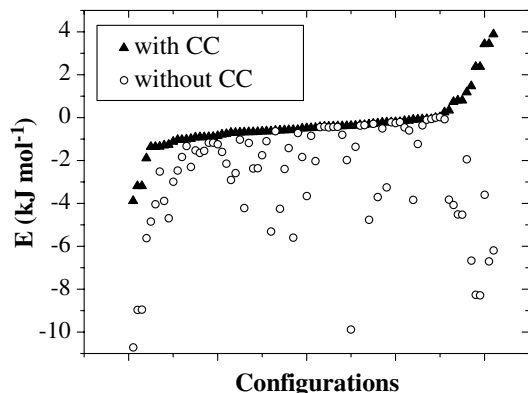
Fig. 2 Calculated non-Coulombic energies with (*solid triangles*) and without (*open circles*) the counterpoise correction (CC) for the BSSE

Fig. 3 Radial distribution functions, $g(r)$, for the Hw–Om, Ow–Hm and Ow–Cm pairs. Methanol (solute) in water

Table 1 United-atoms parameters, q (e), σ (nm) and ϵ (kJ mol^{-1}), for the methanol molecule

Site	AIPAR[a]			OPLS [20]		
	q	σ	ϵ	q	σ	ϵ
H(1)	0.408	0.000 (0.000)	0.000 (0.000)	0.435	0.000	0.000
O(2)	−0.645	0.311 (0.350)	0.500 (0.120)	−0.700	0.307	0.710
C(3)	0.237	0.391 (0.376)	0.590 (0.854)	0.265	0.3775	0.870

[a] The charges, q, were obtained from the CHELPG procedure and were not adjusted during the fitting procedures for obtaining σ and ϵ parameters. The results in parenthesis were obtained using the CHELPG charges for the water molecule

Table 2 Average properties from MC simulations

Property	AIPAR	OPLS
Density (kg m^{-3})	770	860
Average water–water interaction (kJ mol^{-1})	−23.60	−23.89
Average methanol–methanol interaction (kJ mol^{-1})	−13.26	−19.92
Average water–methanol interaction (kJ mol^{-1})	−15.40	−17.36
Enthalpy of vaporization (kJ mol^{-1})	36.32	41.76

carbon site obtained with the AIPAR procedure reflects the discrete presence of the hydrogen atoms in the CH$_3$ united-atoms model when compared to the OPLS procedure. This also leads to a smaller value of the ϵ parameter since they are coupled during the fitting procedure. We consider the agreement between AIPAR and OPLS to be good since the differences are small considering that the parameters are obtained from completely distinct procedures. The OPLS parameters are obtained by fitting to experimental data (density, heat of vaporization, radial distribution functions, etc.) for the liquid, whereas the AIPAR parameters are obtained from fitting ab initio molecular orbital calculations for the solute–water pair. Despite of the absolute differences being small, the question about their effects in the computer simulation of solutions still remains. We have thus performed computer simulations with the AIPAR and OPLS [21] parameters for methanol as a solute in water and for an equimolar methanol–water solution. For the former system, the average methanol–water interaction energies are −80.37 ± 1.42 and −67.28 ± 1.34 kJ mol^{-1} for the OPLS and AIPAR models, respectively. The larger stability for the OPLS model is probably due to the larger charge separation observed for this model compared to the AIPAR charges (see Table 1), since the Coulombic contribution for
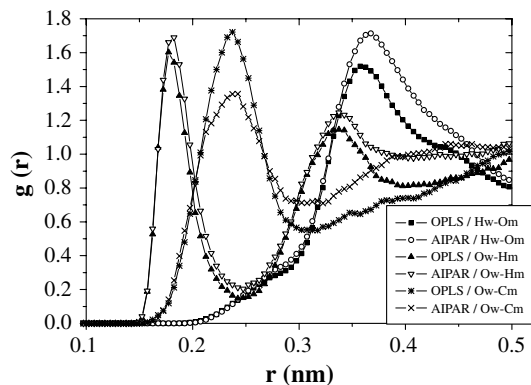
the intermolecular energy is dominant in the methanol–water interaction.

