A Force Field for Liquid Dimethyl Sulfoxide and Physical Properties of Liquid Dimethyl Sulfoxide Calculated Using Molecular Dynamics Simulation

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Abstract: A computational model of dimethyl sulfoxide (DMSO) is presented. The model is rigid and uses a pairwise additive potential energy function. It is based on parameters of existing models and the GROMOS force field. In trial molecular dynamics simulations the parameters were optimized with respect to the experimental density, the heat of vaporization, and the self-diffusion coefficient of liquid DMSO. Simulations using the final model reproduced these properties. It is important for a reliable model to be able to reproduce experimental data not used in the parameterizing procedure. Other physical properties of liquid DMSO, including rotational correlation time, thermal expansion coefficient, isothermal compressibility, specific heat, excess Helmholtz free energy, static dielectric permittivity, and shear viscosity have also been calculated from molecular dynamics simulations using the model. The results are in good agreement with experiment. However, the comparison with experimental data also suggests that the model slightly overestimates the mobility of DMSO molecules in the liquid.

Introduction

Molecular dynamics simulations are being applied to an increasing range of problems, among which the structure and dynamics of biological macromolecules is not the least important.[1] So far, most of the molecular dynamics studies of such macromolecules have been limited to simulations in vacuo, in the crystal or in aqueous solution, while many of the corresponding experiments have been carried out in organic solvents, dimethyl sulfoxide (DMSO) being one of those commonly used. It is important to describe the solvent properly if environmental effects are large and are to be analyzed via simulations. A well-behaved microscopic computational model of the organic solvent tested against experimental data not only makes this incorporation practical but also gives one more confidence in the results from such simulations. On the other hand, comparison with experimental properties may also suggest possible shortcomings of a model and indicate the necessary caveats when results of further work using the model are interpreted.

To our knowledge, only a limited number of molecular dynamics studies of liquid DMSO have been reported so far. Rao and Singh[2] have suggested a model and used it to determine the differences in the free energy of solvation of DMSO and methanol in water. This model has been used by Vaisman and Berkowitz[3] in their study of DMSO–water mixtures and by Mierke and Kessler[4] in their study of a hexapeptide in DMSO. Luzar, Soper, and Chandler carried out neutron diffraction and computer simulation studies of liquid DMSO.[5] They presented two models based on test simulations adjusted to the experimental density, the heat of vaporization, and the dipole moment. Comparing the intermolecular atom pair distribution functions from simulations with their neutron diffraction results, they concluded that their models and that of Rao and Singh all gave results in good agreement with the neutron diffraction data, but there also are some minor discrepancies. While the model of Rao and Singh gives the best structural results (the weighted sum of the heavy atom–heavy atom pair distribution functions) in comparison with the neutron diffraction data,[5] we found that it underestimates the heat of vaporization of liquid DMSO by about 30% and overestimates the self-diffusion coefficient by a factor of 3 compared to experimental results. We found the model of Luzar, Soper, and Chandler to give a factor 1000 too high pressure. Therefore, we decided to search for a model which gives optimal agreement for the density, heat of vaporization, and self-diffusion coefficient: properties that are essential for it to serve as a solvent model.

We present here a molecular dynamics simulation study of liquid DMSO with the GROMOS programs.[6] Our purpose is to develop a simple model of DMSO suitable for computer simulation work of systems with DMSO as a solvent. Although recent quantum-chemical calculations carried out by one of us showed the methyl groups of DMSO to be fairly polar (the fitted charges on each hydrogen atom range from 0.15 to 0.2 e using different methods),[7] we confined ourselves to a united-atom model, that is, each of the two methyl groups is treated as one single atom or interaction site as in the previous models.[2,5] Otherwise there would be six more interaction sites per molecule and the model would be computationally too expensive for our purpose. We also kept the model rigid and the potential energy function pairwise additive, taking into account polarization and other effects only in an effective way.[8] We used the GROMOS force field parameters for similar atom types[6] as a starting point. This may lead to a model more consistent with the existing

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[1] (a) McCammon, J. A.; Harvey, S. C. *Dynamics of Proteins and Nucleic Acids*; Cambridge University Press: Cambridge, 1987. (b) Karplus, M.; Petsko, G. A. *Nature* **1990**, *347*, 631–639. (c) van Gunsteren, W. F.; Berendsen, H. J. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 992–1023.

