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On using the NMR chemical shift to assess polar–nonpolar cross-intermolecular interactions

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Abstract

The possibility of using the NMR chemical shift to evaluate and develop intermolecular potentials for cross-interactions between polar and nonpolar molecules has been examined using the method of molecular dynamics. Such interaction potential models are known to be notoriously difficult to develop. Our work has shown that chemical shift can be obtained quite efficiently in simulations and converges much faster than other properties traditionally used for such evaluations (for example, the infinite dilution activity coefficients, Henry's constants or the solubility of solutes in solvents). We have also found chemical shift to be quite sensitive to the intermolecular potentials which makes it a rather promising property to investigate polar–nonpolar interactions in fluids.

1. Introduction

The determination of cross-intermolecular interactions of polar–nonpolar fluids is one of the most challenging problems in classical and molecular/statistical thermodynamics [1] of liquids. These interactions are needed in classical theories for determining characterization parameters for mixtures, using so-called mixing rules. In addition, they are also needed in all molecular theories of mixtures [2] as well as in molecular simulation methods [3]. The main challenge in obtaining accurate descriptions of such interactions comes from the difficulty of isolating the cross-interactions from the like pair interactions (that are usually better understood). They are usually determined from the properties of dilute mixtures, where at least one pair of like interactions (solute–solute) is unimportant. Such properties include infinite dilution activity coefficients, Henry's constants and infinite dilution partial molar volumes, etc. [1]. The problem with these properties is that they are not particularly simple to estimate using either molecular theories or molecular simulations, except for rather simple fluids [2,3]. In this note we explore the possibility of using the nuclear magnetic resonance (NMR) chemical shift to investigate cross-interactions for polar–nonpolar fluids.

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We will examine the system xenon–water. This system, apart from being of obvious fundamental interest, is also important in many other applications such as biomolecular probes using Xe NMR spectroscopy [4–6]. NMR spectroscopy has become a powerful tool in part because the chemical shift can sensitively distinguish local chemical environments of any chosen nucleus of nonzero spin (e.g., ^{1}H, ^{13}C, ^{129}Xe) [7]. The chemical shift is usually expressed in ppm, although frequency differences are actually measured. High resolution, of the order of better than 1 part in 10^5 of the range of chemical shift values of a nucleus in typical chemical environments, is easily achieved. At the same time, with powerful computers being widely available, chemical shifts for nuclei in an isolated molecule can presently be calculated using ab initio methods or density functional theories. These calculated values have been found to be quite accurate even for complex molecules [8].

The chemical shift is a sensitive function of configuration of atoms constituting the physical system. In particular, intermolecular contributions to the chemical shift are a function of the coordinates of neighboring atoms or molecules relative to the nucleus observed. The observed chemical shift is an average over the configurations of the system, weighted according to their relative probabilities. For a solute in a liquid solvent, the average chemical shifts of the nuclei in the solute therefore depend on the solute–solvent intermolecular interactions. Therein lays the connection between the average (observed) chemical shifts and the intermolecular potentials. We illustrate with the Xe atom as a solute possessing a very wide range of intermolecular chemical shifts and water as a solvent with well-known liquid potentials previously tested against many bulk liquid properties. The Xe–water intermolecular potential serves as a good example of polar–nonpolar interactions.

Because of the strong dependence of the intermolecular chemical shift on the distance between the nucleus (Xe in our solute example) and the individual atoms of the neighboring solvent molecules, the average chemical shift is sensitive to the Xe–solvent potential over a range of distances typically 3–6 Å. With a given description of the dynamic liquid structure of the pure solvent, the Xe–solvent interaction parameters may be determined. For the same reason, the average Xe chemical shift in solution is also sensitive to the 'free volume' provided by the dynamic liquid structure. The solute chemical shift can therefore be used to discriminate between descriptions of pure liquid solvents, when the site–site solute–solvent interactions are well known. This makes the average chemical shift a particularly attractive property for the determination of cross-interactions for complex fluids.

2. Method

The averaging to obtain chemical shift can be carried out in various ways. In this Letter, we suggest a molecular dynamics based method using an algorithm developed by us to study the solubility of gases in liquids. The method has been described in previous publications [9,10] so we will only summarize it here. It consists of a solvent/solution compartment separated from the gas compartment by a semi-permeable membrane. A schematic diagram of the simulation system is shown in Fig. 1. Periodic boundary conditions then lead to a system infinite in the y- and z-directions (parallel to the membranes). In the x-direction this leads to alternating gas and solvent sections of width $L_x/2$ (L_x is the system size in the x-direction, i.e., perpendicular to the membranes). In this study the membrane simply consisted of a single layer of atoms arranged in an FCC configuration. The membrane is formed by tethering the atoms that constitute the membrane to their equilibrium positions with a simple harmonic potential, although other potentials could also be used. The membrane is made permeable to the gas molecules but not the solvent molecules. This has been accomplished for these studies by adjusting the pore size of the membrane, and adjusting the intermolecular interaction between the solvent or gas molecules and the membrane [10].

