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An improved dimethyl sulfoxide force field for molecular dynamics simulations

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Abstract

A united-atom molecular simulation force field for liquid dimethyl sulfoxide has been found to produce unacceptably inaccurate densities when used with a reaction-field or Ewald treatment of the electrostatic interactions. The force field is mildly reparameterized leading to a smaller dipole moment and slightly larger methyl groups. In addition to being compatible with the more sophisticated treatment of Coulombic interactions, the new force field also results in a significantly better description of the diffusion coefficient, the shear viscosity and the dielectric constant. Other liquid properties remain at the satisfactory quality of the Liu et al. model.

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1. Introduction

Liquid dimethyl sulfoxide (DMSO) is a popular polar aprotic solvent in chemistry and biochemistry. Consequently, it also appears in many simulations of (bio)chemical systems. A trustable computational model (force field) is therefore needed. One of us was involved in developing a united-atom force field [1] for DMSO some time ago. This force field continues to be used, as

evidenced by nearly 40 citations to Ref. [1] to date. However, it appears that the parameterization of this model (called the ‘1995’ model from here on) is rather specific to the treatment of the electrostatic interactions used at the time in the GROMOS87 package (molecule-based pairlist, twin-range multiple time step scheme with electrostatic interactions included to a cutoff of 0.9 nm in every step and to 1.5 nm every 10 steps). If used with Ewald sums or a reaction-field correction this force field produces a density which is too large by up to 5%. This deficiency was discovered using Ewald sums [2]. Subsequent calculations by ourselves showed that the density is strongly influenced by the cutoff distance not only when a reaction field is used, but also for the original treatment of electrostatics: The density at 298 K is

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1200 kg/m³ with twin-range cutoffs of 0.8/1.4 nm, rather than 1099 kg/m³ with 0.9/1.5 nm reported in [1] (exper. 1095 kg/m³).

We have reparameterized the 1995 model in order to reproduce thermodynamic properties of DMSO at ambient conditions in simulations with reaction-field or Ewald-sum treatments of the electrostatic interactions. As the 1995 model is well behaved in many other respects, we have tried to improve it by minimal changes. Our automatic force field parameterization procedure [3] allowed us to quickly try out different possibilities. In the end, an increase of the diameter of the united-atom methyl groups and a decrease of the molecular dipole moment turned out to be sufficient. The new model is described in detail and is validated by calculating a number of thermodynamic and transport properties of liquid DMSO. It is compared to the 1995 model. Skaf [4] has extensively compared DMSO force fields including the 1995 model. This discussion is not repeated here.

2. Computational details

We follow as closely as possible the computational protocol of Ref. [1] to ensure comparability of the new force field with the 1995 version. We use longer simulation times and, in places, different but equivalent computational schemes. The system is composed of $N = 432$ completely rigid DMSO molecules with four sites, where the CH₃ groups are considered as united atoms. The molecular geometry (Table 1) is fixed by six distance constraints maintained by the SHAKE [5] procedure. As the model has no intramolecular degrees of freedom, the total potential energy is equal to the non-bonded energy. The form of the potential energy function is

$$U = \sum_{ij} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0} \left(\frac{1}{r_{ij}} + \frac{\epsilon_{\text{RF}} - 1}{2\epsilon_{\text{RF}} + 1} \frac{r_{ij}^2}{r_{\text{cutoff}}^3} \right), \quad (1)$$

where r_{ij} denotes the distance between atoms i and j belonging to different molecules, ϵ_0 is the vacuum permittivity. Electrostatic interactions are handled

Table 1
Geometry (rigid) and force field parameters of the DMSO model

Atom type	S	O	CH ₃
Distance to O (nm)	0.153		
Distance to CH ₃ (nm)	0.195	0.28041 ^a	0.29299 ^a
ϵ (kJ/mol)	1.297	1.7154	0.9414
σ (nm)	0.356	0.263	0.3739 (0.366) ^b
q (e)	0.11674 (0.139) ^b	−0.43674 (−0.459) ^b	0.16
Mass (amu)	32.0600	15.9994	15.0350

^a These distances correspond to bond angles of 106.75° (O–S–CH₃) and 97.4° (CH₃–S–CH₃).