The radial distribution functions (RDFs) for the hydrogen atom of the water and the oxygen atom of the methanol, Hw–Om pair, the oxygen atom of the water and the hydrogen atom (H1) of the methanol, Ow–Hm pair and the oxygen atom of the water and the carbon site of the methanol Ow–Cm pair, are shown in Fig. 3.

It can be observed from Fig. 3 that the liquid structure, including the hydrogen bond patterns, is very similar for the two models (OPLS and AIPAR). The positions of the maxima and minima are almost coincident and the heights of the peaks are very similar, except for the Ow–Cm pair, probably due to the differences between the σ and ϵ parameters.

For the equimolar methanol–water mixture, the average results obtained in the MC simulations for each model are shown in Table 2.

The smaller charge separation in the AIPAR compared to the OPLS procedure has important consequences in the thermodynamic properties of the binary mixture. The electrostatic interactions are smaller, leading to smaller densities and enthalpy of vaporization. It should be noted, however, that the methanol parameters were obtained from ab initio calculations of the methanol–water pair and are now being used to describe methanol–methanol interactions. As a result, this equimolar mixture simulation can be considered a

very stringent test of the AIPAR procedure, which seems to be quite satisfactory to confirm the transferability of these parameters.

Regarding the structural properties of the liquid mixture, they were analyzed through the RDFs for the following pairs: (1) Om–Hw represents the methanol oxygen atom and the hydrogen atoms of water molecule, (2) Ow–Cm the water oxygen atom and the methanol carbon site, (3) Om–Hm the oxygen and the hydroxyl hydrogen atoms of the methanol molecules and (4) Om–Cm the oxygen atom and the carbon site of the methanol molecules. The RDFs for the pairs defined in (1) and (2) and (3) and (4) are presented in Fig. 4a, b, respectively.

As expected, the agreement between the AIPAR and the OPLS procedures is very good for the pairs involving water and methanol molecules. However, for the pairs between methanol molecules, the discrepancies are larger, mainly for the heights of the peaks in the RDF. Although these results are not as good as the former ones, they demonstrate the transferability of the AIPAR parameters for methanol, at least for structural properties.

The distributions of the average intermolecular energies with respect to the intermolecular distance and the relative number of molecules are presented in Fig. 5a, b, respectively.
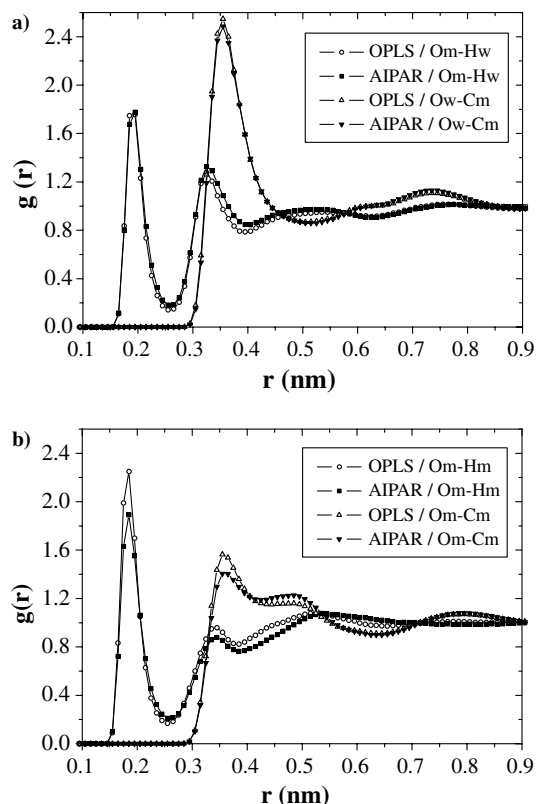
It can again be observed from Fig. 5 that the geometric (a) and energetic (b) results for the hydrogen bonds between methanol–water obtained with the AIPAR parameters are in better agreement with the OPLS results than between methanol–methanol. It should also be noted that the OPLS model for the methanol molecule predicts hydrogen bonds slightly more stable than the AIPAR procedure, but it does not affect the O···H distances in hydrogen bonds observed in the RDF's (Fig. 4).

