Importance of Polarization for Dipolar Solutes in Low-Dielectric Media: 1,2-Dichloroethane and Water in Cyclohexane

William L. Jorgensen,* Nora A. McDonald,
Massimo Selmi, and Paul R. Rablen

Department of Chemistry, Yale University
New Haven, Connecticut 06520-8107

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The intermolecular potential functions that are commonly used for the simulation of biomolecular systems in programs such as AMBER, BOSS, CHARMM, and GROMOS are pairwise-additive; polarization effects are only represented in an average sense through the use of partial charges that yield gas-phase dipole moments enhanced 10−20% over experimental values.[1] This approach has been remarkably successful for simulations of a wide range of systems including pure water,[2] aqueous solutions of neutral organic molecules,[3] and even $Cl^-(H_2O)_n$ and $Na^+(H_2O)_n$ clusters.[4] However, without polarization, energetic errors become increasingly unacceptable for stronger ion−molecule interactions.[5] Furthermore, it was noted by Kumpf and Dougherty that alkali cation−π interactions are too weak by ca. 50% with the OPLS model of benzene and Åqvist's ion parameters.[6] The problem also occurs for ammonium ion−benzene interactions and can be remedied by explicit consideration of polarization, as recently reported by Caldwell and Kollman.[7] Though the need for polarization with such strong interactions is not unexpected, we document here that polarization is also important for polar molecules in low-dielectric media, e.g., hydrocarbon solvents or hydrophobic regions in proteins.

The $(\epsilon - 1)/(2\epsilon + 1)$ dependence in the Kirkwood−Onsager expression for the free energy of solvation of a dipole states that 40% of the free energy of transfer from the gas phase to a solvent with high dielectric constant ($\epsilon \rightarrow \infty$) is achieved at $\epsilon = 2$.[8] Thus, for example, in conformational or tautomeric equilibria for isomers with different dipole moments μ, a significant portion of the maximal solvent effect should be apparent in a hydrocarbon solvent. Accurate experimental data on this point covering both the gas phase and a range of solvents are not plentiful.[9] An exception is for the gauche/trans equilibrium of 1,2-dichloroethane (DCE); the recent IR results of Wiberg et al. are shown in Table 1.[10] In support of the Kirkwood−Onsager model, there is a reduction in the gauche ($\mu \approx 3.5$ D) − trans ($\mu = 0$) free energy difference, ΔG, of 0.50 kcal/mol between the gas phase and cyclohexane, which is 35% of the $\Delta\Delta G$ upon transfer to acetonitrile, 1.42 kcal/mol. The importance of polarization in nonpolar solvents is also apparent in the recent development of semiempirical quantum mechanical solvation models.[11]

Table 1. Trans Populations and Gauche − Trans Free Energy Differences (kcal/mol) for DCE at 25 °C

		expt[a]		Monte Carlo[b]		SCRF[a,c]	
medium	ϵ	% trans	ΔG	% trans	ΔG	% trans	ΔG
gas phase	1.0	79.1	1.20	78.3	1.17	(79.1)[d]	(1.20)[d]
cyclohexane	2.0	62.0	0.70	75.3	1.07	66.5	0.81
cyclohexane-SSPM[e]				60.5	0.66		
di-*n*-butyl ether	3.1	54.2	0.51			58.3	0.61
tetrahydrofuran	7.6	37.6	0.11	29.2	−0.11		
neat DCE	10.4	35[f]	0.04[f]	36.1	0.07		
acetone	20.7	28.3	−0.14			37.6	0.11
acetonitrile	36.0	25.6	−0.22	22.2	−0.33	36.5[g]	0.08[g]

[a] Reference 10. [b] This work. Uncertainties (1σ) for percent trans and ΔG are 3% and 0.1 kcal/mol. [c] Becke3LYP/6-311+G**. [d] Fixed. [e] MC results with solvent polarization. [f] Tanabe, K. *Spectrochim. Acta, Part A* **1972**, *28A*, 407. [g] Extrapolated.