^b Given in parentheses are the corresponding parameters of the 1995 model [1] where different.

by the reaction-field method [6] with a reaction-field dielectric constant $\epsilon_{\text{RF}} = 46$, the experimental value of DMSO. Given the high dielectric constant, the reaction-field method has to yield results identical to those obtained with Ewald summations. Lennard–Jones parameters ϵ_{ij} and σ_{ij} for interactions between unlike atoms are obtained using the Lorentz–Berthelot mixing rules [7]. For the Lennard–Jones interactions, a long-range correction is used beyond the cutoff [7].

Both constant-volume NVT and constant-pressure NPT simulations have been carried out with the molecular dynamics package YASP [8]. Temperature $T = 298$ K and pressure $P = 0.1013$ MPa are kept constant by using the Berendsen method [9] with coupling times of 0.1 ps (T) and 0.5 ps (P) (the isothermal compressibility in the manostat is set to 5.10^{-7} kPa^{−1}). The atomic cutoff r_{cutoff} is 1.3 nm. The neighbour list cutoff is 1.4 nm, with an update every 10 steps. The time step is 2 fs and configurations are saved every 2 ps.

The force field optimization is performed with our simplex algorithm, for details see [3]. It iteratively adjusts selected force field parameters until certain known target properties are reproduced. Following the strategy behind the 1995 model, the target properties of this work are the density ρ and the enthalpy of vaporization ΔH_{vap} . In accordance with Ref. [1] the latter is defined as $\Delta H_{\text{vap}} = -UN_{\text{Avogadro}}/N$. Every iteration is started by 1 ps of

NVT pre-equilibration. This is followed by an *NPT* equilibration of at least 100 ps. From another 100 ps of production in the *NPT* ensemble, system properties, especially the target properties, are evaluated. Simplex steps are repeated until a penalty function

$$\frac{|\rho_{\text{sim}} - \rho_{\text{exp}}|}{\rho_{\text{exp}}} + \frac{|\Delta H_{\text{vap}}^{\text{sim}} - \Delta H_{\text{vap}}^{\text{exp}}|}{\Delta H_{\text{vap}}^{\text{exp}}}$$

converges to within 0.02. We optimized the size (σ) of the methyl groups and the partial charge (q) of oxygen with a compensating adjustment of the sulfur charge. The optimized parameters are listed in Table 1. With the new charges, the dipole moment is 4.39 D, slightly smaller than for the 1995 model and some other models (so-called P2 [10], RS [11] and OPLS [12], compared in [4]). However, it fully agrees with correlated quantum-chemical estimates of the dipole moment of DMSO in the liquid: MBPT2/6-311(2d, p) calculations with a self-consistent reaction-field treatment ($\epsilon = 46$) give 4.40 D [13]. The density is equal to its experimental value with a very small error bar. The heat of vaporization is very close to its experimental value, the residual deviation of 0.4 kJ/mol being within the experimental error. Inclusion of the σ of oxygen into the set of optimizable parameters did not significantly improve these results.

From the final optimized parameter set (Table 1), we have calculated several physical properties of DMSO that are experimentally known at 298 K and ambient pressure (Tables 2 and 3). For direct comparison, we have also calculated them with the 1995 parameters, but under the same simulation conditions as for the new model, and included them in Table 2. The diffusion coefficient has been calculated from the slope of the centre-of-mass mean-square displacement in 200 ps of *NPT* simulation (least-squares fit between 30 and 150 ps). The thermal expansion coefficient, the isothermal compressibility and the specific heat were calculated by finite differencing using two additional simulations of 200 ps each: *NPT* at 283 and 313 K (thermal expansion coefficient), *NVT* at 1.102 and

Table 3
Rotational correlation times

Bond vector	S–O	S–CH ₃
Stretched exponential		
τ_1 (ps)	10.58	8.71
τ_2 (ps)	3.50	3.14
τ_1/τ_2	3.02	2.77
Debye model		
τ_1 (ps)	10.18	8.43
τ_2 (ps)	3.21	2.89
τ_1/τ_2	3.17	2.92