Another structural property analyzed was the angular distribution between methanol–water and methanol–methanol pairs. This angular distribution is represented by the average of the cosine of the angle (ϕ) between the dipole moments of the molecule pair. The results for the AIPAR and OPLS models are shown in Fig. 6. The qualitative agreement of the AIPAR angular distributions with the OPLS ones is very good, and similarly to the radial distribution functions. The discrepancies are in the peak heights.

Thus, the AIPAR procedure seems appropriate for yielding structural properties of aqueous solutions and even of equimolar binary mixture of methanol and water.

In addition to methanol, several other molecules representing a wide range of organic functional groups

Fig. 4 Radial distribution functions, $g(r)$, for the Om–Hw and Ow–Cm pairs (a) and the Om–Hm and Om–Cm pairs. (b) Equimolar methanol–water mixture
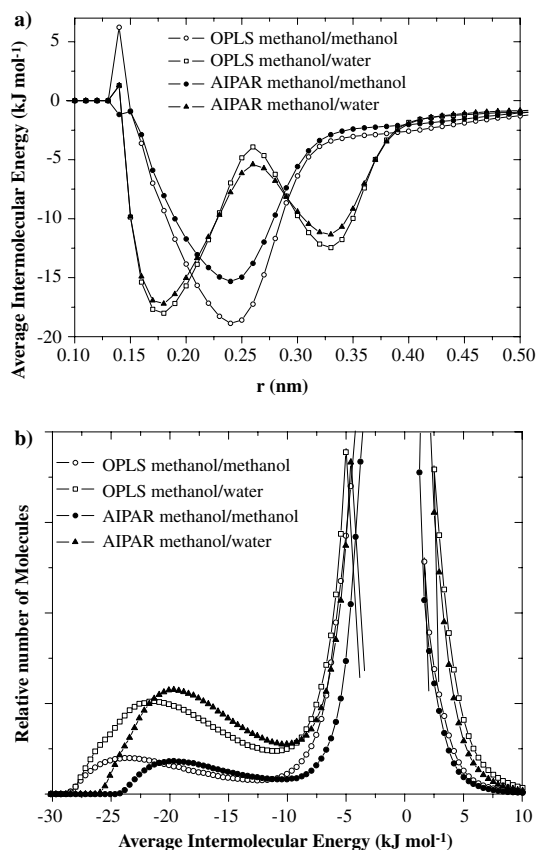

Fig. 5 Dependence of the average intermolecular energies with the (a) intermolecular distances (Hm−Ow pair for the methanol/water and Hm−Hm pair for the methanol/methanol interactions) and (b) relative number of molecules
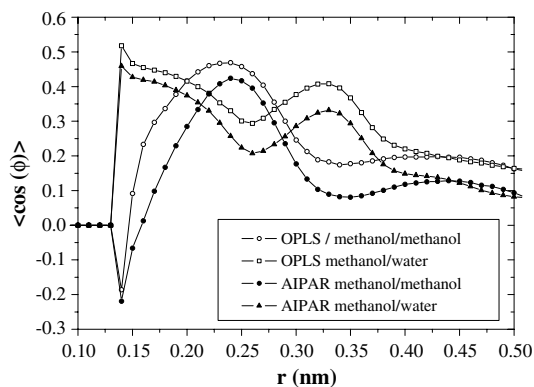
Fig. 6 Dependence of the average cosine between the vectors defined by the molecular dipole moments with respect to the intermolecular distance

have been parametrized with the AIPAR procedure. These molecules and the atomic labels are shown in Fig. 7.

