Polarization-consistent force field for ketones

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ABSTRACT

Ketones are some of the most widely used solvents, with a variety of applications. In addition, molecules with ketone functional groups feature prominently in pharmaceutical APIs. However, they present a particular challenge for modelling, particularly when considering solutions and mixtures. In this paper, we present a new classical nonpolarizable model for ketones, based on our recently-proposed Polarization-Consistent Approach (PolCA). PolCA is based on a theoretically-grounded consideration of polarization effects in a nonpolarizable framework, which lead to an optimal selection of the model's effective dipole moment and point charges, as well as to the derivation of *post facto* corrections for solvation free energy and dielectric constant predictions. This allows us to effectively account for the missing effects of polarization in a computationally expedient way. At the core of this approach is a realistic estimate of the dipole moment of ketones in the liquid phase, which we obtain by applying the recently-developed Self-Consistent Electrostatic Embedding (SCEE) method. The new model, developed under this paradigm, provides significantly improved predictions over the state-of-the-art TraPPE model, and shows improved transferability to heterogeneous systems.

1. Introduction

Classical non-polarizable (also known as "fixed-charge") models are the workhorses of most molecular simulation studies of liquids and solutions. In this approach, electrostatic interactions between molecules are accounted for by assigning partial point charges to individual interaction sites followed by the application of Coulomb's law. These are then most often combined with the Lennard-Jones (LJ) potential to describe repulsion and dispersion interactions, and with harmonic and torsional potentials to describe bonded degrees of freedom, giving rise to the standard functional form in generic non-polarizable force fields (e.g. CGenFF [1], GAFF [2], OPLS-AA [3], TraPPE [4]). One problem with this approach is that polarization (also called induction) effects are not explicitly described, but are instead assumed to be incorporated implicitly into effective point charges and LJ parameters. However, this is often done in an *ad hoc* manner with little or no theoretical foundation, which has been shown to lead to inconsistencies and poor transferability [5–11]. Recently, our group has proposed a new approach to parametrize non-polarizable force fields that accounts for polarization effects in a rigorous, theoretically-grounded, way. We call this the Polarization-Consistent Approach (PolCA), which has been applied to

develop a new united-atom (UA) force field for aliphatic alcohols [12]. Importantly, this approach has led to improved predictions of the solvation free energy of alcohols in both polar and non-polar solvents.

In this paper, we apply PolCA to develop a new fixed-charge UA force field for aliphatic ketones. One of the most well-known ketones is propanone, also known as acetone, which is widely used as a solvent for fats, oils, waxes, resins, rubber, plastics, lacquers, varnishes, and rubber cements. This compound dissolves in water in all proportions since the carbonyl oxygen's lone pair electrons can act as a hydrogen bond acceptor, and thus, it forms hydrogen bonds with water. Another excellent solvent for many organic compounds is butan-2-one, also known as methyl ethyl ketone. [13]. Some ketones, like nonan-2-one and undecan-2-one, are found in essential oils [14], and many compounds containing a carbonyl group are relevant to the pharmaceutical industry, like the oral contraceptive norethindrone [13]. Thus, it is important to be able to accurately predict solvation properties of molecules containing ketone groups.

The OPLS-UA force field for propanone [15] was developed by Jorgensen *et al.* in 1989 to reproduce thermodynamic and structural properties of pure liquid propanone, and the authors showed that it was able to predict the free energy change obtained when mutating acetic

acid to propanone in water and chloroform. Later on, Jorgensen et al. developed the OPLS all-atom (AA) force field for many common organic groups, and they included propanone and butan-2-one in its development [3]. Non-bonded parameters were obtained by fitting to densities and enthalpies of vaporization of 34 organic liquids, mostly at 298.15 K. In general, OPLS becomes less accurate for conditions further away from 298.15 K and 1 atm, as has been shown by Martin and Siepmann when developing the TraPPE-UA force field for n-alkanes [16]. Later on, Stubbs et al. extended the TraPPE-UA force field to ketones by fitting the LJ parameters of the carbonyl carbon to the vapor–liquid coexistence curve of propanone [17]. To keep the number of fitting parameters at a manageable level, the carbonyl group's partial charges were taken from OPLS-UA [15], while the LJ parameters for the carbonyl oxygen were taken from the TraPPE force field for carbon dioxide [18].

Another UA force field for ketones focused on vapor–liquid equilibria is the anisotropic united-atom (AUA) force field developed by Kranias *et al.* [19] in 2003. This model is an extension of the AUA4 model by Ungerer *et al.* [20], with partial charges from *ab initio* calculations and new LJ parameters for the carbon and oxygen atoms of the ketone group. The LJ parameters of these two atoms were fitted to reproduce the vapor pressures, enthalpies of vaporization and liquid densities of propanone and butan-2-one at ambient conditions and at a reduced temperature of 0.8. This force field yields good agreement between experimental and simulated data for the coexistence curves of propanone, butan-2-one and pentan-2-one, and it does a very good job at predicting the enthalpies of vaporization of those molecules from 250 to 500 K. The GROMOS-53A6 force field [21] was developed in 2004 to reproduce free energies of solvation in water and non-polar solvents, and in 2011, Horta *et al.* [22] proposed new interaction parameters for ketones by fitting to the liquid density, enthalpy of vaporization, hydration free energy and solvation free energy in cyclohexane of propanone and butan-2-one. Meanwhile, pentan-2-one, pentan-3-one, hexan-2-one and hexan-3-one were part of the validation stage.