Table 2
Physical properties of liquid DMSO at 298 K and 0.1013 MPa

Property	1995 model ^a ([1]) ^b	1995 model ^a (with YASP) ^c	This work ^a	Exper. ^d
Density (kg m ⁻³)	1099	1143 (3)	1095 (2)	1095
Heat of vaporization (kJ mol ⁻¹)	52.87	54.89 (0.07)	52.42 (0.05)	52.88
Diffusion coefficient (10 ⁻⁵ cm ² s ⁻¹)	1.1	0.68 (0.02)	0.88 (0.02)	0.8 ([19])
Rotational correlation time (ps) ^e	3.9	4.18 (0.01)	3.50 (0.01)	5.2 ([20])
Thermal expansion coefficient (10 ⁻³ K ⁻¹)	0.91 (0.11)	0.90 (0.11)	0.87 (0.09)	0.928
Isothermal compressibility (10 ⁻⁷ Torr ⁻¹)	0.90 (0.10)	0.61 (0.09)	0.67 (0.07)	0.70
Specific heat (J mol ⁻¹ K ⁻¹)	108 (7.7)	104 (8)	101 (6)	118.28
Excess Helmholtz free energy (kJ mol ⁻¹)	-29.7 (0.8)	-29.5 (0.4)	-29.8 (0.2)	-29.7
Static dielectric constant	30	55 (8)	49 (4)	46
Shear viscosity (cP)	1.26–1.29 (0.24)	1.8 (0.2)	1.74 (0.14)	1.991

^a Error bars of the calculated properties are given in parentheses.

^b Values calculated with GROMOS, quoted from [1].

^c Values recalculated with YASP in [1] under the same conditions as for the new model.

^d Unless mentioned, experimental data are taken from [18].

^e τ_2 of the S–O vector.

1.111 g/cm³ (isothermal compressibility), and NVT at 283 and 313 K (specific heat).

The excess Helmholtz free energy of liquid DMSO was calculated by thermodynamic integration [14]

$$\Delta A = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda, \quad (2)$$

in which the U is made a function of a parameter λ :

$$U(\lambda) = \lambda^2 \times U. \quad (3)$$

When λ changes from 0 to 1, the system changes from no interaction (ideal gas) to full interaction (liquid DMSO). $\langle \dots \rangle_\lambda$ denotes an ensemble average at a specific λ value. The charges are scaled by λ and the Lennard–Jones ε are scaled by λ^2 , σ not being affected by λ . We have performed 11 simulations of 200 ps each for 11 values of λ from 0 to 1 with an increment of 0.1. The error bar on $\langle \partial U(\lambda)/\partial \lambda \rangle_\lambda$ at each λ value was less than 0.2 kJ/mol. The integral was evaluated numerically using the trapezoidal rule; an integration using cubic splines gave the same value.

The static dielectric permittivity has been determined via the Clausius–Mosotti equation from the fluctuations of the total dipole moment in a 2-ns NVT simulation as in [1]. The shear viscosity has been calculated using our reverse non-equilibrium molecular dynamics (RNEMD) method [15,16]. Two nanoseconds of NPT simulation were performed. The center-of-mass velocities between two molecules were exchanged every 10, 30, 100, 300, 1000 or 3000 time steps. Exchange period between 30 and 1000 steps gave stable results. The values in Table 2 are for an exchange period of 300 ps.

The rotational correlation times τ_k for normalized bond vectors \mathbf{u} (Table 3) are defined as

$$\tau_k = \int_0^\infty C_k(t) dt, \quad (4)$$

where $C_k(t)$ is the orientational correlation function defined by the first and the second Legendre polynomials $C_1(t) = \langle \mathbf{u}(t) \cdot \mathbf{u}(0) \rangle$ and $C_2(t) = \frac{1}{2} \langle 3[\mathbf{u}(t) \cdot \mathbf{u}(0)]^2 - 1 \rangle$, respectively. The integral (4) is evaluated by fitting to $C_1(t)$ and $C_2(t)$ a stretched exponential $\exp(-t/\alpha)^\beta$, which has an analytical