[2] Rao, B. G.; Singh, U. C. *J. Am. Chem. Soc.* **1990**, *112*, 3802–3811.

[3] Vaisman, I. I.; Berkowitz, M. L. *J. Am. Chem. Soc.* **1992**, *114*, 7889–7896.

[4] Mierke, D. F.; Kessler, H. *J. Am. Chem. Soc.* **1991**, *113*, 9466–9470.

[5] Luzar, A.; Soper, A. K.; Chandler, D. *J. Chem. Phys.* **1993**, *99*, 6836–6847.

[6] van Gunsteren, W. F.; Berendsen, H. J. C. *Groningen Molecular Simulation (GROMOS) Library Manual;* Biomos: Groningen, 1987.

[7] Müller-Plathe, F. *Braz. J. Phys.* **1994**, *24*, 965–976.

[8] Berendsen, H. J. C.; Straatsma, T. P. *J. Phys. Chem.* **1987**, *91*, 6269–6272.

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Table 1. Potential Energy Function Parameters and Geometry of the DMSO Model

atom type	S	O	CH_3
ϵ (kJ/mol)	1.2970	1.7154	0.9414
σ (angstrom)	3.56	2.63	3.66
Q (e)	0.139	−0.459	0.160
mass (amu)	32.0600	15.9994	15.0350
$r_{S-O} = 1.53$ Å		$\angle O-S-C = 106.75°$	
$r_{S-C} = 1.95$ Å		$\angle C-S-C = 97.4°$	

GROMOS force field for biological molecules and thus fulfil our purpose better.

A series of trial simulations was first carried out with parameters being adjusted. The set of parameters which best reproduces the experimental density, heat of vaporization, and self-diffusion coefficient and is reasonably consistent with the neutron diffraction data in the literature[5] is presented as our final model. This procedure for developing computational models of small molecules is somewhat "standard" and has been widely used.[8−10] Using the final model we have calculated some other physical properties of liquid DMSO, including thermal expansion coefficient, isothermal compressibility, specific heat, excess Helmholtz free energy, static dielectric permittivity, and shear viscosity. The latter two are directly related to the bulk properties of DMSO as a solvent. Results are compared with experimentally determined properties of liquid DMSO.

Method

Potential Energy Function. Each DMSO molecule is treated as a rigid object, consisting of four interaction sites, corresponding to the S atom, the O atom and the two CH_3 groups (as united atoms), respectively. The geometry is listed in Table 1. It is the same as that in the crystal structure,[11] except for the C−S bond which has been slightly lengthened (the crystal structure gives a C−S bond length of 1.8 Å, see below). Intermolecular interactions between DMSO molecules are of the form

$$V = \sum_i \sum_j Q_i Q_j/(4\pi\epsilon_0 r_{ij}) + \sum_i \sum_j 4\epsilon_{ij}(\sigma_{ij}^{12}/r_{ij}^{12} - \sigma_{ij}^{6}/r_{ij}^{6}) \qquad (1)$$

in which the sums are over pairs of atoms i,j on different molecules. Q_i and Q_j are the partial charges and r_{ij} is the distance between the two atoms. The Lennard-Jones parameters for atom pairs of different atom types are determined by the mixing rules $\epsilon_{ij} = (\epsilon_{ii}\epsilon_{jj})^{1/2}$ and $\sigma_{ij} = (\sigma_{ii} + \sigma_{jj})/2$.

Molecular Dynamics Simulations. The system consists of 432 DMSO molecules in a cubic box. All simulations have been carried out either in the NPT ensemble or in the NVT ensemble. Periodic boundary conditions were imposed. When necessary, the temperature and the pressure were kept constant using the weak coupling method[12] with a relaxation time of 0.1 ps for the temperature and 0.5 ps for the pressure. The internal degrees of freedom of DMSO were constrained using SHAKE.[13] The length of the time steps was 2 fs. Nonbonded interactions were calculated using a molecule-based pair list. Unless otherwise specified, a twin range cutoff method was used with respect to the distance between the centers of geometry of the DMSO molecules. The interactions between two molecules at a distance in between the short-range cutoff and the long-range cutoff were calculated only when the pair list was updated and were added directly to the short-range interactions for intermediate time steps. The short-range cutoff was 0.9 nm and the long-range cutoff 1.5 nm. The nonbonded-pair list was updated every 10 time steps. Since it is not possible to calculate the static dielectric permittivity from a molecular dynamics simulation without a reaction field correction to the long-range interactions (see below),[14] the simulation for calculating the static dielectric permittivity and the shear viscosity has been carried out using a cutoff of 0.9 nm and a reaction field correction to the long-range interactions.[15]