With a united-atom, nonpolarizable (UANP) model for an alkane solvent, there are no partial charges on the CH_n units and there is no electrostatic response to a change in μ for a solute. Simulation of DCE in cyclohexane would be no different than for a chargeless model of DCE, basically butane, which shows no solvent effect for the gauche/trans equilibrium upon transfer from the gas phase to a NP hydrocarbon solvent.[12,13] With all-atom, non-polarizable (AANP) models for alkanes there are partial charges on C and H, e.g., $-0.12e$ and $0.06e$ for OPLS cyclohexane.[13] We set out to see if this would be enough to reproduce the observed conformational shift for DCE. AANP parameters were developed for DCE in the AMBER/OPLS format including harmonic terms for bond stretching and angle bending, Fourier series for torsional energetics, and Coulomb plus Lennard-Jones potentials for 1,4 or greater nonbonded interactions.[1a,b] The potential functions give excellent results for many properties including the gas-phase structure and gauche − trans energy difference (1.12 kcal/mol) as well as the density (1.234 g cm^{-3}; experimental, 1.246 g cm^{-3}) and ΔH_{vap} (8.26 kcal/mol; experimental, 8.40 kcal/mol) of the pure liquid at 25 °C, as obtained from Monte Carlo (MC) simulations.[14] The conformer populations for DCE were then computed in the gas phase, in the pure liquid (AANP), and in the OPLS models for cyclohexane (AANP),[13] tetrahydrofuran (UANP),[15] and acetonitrile (UANP).[16] MC free-energy perturbation (FEP) calculations yielded ΔG at 25 °C and 1 atm as a function of the Cl−C−C−Cl dihedral angle with all other internal degrees of freedom variable for the DCE solute. The computational procedure has been described previously;[13,17] key points are the use of 260 nonflexible solvent molecules in periodic cubes, ca. 14 Å nonbonded energy cutoffs, nine FEP double-wide sampling

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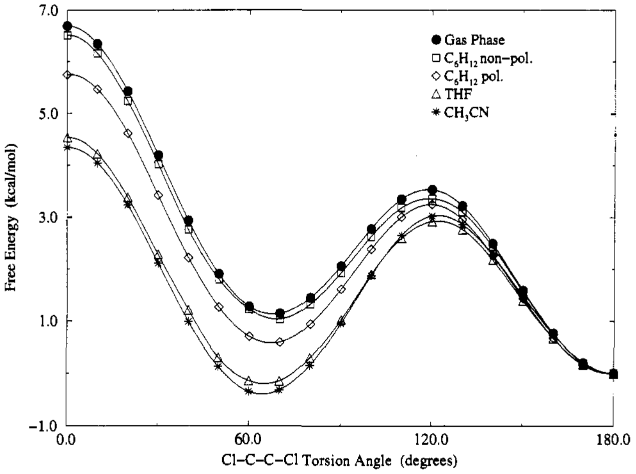

Figure 1. Computed free energy profiles for rotation about the Cl−C−C−Cl bond in 1,2-dichloroethane; the trans and gauche conformers correspond to the wells at 180° and 60°. The average dihedral angle for gauche decreases with increasing solvent polarity.

windows ($\Delta\phi = \pm 10°$), and equilibration and averaging periods of 10^6 and 2×10^6 configurations. Convergence is rapid for such calculations in nonaqueous solvents. The results are summarized in Table 1 and Figure 1.