The AIPAR parameter sets are shown in Tables 3–7, together with the OPLS parameters for comparison. In order to make this comparison more realistic, the "OLPS symmetry" and the united atoms approach, when applicable, have also been used during the AIPAR procedure. For instance, both nitrogen atoms in the imidazole molecule are symmetric regarding the ϵ and σ parameters according to the OPLS procedure. Similarly for the atoms C(2) = C(4) = C(5) and H(6) = H(7) = H(9) for the imidazole molecule, C(2) = C(4) = C(5) and H(6) = H(7) = H(8) for the oxazole molecule and C(2) = C(3) = C(4) = C(5) and H(6) = H(7) = H(8) = H(9) for the furan molecule. From the analysis of the results in Tables 3–7, it can be observed that the AIPAR procedure yields parameters that are well correlated with the OPLS ones. The qualitative trends for the ϵ and σ parameters is always preserved and the quantitative agreement improves when a comparison is made with the OPLS parameters for the all-atoms model (imidazole, oxazole and furan).
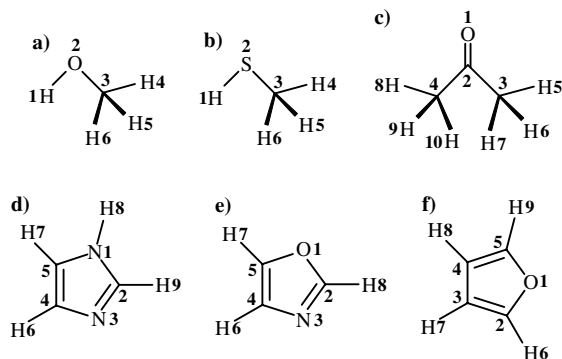

Fig. 7 The molecules (a) methanol, (b) methanethiol (methyl mercaptan), (c) acetone (propanone), (d) imidazole (1,3-diazole), (e) oxazole and (f) furan and atomic labels used for the AIPAR

Table 3 United-atoms parameters, q (e), σ (nm) and ϵ (kJ mol^{-1}), for the propanone (acetone) molecule

Site	AIPAR[a]			OPLS [28]		
	q	σ	ϵ	q	σ	ϵ
O(1)	−0.500	0.304	1.046	−0.424	0.296	0.879
C(2)	0.680	0.381	0.042	0.300	0.375	0.439
C(3, 4)	−0.090	0.395	0.669	0.062	0.391	0.669

[a] The charges, q, were obtained from the CHELPG procedure and were not adjusted during the fitting procedures for obtaining σ and ϵ parameters

The atomic charges for the solute were also obtained with the CHELPG approach and kept constant during the fitting procedure. The inclusion of the solvent effects via the continuum model IPCM [22] on these CHELPG atomic charges was also tested. A significant charge separation that was much larger than the OPLS one was observed, yielding ϵ and σ parameter sets that are in worst agreement with the OPLS data than the results reported in Tables 1 and 3–7.

It is important to note the explicit interest in using a well known and successful model (TIP4P) for describing the water solvent, which is the reason for using its atomic charges when computing the Coulomb contribution for the intermolecular energies. However, it could be argued that the TIP4P model is a polarized water that might not be adequate for calculating solute–water pair interaction energies. Thus, the ϵ and σ parameters for methanol and furan have been refitted using the same solute–water ab initio interaction energies, but employing the CHELPG-derived atomic

Table 4 Same as Table 3 for the methanethiol molecule

Site	AIPAR			OPLS [29]		
	q	σ	ϵ	q	σ	ϵ
H(1)	0.205	0.000	0.000	0.270	0.000	0.000
S(2)	−0.363	0.424	1.632	−0.450	0.355	1.046
C(3)	0.158	0.375	0.628	0.180	0.378	0.866

Table 5 Same as Table 3 for the imidazole molecule

Site	AIPAR			OPLS [30]		
	q	σ	ϵ	q	σ	ϵ
N(1)	−0.226	0.334	1.632	−0.257	0.325	0.711
C(2)	0.202	0.370	0.460	0.275	0.355	0.293
N(3)	−0.512	0.334	1.632	−0.563	0.325	0.711
C(4)	0.181	0.370	0.460	0.185	0.355	0.293
C(5)	−0.257	0.370	0.460	−0.286	0.355	0.293
H(6)	0.061	0.174	3.724	0.075	0.242	0.126
H(7)	0.168	0.174	3.724	0.187	0.242	0.126
H(8)	0.306	0.000	0.000	0.306	0.000	0.000
H(9)	0.077	0.174	3.724	0.078	0.242	0.126