Apart from its practical importance, propanone is also very interesting from a fundamental point of view, particularly because it is able to act as a hydrogen-bond acceptor (through the very electronegative carbonyl oxygen atom) but not as a hydrogen-bond donor. As such, even though propanone molecules cannot form hydrogen bonds in the pure liquid, they are able to do so when mixed with molecules like chloroform, water or methanol, leading to substantial non-ideal effects and anomalies in the mixture thermodynamics [23–27]. In fact, it has recently been argued that one of the reasons for the systematic failure of generic non-polarizable models in predicting the correct thermodynamic behavior in non-ideal mixtures involving propanone is the neglect of polarization effects [26,27]. Although we do not explicitly address the issue of binary mixtures in the present paper (with the exception of solvation free energy in alkanes, as discussed below), we believe that a pure-liquid ketone model that is based on a rigorous treatment of polarization effects will serve as a better basis for testing its performance in predicting thermodynamic properties of solutions and mixtures. The main aim of this paper is precisely to report on the development, validation and testing of a new polarization-consistent model for ketones.

2. Methodology

2.1. Model design and optimization

As in our previous work, we developed the PolCA ketone force field under a united-atom approximation, whereby all aliphatic hydrogen atoms are merged with their adjacent carbon atoms, giving rise to single CH_x interaction sites. Furthermore, the TraPPE-UA force field is used as a basis for development of PolCA. Therefore, all bonded parameters were taken directly from the TraPPE-UA model for ketones [17] without further changes, and they are reported in Table S1 of the Supplementary Information. The LJ parameters for the alkyl chains were taken from our previous work [28], where the original TraPPE-UA aliphatic

hydrocarbon parameters were slightly modified to eliminate systematic deviations in solvation free energies [29]. As observed previously for alcohols [12], combining the modified alkane parameters with standard TraPPE-UA parameters for the functional group (in this case, the carbonyl group) naturally leads to systematic deviations from experimental data, as shown in Figure S1 for the density of aliphatic ketones. Therefore, as expected, the carbonyl group parameters need to be recalibrated to be consistent with the new alkane parameters, as well as to effectively account for polarization effects. In order to keep the number of fitting parameters to a manageable level, thus avoiding overfitting, and after a preliminary sensitivity test, we have opted to keep the LJ parameters of the carbonyl carbon identical to the original TraPPE-UA values, while reparametrizing the LJ parameters on the oxygen atom alone.

The TraPPE-UA model for ketones represents electrostatic interactions of the carbonyl group through point charges of equal magnitude and opposite sign on each of its atoms, i.e. the adjacent alkyl groups are assumed to be electronically neutral. However, other models assign a non-negligible charge to the alkyl groups connected to the carbonyl carbon [15,25,27]. To ascertain whether the approximation applied in TraPPE-UA was valid, we carried out a quantum mechanical (QM) calculation on a propanone molecule surrounded by a dielectric continuum to represent a pure liquid environment. The calculation was carried out on Gaussian 09 [30] using the B3LYP functional [31,32] and the aug-cc-pVTZ basis set [33], which includes diffuse functions. The dielectric continuum was described using the IEFPCM model [34] with default parameters for propanone. Atomic charges were calculated from the optimized wavefunction using the CHelpG scheme [35].

The result of the QM calculation on propanone is shown in Fig. 1, where we have grouped together the charges belonging to each aliphatic CH_3 group, in line with the UA formalism. As we can see, the charges on the aliphatic sites adjacent to the carbonyl group, although small, are clearly non-negligible. It is important to note that simple dielectric continuum models have been shown to significantly underestimate the degree of polarization observed in a realistic liquid environment due to the neglect of local solvation effects [36–41], and therefore the magnitude of the solute's multipole moments (and consequently of its point charges) is likely to be underestimated. However, we expect the dielectric continuum model to yield a reasonable description of the *relative* charge distribution over the different atoms of the molecule. On this basis, we chose to include a small partial charge on the alkyl groups adjacent to the carbonyl carbon in order to better represent the electronic distribution of solvated ketones, as done in previous models of propanone [15,25,27]. However, we optimized the overall magnitude of the charges (and hence the dipole moment of the model) by applying a
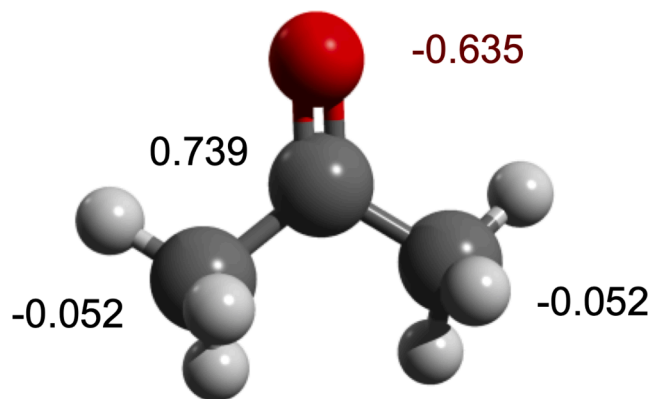

Fig. 1. CHelpG partial charges for propanone (acetone) calculated at the B3LYP/aug-cc-pVTZ level of theory using the IEFPCM polarizable continuum model to represent the effects of the surrounding liquid phase. The charges on the CH_x groups (bottom) were added together in accordance with the united-atom approach.

scaling factor of 0.961 to the CHelpG charges shown in Fig. 1, as discussed in detail in section 2.3.