Trial simulations were carried out in the NVT ensemble at 298 K with the experimental density of liquid DMSO (length of the box sides is 3.712 17 nm). For each set of the trial energy function parameters, the initial system was first subjected to 200 steps of energy minimization. Then a 40 ps molecular dynamics simulation was used for equilibration. Potential energy, pressure, self-diffusion coefficient, and atom pair distribution functions were then averaged over a 50-ps simulation. For the optimization of Lennard-Jones parameters we started from the GROMOS[6] parameters for similar atom types and tried various modifications. The quantum-chemical calculations of DMSO by Müller−Plathe showed that the methyl groups are quite polar.[7] To account for this effect within a united-atom model, we used slightly lengthened S−C bonds. This modification leads to better agreement with experiment for the properties considered here. Modifying the atomic partial charges in the Rao and Singh model has also been tried but did not give better results. The charge distributions calculated in ref 7 are also very close to the values in that model. So our final model adopts the same charge distribution as the Rao and Singh model. This leads to a dipole moment of 4.59 D for a DMSO molecule with the modified S−C bond length. The experimental dipole moment of DMSO in the gas phase or in nonpolar solvent is 3.96 D.[16] Quantum-chemical calculations on DMSO using a reaction-field approximation for the surrounding solvent[7] indicate that the dipole moment of DMSO in the liquid phase is more like 4.4−4.5 D. It has also been found necessary to use dipole moments larger than the gas-phase value in water models to account for the effects of polarization in the liquid phase.[8]

The final parameter set of our model is listed in Table 1. This set has been used in calculating the physical properties of liquid DMSO. A 60-ps constant-pressure simulation was carried out with this parameter set and the average box length (3.708 nm) from this simulation has been used in further constant-volume simulations. The density, heat of vaporization, self-diffusion coefficient, rotational correlation time, and atom pair distribution functions reported below have also been calculated using this 60-ps simulation.

The thermal expansion coefficient was calculated from two 50-ps NPT simulations with different temperatures, 283 and 313 K, respectively; the isothermal compressibility was calculated from two 60-ps NVT simulations with different volumes, the length of the box sides being 3.705 and 3.695 nm, respectively; and the specific heat was calculated from two 120-ps NVT simulations with different temperatures, 298 and 313 K, respectively. Unless noted otherwise, the remaining *simulation parameters* for these simulations were as follows: temperature, 298 K; pressure, 1 atm; and box length, 3.708 nm. Finite differences were used to estimate these quantities which are derivatives in a strict sense. We did not calculate them from the fluctuations of corresponding quantities, since in practical simulations, these fluctuations are affected by the cutoff and the manner of coupling to the temperature or pressure bath.

The excess Helmholtz free energy of liquid DMSO was calculated by using the thermodynamic integration formalism[17]

$$\Delta A = \int_0^1 \langle \partial V(\lambda)/\partial\lambda \rangle_\lambda \, d\lambda \qquad (2)$$

in which the potential energy function of the system is coupled with a parameter λ. When λ changes from 0 to 1, the system changes from

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(9) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926−935.

(10) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J. In *Intermolecular Forces*; Pullman, B., Ed.; Reidel: Dordrecht, 1981; pp 331−342.

(11) Thomas, R.; Showemaker, C. B.; Eriks, K. *Acta. Crystallogr.* **1966**, *21*, 12−20.

(12) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684−3690.

(13) Ryckaert, J. P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327−341.

(14) Neumann, M. *Mol. Phys.* **1983**, *50*, 841−858.

(15) Barker, J. A.; Watts, R. O. *Mol. Phys.* **1973**, *26*, 789−792.

(16) Glasel, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 372−375.