Table 6 Same as Table 3 for the oxazole molecule

Site	AIPAR			OPLS [30]		
	q	σ	ϵ	q	σ	ϵ
O(1)	−0.208	0.384	0.251	−0.257	0.290	0.586
C(2)	0.401	0.342	0.084	0.511	0.355	0.293
N(3)	−0.523	0.296	4.268	−0.590	0.325	0.711
C(4)	0.155	0.342	0.084	0.169	0.355	0.293
C(5)	−0.127	0.342	0.084	−0.148	0.355	0.293
H(6)	0.082	0.241	1.255	0.091	0.242	0.126
H(7)	0.166	0.241	1.255	0.181	0.242	0.126
H(8)	0.054	0.241	1.255	0.043	0.242	0.126

charges for the water molecule. These results are shown in Tables 1 and 7, in parentheses, and it is clear that using the TIP4P charges yielded ϵ and σ parameters in closer agreement with the OPLS procedure. Another critique of the AIPAR procedure could be related to the limited number (100) of solute–water configurations used to sample the six-dimensional (6-D) configurational space. However, given the good agreement between the AIPAR and OPLS parameters it seems that procedure [12] chosen to generate these configurations is adequate to provide the important configurations of the 6-D space. Also, the level of the ab initio calculations (MP2/6-31G*) can be questioned by modern standards of electronic structure theory. However, since the main goal is to develop an approach that can be used for large solute molecules and because it requires at least a hundred quantum chemical calculations, it appears an appropriate compromise between accuracy and practicality. In addition, this level of ab initio theory has been successfully used in a recent parametrization of the van der Waals potentials in force fields [23].

One of the main differences between the present approach compared to the pioneer work of Clementi et al. [24–29] and also to more recent ones, [30, 31] is the unambiguous procedure for sampling the 6-D space of the intermolecular solute–solvent interactions based on the electrostatic potential. In addition, the present procedure has the potential to decrease significantly the number of points in this interaction space needed to provide an adequate sampling for fitting analytical potentials, thus allowing the use of more sophisticated and high level ab initio methods.

Table 7 Same as Table 1 for the furan molecule

Site	AIPAR			OPLS [30]		
	q	σ	ϵ	q	σ	ϵ
O(1)	−0.156	0.339 (0.310)	0.209 (0.323)	−0.190	0.290	0.586
C(2, 5)	−0.037	0.360 (0.366)	0.293 (0.211)	−0.019	0.355	0.293
C(3, 4)	−0.139	0.360 (0.366)	0.293 (0.211)	−0.154	0.355	0.293
H(6, 9)	0.137	0.207 (0.204)	0.460 (0.480)	0.142	0.242	0.126
H(7, 8)	0.117	0.207 (0.204)	0.460 (0.480)	0.126	0.242	0.126

Conclusions

The AIPAR procedure implemented into the SJBR program has been shown to be a versatile, unambiguous, automated and fully ab initio technique to yield intermolecular interaction potentials between polar molecules and water. The results obtained from the AIPAR-derived parameters compared well with those obtained with the empirical OPLS procedure, including the simulation of aqueous solution of methanol. Even for the equimolar binary mixture (methanol–water), the thermodynamic and geometric results obtained with the AIPAR parameters compare favorably with the OPLS simulations, demonstrating the precision and robustness of the AIPAR methodology. These results also reflect the transferability properties of the AIPAR parameters, which were obtained only for the methanol–water pair, that is, it did not include any explicit information regarding the methanol–methanol interaction.

The AIPAR procedure was applied to several organic molecules covering a wide range of structure and functional groups. The sets of parameters obtained compared well with the OPLS ones, mainly when the all-atoms model is employed in both procedures.

Being an ab initio procedure, AIPAR should be useful in applications were experimental data are scarce or unavailable, such as for excited electronic states of solutes in water.

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