To summarize, we optimized the σ and ε LJ parameters of the carbonyl oxygen atom (σ_O and ε_O, respectively) and the scaling factor (α) for the point charges (i.e. 3 fitting parameters) to match the density, enthalpy of vaporization and self-diffusion coefficient of propanone, hexan-2-one and decan-2-one (i.e. 9 experimental target values). The optimized model was then validated against the same bulk liquid properties for the whole set of linear ketones (i.e. from propanone to decan-2-one), as well as against the dielectric constant and self-solvation free energy of those molecules. Furthermore, we validated the model against experimental data for the solvation free energy of linear ketones in n-hexadecane solvent, to test the transferability of the model. Note that only experimental data up to octan-2-one was available for the solvation in n-hexadecane.

The parameter optimization made use of a similar approach as the one described in our previous paper [12]. In short, meta-models were constructed to predict molecular simulation results for a given set of parameters, in order to more efficiently explore the parameter space [42]. The parameter levels used to construct the grid for meta-model fitting were as follows: $\sigma_O \in$ [0.290, 0.295, 0.300, 0.305, 0.310, 0.315]; $\varepsilon_O \in$ [0.1, 0.2, 0.4, 0.55, 0.657, 0.75, 0.85]; $\alpha \in$ [0.75, 0.95, 1.00, 1.05]. The performance of the meta-models in predicting the target properties is depicted in Figure S2. The objective function took the form of equation (1), where *k* is the target property, *j* is the target compound, $f_{k,j}(X)$ is the value predicted by the meta-model for parameter set *X*, and $y_{exp_{k,j}}$ is the experimental value for the corresponding property and compound.

$$F(X) = \sum_{j=1}^{3} \sum_{k=1}^{3} \left(f_{k,j}(X) - y_{exp_{k,j}} \right)^2 \tag{1}$$

This function was minimised using a steepest descent algorithm with a variable step length and a maximum number of iterations equal to 4000. The lowest value from these iterations was used as the initial point for a second optimisation which used smaller step lengths and a maximum number of iterations equal to 100. Table 1 reports the optimized values of the non-bonded parameters for the PolCA model of ketones.

2.2. Simulation details

To calculate the bulk liquid properties of each molecule, molecular dynamics (MD) simulations were carried out with GROMACS version 5.1.2 [43,44]. The number of molecules introduced in each cubic and fully periodic simulation box was chosen to yield box lengths of ~ 3 nm (the exact number of molecules for each compound is shown in Table S2). The simulation protocol comprised of an initial steepest descent energy minimisation, followed by a 100 ps NVT simulation at 298.15 K to equilibrate the energy, a 100 ps NPT simulation at 298.15 K

and 1 bar to equilibrate the density, and finally a production run of 25 ns in the NPT ensemble, again at 298.15 K and 1 bar. The temperature was controlled using the V-rescale thermostat [45] with a time constant of 0.1 ps, while the pressure was controlled using the Parrinello-Rahman barostat [46] with a time constant of 2 ps and isothermal compressibility of 4.5×10^{-5} bar^{-1}. A leap-frog algorithm [47] was used to integrate Newton's equations of motion with a time step of 2 fs. All bonds were constrained using the LINCS algorithm [48]. The Verlet scheme was chosen for neighbour searching, with a cut-off radius of 1 nm for both van der Waals and electrostatic interactions, and long-range dispersion corrections for energy and pressure were applied. Long-range electrostatic interactions were calculated using PME [49] with a Fourier spacing of 0.16 nm. In total, ten independent simulations were run for each compound and error bars were calculated to give a 95 % confidence interval of the mean. In most cases, the error bars are too small to be visible in the plots.

The bulk liquid density was simply calculated from the system volume at equilibrium using the GROMACS built-in tool *gmx energy*. The enthalpy of vaporization was calculated according to equation (2), where U_{Gas} is the potential energy of an isolated molecule in the gas phase and U_{Liq} is the potential energy per molecule in the liquid phase.

$$\Delta H_{Vap} = \langle U_{Gas} \rangle - \langle U_{Liq} \rangle + RT \tag{2}$$

U_{Gas} was calculated from a 50 ns NVT simulation of a single molecule without periodic boundary conditions or cut-off radii. Both internal energies were computed using *gmx energy*. The self-diffusion coefficient was calculated by applying the Einstein relation, i.e. from the slope of the mean-square displacement, computed using the GROMACS built-in tool *gmx msd*. We have applied finite-size corrections, obtained by extrapolating the self-diffusion coefficient to infinite box size. To achieve this, we ran simulations of each ketone with four box lengths (*L*): 2 nm, 3 nm, 4 nm and 5 nm. The results were plotted against 1/*L* and extrapolated to the origin, with the correction for each compound being determined from the difference between the extrapolated value and the coefficient obtained with the 3 nm (default) box size. For the parameter optimization stage, as done previously [12], the finite-size corrections, shown in Table S3, were computed with the TraPPE-UA force field and assumed to be parameter-independent. This assumption was confirmed to be valid for the final set of PolCA parameters. Finally, the dielectric constant was calculated from the fluctuations of the total dipole moment of the simulation box using the GROMACS built-in tool *gmx dipoles*.