(17) Kirkwood, J. G. *J. Chem. Phys.* **1935**, *3*, 300−313. For a recent discussion, see: King, P. M. In *Computer Simulation of Biomolecular Systems*; van Gunsteren, W. F., Weiner, P. K., Wilkinson, A. J., Eds.; Escom: Leiden, 1993; pp 267−310.

one state to the other. $\langle ... \rangle_\lambda$ denotes an average over the ensemble at a specific λ value. The potential energy function of the system was chosen to be changing with λ as

$$V(\lambda) = (1 - \lambda)^3 \sum_i \sum_j [Q_i Q_j / (4\pi\epsilon_0 r_{ij}) - 4\epsilon_{ij}{\sigma_{ij}}^6 / {r_{ij}}^6] + (1 - \lambda)^5 \sum_i \sum_j 4\epsilon_{ij}{\sigma_{ij}}^{12}/{r_{ij}}^{12} \quad (3)$$

During a 100-ps simulation in the NVT ensemble λ was gradually changed from 1 to 0 and then in another 100-ps simulation changed back from 0 to 1. All DMSO molecules in the box have been annihilated and recreated during this process.

The static dielectric permittivity ϵ can be determined from the fluctuation of the total dipole moment M in the volume V[14]

$$(\epsilon - 1)(2\epsilon_{RF} + 1)/(2\epsilon_{RF} + \epsilon) = (\langle M^2 \rangle - \langle M \rangle^2)/3\epsilon_0 V k_B T \quad (4)$$

ϵ_{RF} is the dielectric permittivity used for the reaction field correction of the long-range interactions[15] during the simulation. This equation shows that when there is no reaction field correction, i.e., $\epsilon_{RF} = 1$, the fluctuation of the dipole moment does not increase linearly with the dielectric permittivity, but quickly approaches a limiting value when the dielectric permittivity increases. We carried out a 1.2-ns simulation in the NVT ensemble, using the reaction field correction[15] with the experimental dielectric permittivity of liquid DMSO at 298 K (ϵ_{RF} = 46). The fluctuation of the total dipole moment of the system was then averaged and the static dielectric permittivity obtained.

The shear viscosity of liquid DMSO was also calculated using the above 1.2-ns simulation, during which the off-diagonal elements of the pressure tensor were saved every time step. The shear viscosity was determined using the time trajectory of these elements in the same manner as in ref 18.

Results and Discussion

General Aspects of the Model. The density and heat of vaporization of liquid DMSO, as well as the self-diffusion coefficient and the rotational correlation time τ_2 of DMSO molecules in the liquid, have been calculated using the final model and are listed in Table 2 together with the corresponding experimentally determined properties at 298 K. The good agreement between the calculated and the experimental density and heat of vaporization is not surprising since the model has been devised to fit these properties. Experimentally, the rotational correlation time has been determined assuming isotropic rotation,[19] while the calculated result in Table 2 corresponds to the reorientation of the S−O vector. The comparison of the calculated self-diffusion coefficient and rotational correlation time with experimental data suggests that the model presented here may slightly overestimate the mobility of DMSO molecules in the liquid. For comparison, we have also calculated the self-diffusion coefficient and rotational correlation time using the model of Rao and Singh[2] and one model of Luzar et al. (noted as P2 in their paper).[5] Using the former model leads to a diffusion coefficient of 2.8 × 10^{-4} cm^2 s^{-1} and a τ_2 of 1.8 ps, and using the latter one leads to a diffusion coefficient of 1.7 × 10^{-4} cm^2 s^{-1} and a τ_2 of 3.2 ps. This suggests that these two models lead to even more mobile DMSO molecules.

Table 2. Physical Properties of Liquid DMSO, Calculated from Simulations and Compared to Experimental Data

property	calcd[a]	exptl[b]
density (g cm^{-3})	1.099	1.095[20]
heat of vaporization (kJ mol^{-1})	52.87	52.88[20]
diffusion coeff (10^{-4} cm^2 s^{-1})	1.1	0.8[21]
rotational correlation time (ps)	3.9	5.2[19]
thermal expansion coeff (10^{-3} K^{-1})	0.91(0.11)	0.928[20]
isothermal compressibility (10^{-7} Torr^{-1})	0.901(0.099)	0.70[20]
specific heat (J mol^{-1} K^{-1})	108.1(7.7)	118.28[b]
excess Helmholtz free energy (kJ mol^{-1})	−29.7(0.8)	−29.7[b]
static dielectric permittivity	30	46[20]
shear viscosity (cP) Einstein	1.26(0.24)	1.991[20]
Green−Kubo	1.29(0.27)	