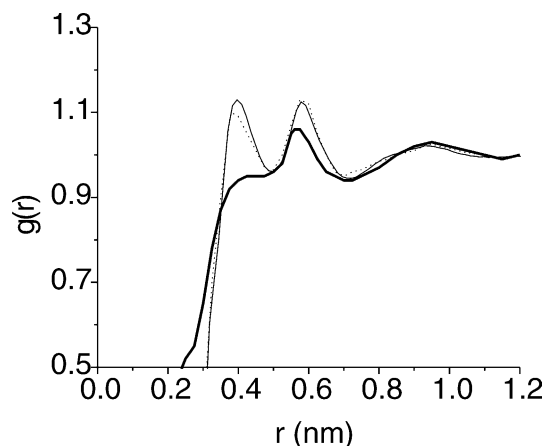


Fig. 1. Pair correlation function $g(r)$ of liquid DMSO (weighted sum) from neutron scattering [17] (thick solid line), from the 1995 model [1] (dashed line) and from this work (solid line).

integral. This is in general more accurate than assuming an exponential form (Debye model) of $C_k(t)$. For comparison with Ref. [1], values obtained from a linear fit to $C_k(t)$ in a semilog representation are given in Table 3 as well. They are slightly smaller than the corresponding correlation times obtained via the stretched exponential. The ratios τ_1/τ_2 , however, are close to 3 for both the S–O and the S–C bonds. This means the molecular reorientation is not far from the idealizing Debye model.

The pair correlation function (weighted sum of heavy-atom contributions with weighting factors from [17]) differs marginally from that of the 1995 model [1] (Fig. 1). Both show the correct peak positions compared to experiment [17] but fail to give the proper relative intensities for the first two peaks. This behavior is also seen for the other four-site models collected by Skaf, see Fig. 1 of Ref. [4].

3. Results and discussion

The new parameterization of the DMSO force field works well with a reaction-field treatment of the electrostatic interactions together with an atomic cutoff. The high dielectric constant of DMSO makes the reaction-field method a very

good approximation, which implies that the parameters will also work well for Ewald-summation or particle-mesh type schemes. Yet, the new parameterization is similar enough to the 1995 model that its performance and applicability as a solvent should not have changed too much.

For most properties, the new model (column 4 in Table 2), performs slightly better than the 1995 model as reported in [1] (column 2), if one takes experiment as the reference (last column). [It performs significantly better, if one compares to the 1995 model under the same simulation conditions as the new model (column 3).] The density is spot-on. The heat of vaporization is marginally worse but the closely related excess Helmholtz free energy marginally better. The derivative properties are of similar quality with the isothermal compressibility slightly improved, the specific heat slightly worse and the two thermal expansion coefficients within their respective error bars. A significant and consistent improvement is found for the transport properties, the relative error in the diffusion coefficient being reduced from 37% to 10% and for the shear viscosity from –35% to –13%. Interestingly, while the translation is slower in the new model, all re-orientational motions are faster, as seen from the re-orientational correlation times (Table 3). Moreover, τ_1 is in good agreement with that of other DMSO models [4]. Consistent with this, the dielectric constant of the new model is larger than of the 1995 model. It agrees with the experimental value to within the error bar, whereas the 1995 model underestimated it by 30%.

As a side effect, the variation of the density with the cutoff distance has been reduced compared to the 1995 model. For $1.0 \text{ nm} \leq r_{\text{cutoff}} \leq 1.7 \text{ nm}$, the 1995 model gives densities between 1136 kg/m^3 (1.1 nm) and 1145 kg/m^3 (1.4 nm), the new model between 1093 kg/m^3 (1.1 nm) and 1097 kg/m^3 (1.5 nm). This corresponds to a reduction of the relative scatter from 0.79% to 0.37%. The enthalpy of vaporization increases almost monotonically with the cutoff in both models. Also here, the increase is smaller in the new model (1.9 kJ/mol from 1.0 to 1.7 nm) than in the 1995 model (3.3 kJ/mol).

In summary, the new model is advantageous if a more rigorous treatment of the Coulomb interactions than the twin-range method is used, or if the density, the transport coefficients or the dielectric properties are crucial.

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