Solvation free energy calculations, both in the pure solvent (i.e. self-solvation free energies) and in n-hexadecane solvent, were carried out with Bennett's acceptance ratio (BAR) method [50,51] using a one-step transformation, i.e. employing the option "couple-intramol = no" in GROMACS. Except for the application of a stochastic dynamics integrator [52] and the corresponding Langevin thermostat, MD simulation details were the same as for the pure liquid simulations. We used 14 values of the coupling parameter λ for the LJ component of the free energy (i.e., 0, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55, 0.7, 0.85, and 1) and 5 λ values for the electrostatic component (0, 0.2, 0.4, 0.7, and 1). During the decoupling of the LJ component, a soft-core function [53] was applied to avoid instabilities close to the noninteracting state, with parameters "sc-power = 1", "sc-sigma = 0.3" and "sc-alpha = 0.5". The LJ contribution to the solvation free energy was simulated for 5 ns while 10 ns were used for the electrostatic component. The λ-states were selected based on their relative entropies to ensure a good degree of overlap between them, as described in detail in our previous paper [12], and the simulation times were chosen to ensure convergence of the free energies of solvation against simulation times (see Figures S3 and S4 in Supplementary Information for examples).

2.3. Polarization corrections and liquid-phase dipole moments

A key element of PolCA is to apply *post facto* corrections to effectively

Table 1

Non-bonded parameters of the PolCA force field for ketones. Only the parameters on the ketone functional group were optimized in this work, while parameters for alkane groups were taken from previous work [28].

Atom type[a]	σ (nm)	ε (kJ/mol)	Charge
C(=O)	0.382	0.333	0.710
O(=C)	0.2955	0.08	−0.610
(**CH₃**)-CH$_x$	0.379	0.833	0
(**CH₃**)-C = O	0.379	0.833	−0.05
(CH$_x$)₂-(**CH₂**)	0.399	0.392	0
(CH$_x$)-(**CH₂**)-C = O	0.399	0.392	−0.05
(CH$_x$)₃-(**CH**)	0.473	0.085	0
(CH$_x$)₂-(**CH**)-C = O	0.473	0.085	−0.05
(CH$_x$)₄-(**C**)	0.646	0.00426	0
(CH$_x$)₃-(**C**)-C = O	0.646	0.00426	−0.05

[a] – Parameters refer to the atoms/sites in bold face font.

account for polarization effects when comparing the predictions of classical non-polarizable models against experimental data. No polarization corrections are needed for bulk-phase properties that depend only on the Potential Energy Surface (PES) of the liquid, such as the density and self-diffusion coefficient (although the latter requires finite-size corrections, as discussed in section 2.2). However, the dielectric constant needs to be corrected for polarization, because it depends strongly on the Dipole Moment Surface (DMS) of the liquid [9]. The correction needs to take into account two effects: i) the contribution of purely electronic degrees of freedom of the liquid, which are not present in classical non-polarizable models [7], and can be quantified by the infinite-frequency dielectric constant (ε_∞); ii) the difference between the (fixed) dipole moment used in the non-polarizable model (μ_M) and the dipole moment of the real liquid (μ_L). The correction thus takes the form of equation (3) [10], where ε_{Exp} is the dielectric constant for comparison with experimental data and ε_{MD} is the dielectric constant calculated in the non-polarizable MD simulation.

$$\varepsilon_{Exp} = \varepsilon_\infty + \left(\frac{\mu_L}{\mu_M}\right)^2 (\varepsilon_{MD} - 1) \tag{3}$$

We note that equation (3) can be applied regardless of whether ε_{MD} is calculated from the dipole moment fluctuation formula [54] or from the Kirkwood expression [55] where the so-called Kirkwood g-factor describes the mutual orientation of the molecular dipoles [56]. It has been shown that application of equation (3) can eliminate systematic deviations between simulated and experimental dielectric constants for a wide range of pure compounds, as well as mixtures [10,11].

In order to apply equation (3), it is necessary to obtain a realistic value for the molecular dipole moment in the liquid phase. This is very challenging to achieve experimentally, and we are only aware of one such study for liquid water [57]. Therefore, we need to rely on theoretical methods to calculate this property. The advantages and disadvantages of different theoretical approaches for calculating liquid phase dipole moments have been discussed in detail previously [36]. Here, we apply the Self-Consistent Electrostatic Embedding (SCEE) method [36,37] to calculate the liquid dipole moments of propanone and butan-2-one. SCEE is based on a QM/MM approach, which strikes a good balance between accuracy and computational efficiency, and has been shown to predict dipole moments in good agreement with experiment for the case of water [36] and with *ab initio* MD simulations for both water and methanol [36,37].

The SCEE method has been described in detail elsewhere [37], and only a brief summary is provided here. To begin with, 200 evenly-spaced configurations were extracted from equilibrated classical MD simulations of each pure liquid, which in this case were carried out with the PolCA force field for ketones, as described in section 2.1. Dummy aliphatic hydrogen atoms were added to the central "solute" molecule to ensure compatibility between the united-atom PolCA model and the subsequent fully atomistic QM calculation. For each of the 200 extracted configurations, a spherical cluster of radius 2.0 nm centered on the solute molecule was generated and converted to the appropriate input format for Gaussian 09 software [30] using an in-house script [37]. In all QM/MM calculations, only the central molecule was treated at the QM level, while surrounding molecules of the cluster were described at the MM level. Three input files were generated, each with a different value for the dipole moment of the surrounding MM liquid molecules. For each of these values and each configuration (i.e. a total of 600 calculations), an initial geometry optimization of the central QM solute at the B3LYP/cc-pVTZ level of theory was carried out with the ONIOM method [58,59] to ensure the correct liquid-phase environment was replicated. This was followed by two single-point calculations at the B3LYP/aug-cc-pVTZ and B3LYP/aug-cc-pVDZ levels of theory using electrostatic embedding, to accurately calculate the dipole moment of the central QM molecule.