[a] When calculating the specific heat we have used the experimental ideal gas heat capacity of DMSO.[20] The shear viscosity has been calculated using two methods as in ref 18 and both results are listed in the table. The first one has been calculated using a formula based on the Einstein relation and the second one using a formula based on the Green−Kubo relation.[18] They have been averaged over the results obtained by using each of the three off-diagonal elements of the pressure tensor separately, and errors are estimated as the standard errors of this averaging. If available, estimates of error of the calculated results are given in parentheses. These errors (except for those of the excess Helmholtz free energy and the shear viscosity) are determined by partitioning the simulations into blocks and determining the standard errors of the results averaged over different blocks. The error for the excess Helmholtz free energy is taken as the hysteresis between the two results from the forward and the backward simulations. [b] Experimental data are for liquid DMSO at 298 K. The experimental value for the excess Helmholtz free energy has been derived from the experimental vapor pressure taken from ref 20. The experimental value for the specific heat has been derived using the experimental heat capacity, isothermal compressibility, and thermal expansion coefficient taken from ref 20.

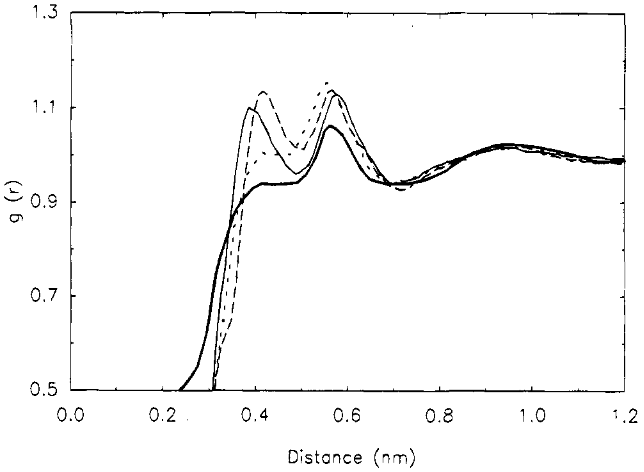

Figure 1. Weighted sum of the heavy atom−heavy atom pair distribution functions of liquid DMSO, calculated from molecular dynamics simulations using the models presented here (—), suggested by Rao and Singh[2] (- - -), and suggested by Luzar et al[5] (— —). Experimental data taken from ref 5 are also shown as a thick solid line. The weighting factors are the same as in ref 5.

The radial distribution functions $g(\mathrm{r})$ between different atom pairs have been calculated and compared with those calculated from simulations using the model suggested by Rao and Singh[2] and Luzar et al.[5] The results from using the latter two models are essentially the same as those given in ref 5. Generally, the structural properties are not very sensitive to the potential energy function parameters used. The weighted sum of heavy atom−heavy atom pair distribution functions has been determined experimentally using neutron diffraction.[5] Figure 1 shows this distribution (experimental weighting factors[5] have been used) calculated using the model presented here and the other two models, together with the experimental results taken from ref

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(18) Smith, P. E.; van Gunsteren, W. F. *Chem. Phys. Lett.* **1993**, *215*, 315−318.

(19) Kovacs, H.; Kowalewski, J.; Maliniak, A. *Acta Chem. Scand. A* **1987**, *41*, 471−479.

(20) Riddick, J. A.; Bunger, W. B.; Sakand, T. K. *Organic Solvents Physical Properties and Methods of Purification*; John Wiley and Sons: New York, 1986.

(21) Cebe, E.; Kaltenmeier, D.; Hertz, H. G. *Z. Phys. Chem. (Neue Folge)* **1984**, *140*, 181−189.

5. When the first peak along the curve is considered, the model presented here leads to slightly better agreement with the neutron diffraction data[5] than model P2 in ref 5, but worse than the model of Rao and Singh.[2] When the second peak is considered, our final model leads to slightly better agreement with experiment than the other two models. However, all three models have discrepancies with experiment at shorter distances probably due to the polar nature of the methyl groups and the limitation of the united-atom description.[5] The comparison of simulated radial distribution function data with experimental neutron diffraction data is notoriously prone to uncertainties, due to the fact that the "experimental" $g(r)$ is a weighted sum over a Fourier transformed set of differential neutron scattering cross sections, assuming incoherent scattering to be absent. Having to choose between a better reproduction of $g(r)$ with a 30% too low heat of vaporization (model of ref 2) and a worse reproduction of $g(r)$ with correct energy, density, diffusion, etc. (our model, Table 2), we chose the latter in view of the uncertainty in neutron diffraction data.