The MC results are in close accord with the experimental data for the dipolar solvents and nicely reproduce the observed range from the gas phase to acetonitrile. It is likely that the polarization term is being absorbed by the choice of partial charges for the dominant Coulombic terms in these cases. However, only 3% of the observed 17% reduction in percent trans or 0.1 of 0.5 kcal/mol in ΔG between the gas phase and cyclohexane is obtained with the AANP model. We then pursued a simple solvent polarization model (SSPM) for low-dielectric media ($\epsilon < 5$) by just adding the polarization of solvent molecules by the solute. Solvent−solvent polarization, which is also present in the pure liquid, is assumed to be small and reflected in the OPLS parametrization. The electric field $\mathbf{E}^q{}_i$ is calculated at non-H atoms of the solvent molecules from only the permanent charges of the solute atoms and the induced dipoles are then given by $\boldsymbol{\mu}_i = \alpha_i \mathbf{E}^q{}_i$. Similar models have been considered by others.[18] An effective polarizability α for the solvent is used based on the high-frequency dielectric constant or the optical density as $\epsilon_{HF} = n^2 = 1 + 4\pi\alpha/V$, where V is the volume per molecule.[19] For cyclohexane, the polarizability is divided between the carbons such that $\alpha_i = 2.39$ Å^3 for each (with $\mu = 0$, $\epsilon \approx n^2 = 2.0$). Optional code was added to BOSS to compute the electric field at the solvent sites and $U_{pol} = -(1/2)\Sigma \mathbf{E}^q{}_i \cdot \boldsymbol{\mu}_i$. With no optimization of this model or α_i, the MC simulations were repeated and percent trans for DCE dropped to 60.5%, in excellent agreement with experiment (Table 1). The best SCRF results of Wiberg et al.[10] with a Tomasi-like procedure are also reported in Table 1; the overall range for ΔG is compressed somewhat in this case.

Given this behavior, it is apparent that the NP solvent models cannot provide adequately favorable solvation for any dipole in low-dielectric media. As another example, one can consider a water molecule in cyclohexane. Wolfenden and Radzicka have recently addressed free energies of transfer of small molecules from the gas phase to cyclohexane and used the results to argue against the likelihood of single water molecules entering nonpolar cavities in proteins.[20] This position has been challenged by an NMR study of interleukin-1β in which water was detected in a cavity lined only with hydrocarbon side chains.[21] With MC-FEP calculations[13] we have computed the free energy of solvation of a TIP4P water molecule[2a] by annihilation in the OPLS UANP,[22] AANP,[13] and AA-SSPM models of cyclohexane. The results below show that the solvation of water is indeed too unfavorable by 0.6−1.0 kcal/mol with the NP models.

$$H_2O \longrightarrow 0$$

	ΔG in C_6H_{12}
UANP	-0.99 ± 0.16
AANP	-0.56 ± 0.15
AA-SSPM	0.30 ± 0.08
exptl[20]	0.04

Inclusion of the SSPM brings the accord within 0.26 ± 0.08 kcal/mol with water a bit too favorably solvated;[23] the difference can be attributed to the enhanced dipole moment of a TIP4P water molecule, 2.18 D, vs the experimental gas-phase value of 1.85 D. Specifically, an MC-FEP calculation for scaling the TIP4P charges down to yield the gas-phase μ gives a free energy change of 0.28 ± 0.01 kcal/mol in AA-SSPM cyclohexane, which eliminates the discrepancy with the experimental data. AA methane[13] was also annihilated in UANP and AA-SSPM cyclohexane; the ΔGs of -0.34 ± 0.19 and -0.37 ± 0.09 kcal/mol are in good accord with the observed −0.23 kcal/mol.[20] Clearly, explicit polarization is less important with a nonpolar solute in view of the lessened electric field.

In summary, molecular models lacking polarization can lead to significant errors on important issues including conformational equilibria in hydrocarbon solvents and water in proteins. The general solution is to develop a full set of potential functions that incorporate polarization in all cases; however, this is a large undertaking, significantly more computer time is required for use of such potentials, and existing two-body potential functions have been shown to be effective for many problems.[2−4] An alternative for low-dielectric environments is to add to the existing force fields point polarizabilities on nonpolar CH_n units. The present SSPM is particularly attractive as it does not entail iterative solution for the electric field; the use of just first-order polarization also warrants exploration for ion−molecule interactions.

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Supporting Information Available: Force field parameters for DCE and plots of ΔG vs the coupling parameter λ for the annihilations of water and methane and for the TIP4P to experimental μ perturbation in polarizable cyclohexane (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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