From the results of the above calculations, we obtained an analytical

correlation (essentially a quadratic function) between the QM dipole moment (μ_{QM}) and the pre-set dipole moment of the surrounding MM molecules (μ_{MM}) for each configuration, from which we were able to calculate the self-consistent liquid phase dipole – i.e. the value for which $\mu_{QM} = \mu_{MM}$. Statistical analysis of the 200 configurations was carried out using Tukey's method [60] to remove any outliers (typically about 3% of the configurations were removed), and to then compute the average liquid phase dipole moment. These values were then corrected for purely electronic polarization effects using the approach described previously [37], based on QM calculations of the central molecule surrounded by an IEFPCM dielectric continuum model [34]. Finally, the corrected average dipole moments obtained at the aug-cc-pVDZ and aug-cc-pVTZ levels were used to extrapolate the result to infinite basis set, using the method proposed by Truhlar [61], thus yielding the final value of the SCEE dipole moment for the target liquid.

In our previous work for water and methanol [36,37], the chosen B3LYP/aug-cc-pVTZ level of theory was able to very accurately match the experimental gas-phase dipole moment for both molecules. However, here we found it somewhat overestimated the gas-phase dipole moment of ketones – we obtained 3.07 D for propanone and 2.92 D for butan-2-one, compared to the experimental values of 2.88 D and 2.78 D, respectively. To mitigate for this discrepancy, our final value of the liquid phase dipole moment was calculated from equation (4):

$$\mu_L = \left(\mu_L^{SCEE} - \mu_G^{SCEE}\right) + \mu_G^{Exp} \tag{4}$$

The inherent assumption in equation (4) is that any inaccuracies due to the QM level of theory are identical in the calculation of the gas-phase and liquid-phase dipole moments. In other words, we argue that SCEE will still provide an accurate estimate of the induced dipole moment (i.e. $\mu_L - \mu_G$, or $\Delta\mu$), even if the absolute values of the gas phase dipole moments are not entirely accurate. As mentioned above, the liquid phase dipole moment thus obtained was used in equation (3) to correct the dielectric constant predictions.

Polarization corrections are also relevant for properties that characterize a change of phase, such as the enthalpy of vaporization or the solvation free energy. These corrections should account for: i) the unfavorable energetic cost of distorting the electronic wavefunction of the molecule from its ground state in the gas phase to its polarized state in the liquid/solution [62,63]; ii) the favorable interaction energy between the polarized molecule and the electronic degrees of freedom of the liquid environment [7]. However, it has been shown that, at least for pure polar liquids, these two terms largely cancel out [6,8]. Furthermore, when the dipole moment used in the non-polarizable model is approximately halfway between that of the gas and of the liquid phase, it has been shown theoretically (under a linear response approximation) that the net polarization correction to the energy of a pure liquid phase is negligible [64–67]. In other words, by selecting a model dipole moment with an intermediate degree of polarization between the gas and the liquid dipoles, one can avoid having to apply polarization corrections to the enthalpy of vaporization and self-solvation free energy of pure polar liquids. We adopt this approach here.

To determine the optimal value for the model dipole moment (and hence the magnitudes of its point charges), we adopted the approach of Karamertzanis et al. [64] with a slight modification to account for a second-order error term that was assumed to be negligible in those authors' treatment of polarization effects. This leads to the following expression, a detailed derivation of which is provided in Supporting Information (section S2):

$$\mu_M = \mu_G + \frac{(1 - \delta)}{2}(\mu_L - \mu_G) \tag{5}$$

In the above equation, μ_M is the (intermediate) dipole moment of the non-polarizable model, from which all forces are computed during the MD simulations, while μ_L is the dipole moment of the fully polarized liquid phase and μ_G is the dipole moment of an isolated molecule in the

gas phase. The factor δ represents the residual second-order term, which we estimated to be $\sim$ 10 % of the total induction energy (see SI for details). Substituting this value in equation (5) yields:

$$\mu_M = \mu_G + 0.45 \times (\mu_L - \mu_G) \qquad (6)$$

Note that this implies that the optimal dipole moment for the model, which implicitly captures induction effects and provides the best description of the Potential Energy Surface of the liquid, turns out to be slightly lower than the arithmetic average between the gas- and liquid-phase dipole moments. Using equation (6) together with experimental values of μ_G and results for μ_L obtained with the SCEE method [37], we estimate the following model dipole moments: water = 2.262 D; methanol = 2.108 D; acetone = 3.245 D. The estimated optimal dipole moment for water is quite close to the value for TIP4P/2005 (2.305 D) [68], widely considered to be one of the best classical non-polarizable models for water [69]. The estimated dipole moment for methanol, on the other hand, is very close to the value for our previous PolCA model of alcohols (2.07 D) [12], which was optimized to reproduce a wide range of liquid thermodynamic properties. This gives us confidence in using the value of 3.245 D for the optimal dipole moment of our new PolCA model for ketones, which we adopt by applying a fixed scaling factor of 0.961 to the point charges shown in Fig. 1.