Physical Properties of Liquid DMSO. The calculated thermal expansion coefficient α, isothermal compressibility β, and specific heat C_V are listed in Table 2 together with their experimental values. The calculated α value agrees quite well with the experimental value. The β is overestimated. C_V is underestimated by about 10 J mol^{-1} K^{-1} compared to the experimental value. The calculated $d\langle U\rangle/dT$ is 26.7 ± 7.7 J mol^{-1} K^{-1} ($\langle U\rangle$ denotes the averaged intermolecular interaction energy). There is quite a large statistical error in the calculated quantity. However, another possible cause of this underestimation may be that the united-atom model ignores the coupling between the internal rotation of the methyl groups with the intermolecular interactions in the liquid phase. The contribution of the internal rotation to the specific heat has been included in the ideal gas heat capacity, but not calculated in the simulation. Since the hydrogen atoms are fairly polar,[7] the coupling may be strong and may potentially influence the heat capacity at the given temperature.

The calculated excess Helmholtz free energy is also in good agreement with experimental results (Table 2). Figure 2 shows the free energy as a function of λ from both the forward and the backward simulations. The hysteresis is reasonably small, suggesting that the process was reversible and the resulting free energy value has converged well.

The fluctuation of the total dipole moment of the system has converged in the 1.2-ns simulation. The calculated static dielectric permittivity is smaller than the experimental value (Table 2). However, the agreement is good enough to make our model useful in practical simulations of macromolecules in DMSO solution. The calculated shear viscosity is also smaller than the experimental result (Table 2). This is consistent with the observation that the model overestimates the mobility of DMSO molecules in the liquid. When the simple nature of the model is considered, the agreement between the calculated and experimental values of these bulk solvent properties is also good. We believe that agreement with experiment can only be improved by going to an all-atom or even polarizable model.

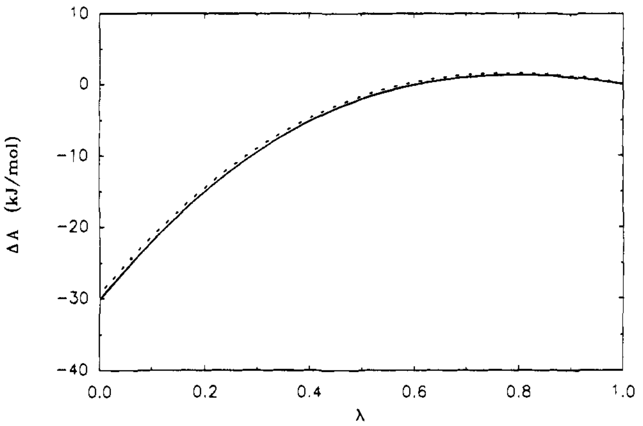

Figure 2. Free energy change as a function of λ in simulations aimed at calculating the excess Helmholtz free energy of liquid DMSO. The forward perturbation is shown as a solid line and the backward as a dashed line.

Conclusions

We have presented a computational model for DMSO modified from existing models and the GROMOS force field. The final model is based on trial simulations to reproduce the experimental density, the heat of vaporization, and the self-diffusion coefficient. Other properties of liquid DMSO, including the thermal expansion coefficient, isothermal compressibility, specific heat, and excess Helmholtz free energy, have been calculated using this model and are in good agreement with experimental data. The static dielectric permittivity and viscosity have also been calculated and found to be in reasonable agreement with experimental results. The mobility of DMSO molecules in the liquid is somewhat overestimated by the model, as can be seen when the self-diffusion coefficient and the shear viscosity are compared with experimental values. For practical reasons, that is, for use as a solvent model in biomolecular simulations, we prefer a computationally inexpensive rigid united-atom model to more sophisticated models such as polarizable or all-atom models. We have shown that such a simple model can be parametrized to give good agreement between calculated and experimental properties of liquid DMSO.

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