As explained above, using a dipole moment for the model determined through equation (6) means that energetic induction effects are implicitly accounted for in simulations of pure liquids. However, when a molecule is transferred from the gas phase to a solvent that is different from the pure liquid, the two energetic contributions described above no longer cancel out, and explicit polarization corrections need to be applied. This is particularly the case when the solute is polar and the solvent is non-polar, e.g. alkanes. In such cases, we have calculated the energetic polarization corrections using SCEE, as described in detail elsewhere [37], by carrying out two additional single-point calculations on the 200 configurations optimized with ONIOM – one in which the surrounding environment is removed, corresponding to a fully polarized solute molecule in vacuum, and another in which the solute is surrounded by an electronic continuum (using the SCIPCM method [70]) with a dielectric constant equal to the experimental value of ε_∞ for the liquid. We have previously shown that this approach significantly improves the transferability of classical non-polarizable force fields for heterogeneous systems, namely when predicting the solvation free energy of alcohols in alkane solvents [12].

3. Results and discussion

In Table 2, we report the results of the SCEE calculations on propanone and butan-2-one. The distributions of liquid dipole moments for both compounds are shown in Fig. 2, together with fits to a Gaussian expression. We can see that both distributions conform to the expected approximately Gaussian shape. Although the absolute value of the liquid phase dipole moment is slightly higher for propanone than for butan-2-one, the value of the dipole enhancement (i.e. the induced dipole) is identical for both compounds. The observed enhancement, 0.81 D, is somewhat lower than that observed for both water and methanol, which was $\sim$ 0.9 D [37]. The difference becomes even more pronounced if we consider the relative enhancement with respect to the ground state gas-
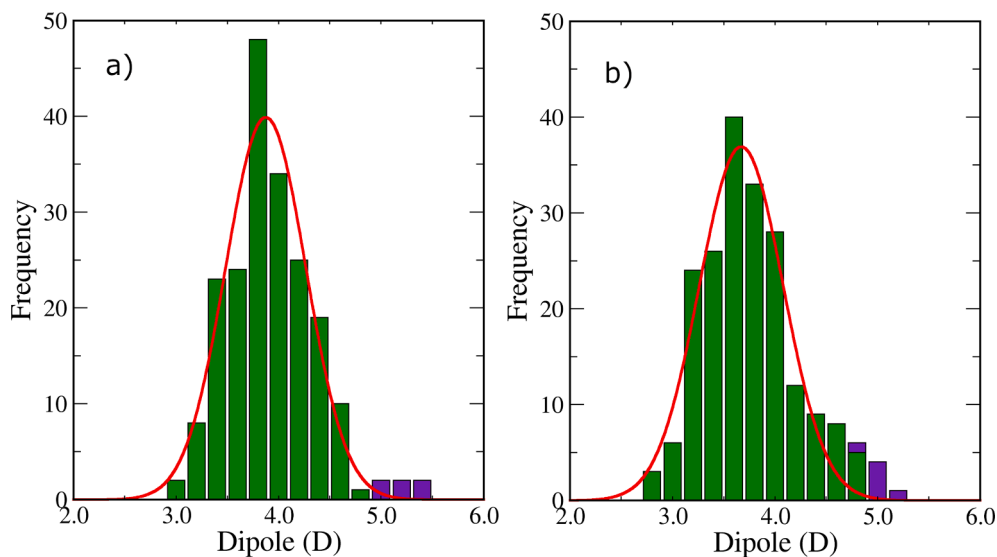
phase dipole moment – $\sim$50 % for water and methanol, compared to $\sim$ 26 % for ketones. This difference is most likely due to the lack of hydrogen bond formation in pure liquid ketones, a phenomenon which was shown to contribute significantly towards polarization in water and methanol [37]. Interestingly, the dipole enhancement obtained with SCEE for ketones is comparable (in fact, even somewhat lower) than that obtained using a simple dielectric continuum – we obtained values of 0.93 D and 0.98 D for propanone and butan-2-one, respectively, using an IEFPCM solvation model. This is in marked contrast to water and methanol, where a full account of local configurational effects was necessary to yield an accurate description of liquid phase polarization [36,37]. We are currently carrying out additional studies of molecules with different functional groups to determine if this is a general phenomenon or if, on the contrary, it is fortuitously observed for ketones.

In Fig. 3, we compare the predictions of our new PolCA model for ketones against experimental data and results obtained with the original TraPPE-UA model [17]. Both PolCA and TraPPE-UA are able to correctly predict the densities of linear ketones (Fig. 3a), although a systematic underestimation is observed for butan-2-one and pentan-2-one in both models; at the moment, it is not clear what might lead to this effect. PolCA arguably does a slightly better job at predicting the densities, particularly for propanone, although it should be considered that this was one of the target properties in the fitting procedure. For the enthalpy of vaporization (Fig. 3b), however, PolCA yields significantly improved predictions over TraPPE-UA, and solves the systematic underestimation observed in the predictions of that model. A similar improvement is observed for the self-diffusion coefficient (Fig. 3c), where PolCA eliminates the systematic overestimation observed in TraPPE-UA. Finally, the predictions of the self-solvation free energy (Fig. 3d) are comparable for both models, although again PolCA provides slightly improved predictions.

The fact that both the enthalpy of vaporization and the self-solvation free energy of pure ketones can be reproduced without the need to apply polarization corrections lends further support to the validity of the halfway-charge approximation, which states that by choosing model dipole moments that are intermediate between the gas and the liquid leads to an implicit account of the energetic contributions to polarization [64–67]. However, such energetic polarization corrections, which cancel out in the pure liquid, become important in heterogeneous systems, particularly when a polar molecule is solvated in a non-polar solvent. We have estimated the distortion and electronic contributions to the polarization correction using SCEE (see section 2) for propanone dissolved in n-hexadecane. As expected, the propanone molecule is much less polarized in an alkane environment than in the pure liquid – the dipole moment of propanone in n-hexadecane is only 3.44 D. This leads to a very small distortion energy, 1.0 ± 0.5 kJ/mol, but to a still significant electronic energy, -7.0 ± 0.1 kJ/mol. As a consequence, the total polarization correction is strongly negative, at -6.0 ± 0.1 kJ/mol, as observed previously for alcohols in n-hexadecane [12]. This correction was applied to the predictions obtained from the PolCA and TraPPE-UA models. In Fig. 4, we compare the predictions of both models for the solvation free energy of ketones in n-hexadecane, where we can see that, although not providing perfect predictions, PolCA improves the transferability of the force field for heterogeneous systems.

Finally, Fig. 5 shows the predictions of the dielectric constant using PolCA and TraPPE-UA. As we can see, when polarization corrections are applied according to equation (3) [10,11], both models are able to accurately describe the dielectric constants of all linear ketones. The results for the uncorrected TraPPE-UA model (full black squares) emphasize the importance of accounting for the difference between the effective model dipole moment (μ_M) and the real liquid-phase dipole moment (μ_L) when attempting to predict properties that depend strongly on the dipole moment surface [9].

Table 2

Dipole moments for ketones obtained from experiments and SCEE calculations. For the latter, the results are averages over $\sim$ 200 MD configurations with the B3LYP functional, extrapolated to the infinite basis set limit. The final estimates of the liquid phase dipole moment were calculated from equation (4).

Molecule	μ_G^{Exp}(D)	μ_G^{SCEE}(D)	μ_L^{SCEE}(D)	$\Delta\mu$ (D)	μ_L(D)[1]
propanone	2.88	3.07	3.88 ± 0.02	0.81 ± 0.02	3.69 ± 0.02
butan-2-one	2.78	2.92	3.73 ± 0.03	0.81 ± 0.03	3.59 ± 0.03

1 – Calculated from equation (4).

Fig. 2. Dipole moment distributions for liquid propanone (a) and butan-2-one (b). Results were sampled over 200 configurations obtained with the PolCA model, using SCEE at the B3LYP/aug-cc-pVTZ level of theory. The purple bars show configurations that were discarded in the outlier removing step. The red line shows the best fit of the resulting distribution to a Gaussian expression.
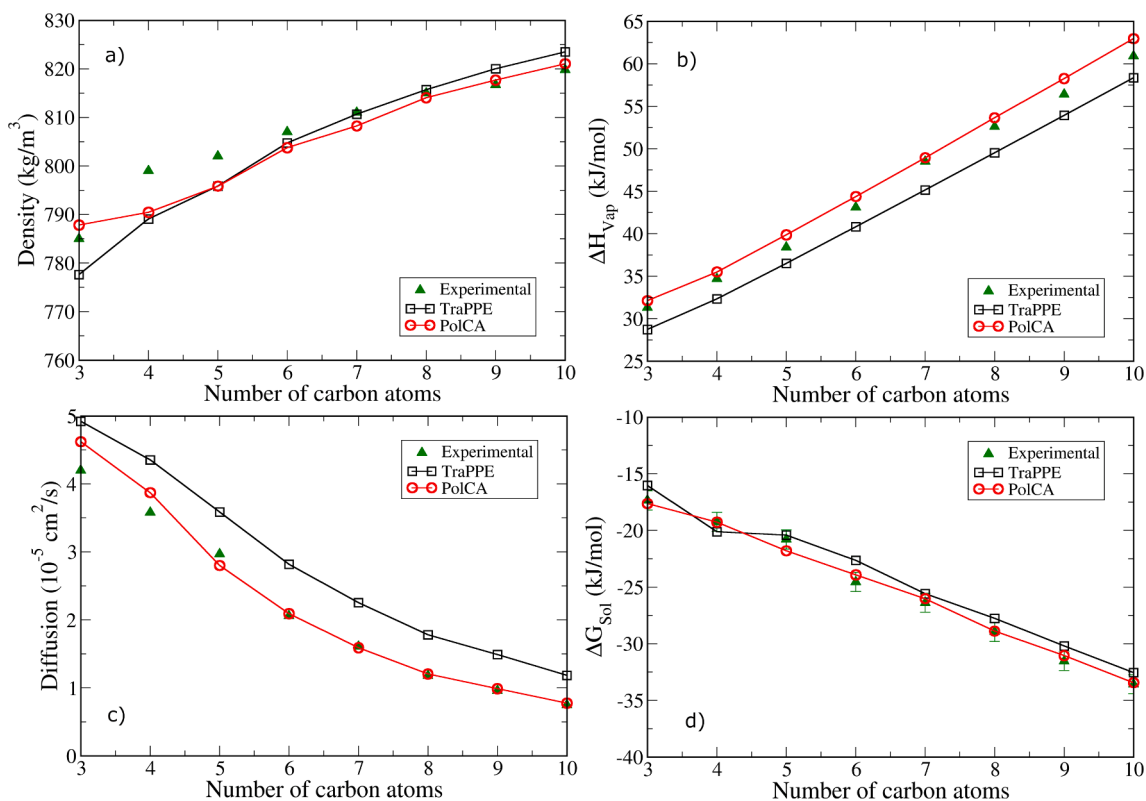
Fig. 3. Thermodynamic properties of pure liquid ketones predicted using the new PolCA model (red circles) and the original TraPPE-UA model (black squares), compared against experimental data (green triangles). Different panels correspond to: a) Density; b) Enthalpy of vaporization; c) Self-diffusion coefficient; d) Self-solvation free energy. Except where visible, error bars are smaller than the symbols used.

4. Conclusions

In this paper, we extend our polarization-consistent approach [12] to develop a new PolCA united-atom force field for ketones. The new model improves the predictions of thermodynamic and electronic properties of the pure liquids over the state-of-the-art TraPPE-UA force field. Crucially, our work demonstrates the importance of adequately accounting for polarization effects when parametrizing liquid-phase force

fields. While energetic polarization corrections cancel out in the pure liquid if an appropriate effective dipole moment is chosen for the non-polarizable model – approximately halfway between the dipole moments of the gas and the liquid [67] – such corrections must be applied for heterogeneous systems, including solutions and mixtures. Both the present work and our previous PolCA model for alcohols [12] show that this is indeed the case for solvation of polar molecules in alkanes. However, further tests are needed over a wider range of solute/solvent
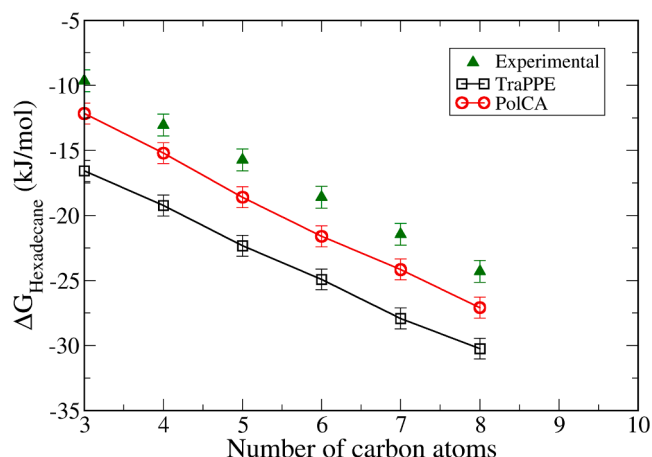
Fig. 4. Solvation free energy of linear ketones in n-hexadecane solvent predicted using the new PolCA model (red circles) and the TraPPE-UA model (black squares), compared against experimental data (green triangles).
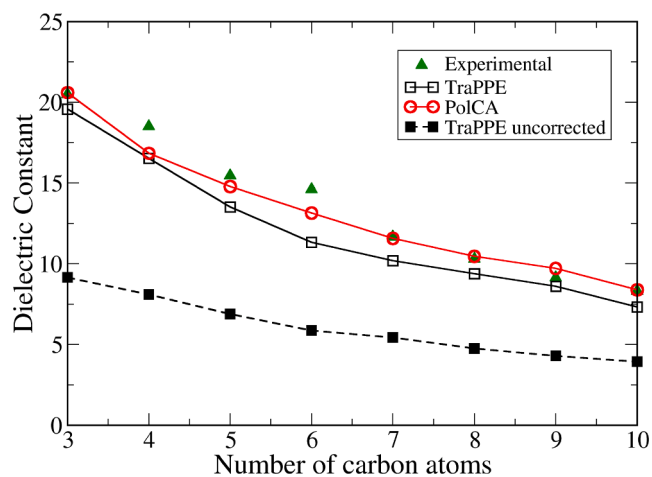

Fig. 5. Dielectric constants of pure liquid ketones predicted using the new PolCA model (red circles) and the TraPPE-UA model (black squares), compared against experimental data (green triangles). For TraPPE-UA, we show results with and without the polarization corrections described by equation (3).

pairs. We plan to extend the PolCA force field to molecules with other functional groups, which will provide the necessary framework for such tests to be carried out in the future.

We have also reported results for the liquid phase dipole moments of propanone and butan-2-one determined using the self-consistent electrostatic embedding method [36,37]. The enhancement of the dipole moment by the liquid environment, compared to the gas phase dipole, is not as pronounced as observed previously for water and methanol, due to the absence of hydrogen bond formation in pure liquid ketones. However, we expect such effects to become prevalent when ketones are mixed with hydrogen-bond donors like water and alcohols, leading to a more significant extent of polarization. We are currently carrying out such calculations using the SCEE method, and will report on those results in due course. Our estimates of the liquid phase dipole moments were used to apply polarization corrections to the dielectric constant predicted in the MD simulations of the non-polarizable models. Applying such corrections leads to excellent agreement with experiment, eliminating systematic deviations caused by a mismatch between the model and liquid-phase dipole moments. This confirms the conclusions of previous studies on a wider range of pure liquids and mixtures [10,11].

Overall, PolCA represents a paradigm change in the development of classical non-polarizable force fields, based on a theoretically grounded treatment of polarization effects. Although fully polarizable force fields are likely to be necessary for systems in which the degree of polarization of a solute molecule varies spatially (e.g. interfacial transfer) or dynamically (e.g. protein–ligand binding), our approach can effectively account for polarization effects in a much more computationally efficient non-polarizable framework for thermodynamic and electronic properties of pure liquids and mixtures.

CRediT authorship contribution statement

Maria Cecilia Barrera: Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft. **Jordan Cree:** Methodology, Formal analysis, Investigation. **José R.B. Gomes:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Writing – review & editing. **Miguel Jorge:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data underpinning this publication are openly available from the University of Strathclyde KnowledgeBase at https://doi.org/10.15129/bfce60be-baf6-40ad-a2a9-4e6e93344281.

Appendix A. Supplementary material

Additional simulation details. Detailed derivation of equation (5). Spreadsheets with analysis of SCEE data (zip file).

Supplementary data to this article can be found online at http://doi.org/10.1016/j.molliq.2023.122070.

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