The density and temperature of the solution compartment can be fixed to correspond to the state condition of interest. In this study, the density of the liquid phase was set equal to the

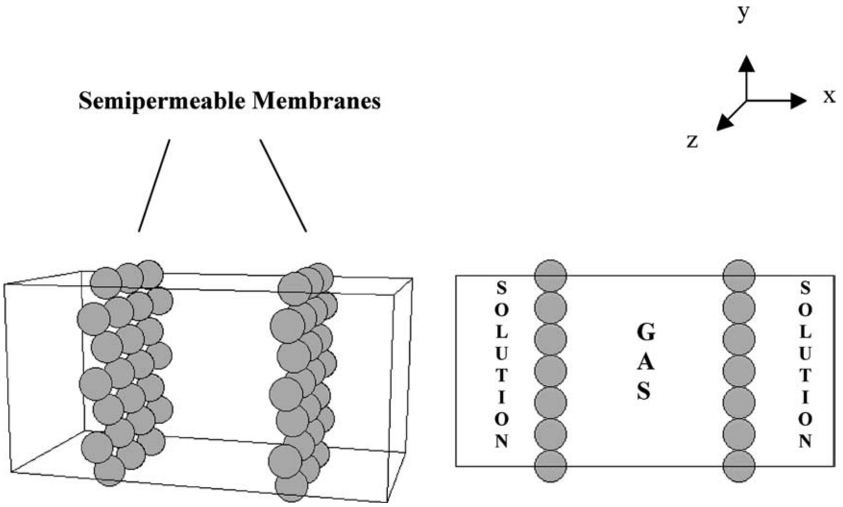

Fig. 1. The basic simulation system for investigating chemical shift and solubility of gases dissolved in liquids. Lines represent the periodic boundaries of the system.

experimental density of water at the temperature of interest. This establishes the volume of the solution compartment once the number of molecules to be included in the solvent compartment is fixed. In these simulations, the solution compartment consisted of 480 molecules (divided between solvent and solute molecules, if desired) and the two membrane walls were constructed of 64 atoms. The volume of the gas compartment has been set to be equal to the solvent compartment (although this is not essential). In the initial setup the gas compartment would also have 480 molecules. However, an arbitrary number between 0 and 480 can then be removed to give the gas any desired density/pressure. The length of the simulation system perpendicular to the membrane has been set to four times that parallel to the membrane. Further, the lengths parallel to the membrane were set to be the same ($L_y = L_z$). These relative dimensions minimize the effect of the membrane on the overall system. The molecules were given a Gaussian velocity distribution corresponding to the system temperature being investigated.

In these simulations, our primary objective is to investigate the ease (or difficulty) of obtaining the average chemical shift from a molecular dynamics simulation for the *chosen* potential model compared to other dilute solution properties such as gas solubilities, or Henry's constants for the *same* potential model. The accuracy with which the chosen potential model predicts these properties was not the focus of this study, although it obviously would be of considerable interest. For this purpose we have initially picked existing intermolecular potential models for xenon and water. In addition, the interactions of these molecules with the membrane walls were fixed so that only xenon atoms, not the solvent molecules, can permeate the membrane. For water, we have tested two widely used potential models, the SPC model and the TIPS4P model. The Xe–Xe potential is irrelevant to the calculations of Xe chemical shifts in this study since the solubility of Xe in the solvent is very small.

The parameters used in our studies are shown in Table 1. The potential models are of the form

$$u = \sum_{i,j} 4\varepsilon_{ij} \left[\left(\frac{r_{ij}}{\sigma_{ij}} \right)^{-12} - \left(\frac{r_{ij}}{\sigma_{ij}} \right)^{-6} \right] + q_i q_j / r_{ij}, \quad (1)$$

where ε and σ are the Lennard-Jones (12:6) energy and size parameters, q the charge, i and j the active sites, while r_{ij} is the scalar distance between the active sites ij. These potential models are known to give a reasonable quantitative picture of a wide range of thermodynamic properties of liquids [2].

Table 1
Interaction parameters for potential models used

	Interacting sites	σ (10^{-10} m)	ε (kJ/mol)	q (e)
Water (SPC)				
	O	3.17	0.65	−0.82
	H	0.0	0.0	0.41
Water (TIPS4P)				
	O	3.1536	0.6491	0
	H	0	0	0.520
	P	0	0	−1.04
Xenon				
	Xe–O	3.26 −3.70	0.65 −1.12	0
	Xe–Xe[a]	3.36–4.23	0.65 −1.93	0

[a] For the results reported here the Xe–Xe parameters are unimportant (except in the behavior of the gas compartment, which is not of direct interest).

The time evolution of this initial system setup was then followed using a fifth-order predictor–corrector scheme for the translational motion and a fourth-order scheme using quaternions for the rotational motion [3]. Temperature was kept constant using a Gaussian thermostat. The simulation system was allowed to equilibrate for 60 000–100 000 time steps. After this, production runs were carried out for 500 000–1 000 000 time steps, each of size 2×10^{-16} s.

After the initial equilibration run, the chemical shift can be obtained during the simulation using the chemical shift function shown in the following equation:

$$\delta = \sum_{O(i)} \sum_{j=6}^{12} O_j/r_i^j + \sum_{H(k)} \sum_{j=6}^{12} H_j/r_k^j. \qquad (2)$$

The values for O_j and H_j that were used in our studies are given in Table 2.

In the molecular dynamics simulations, to ensure that only xenon atoms completely surrounded by water molecules were included in this sum (i.e., to exclude xenon molecules near the membranes for the purpose of averaging the properties of xenon atoms in the solution), only those xenon atoms in the middle half of the solution compartment (see Fig. 1) were included in accumulating the sum in Eq. (2).

Eq. (2) uses a site–site additive approximation for Xe intermolecular shifts. The functions $\sum_{j=6}^{12} O_j/r^j_{\text{Xe–O}}$ and $\sum_{j=6}^{12} H_j/r^j_{\text{Xe–H}}$, taken together, may be considered as the universal chemical shift functions for Xe in the presence of neighboring H_2O molecules. The chosen functional form is based on the form of the calculated ab initio Xe-rare gas intermolecular shift functions that reproduce the mixed second virial coefficients of the Xe chemical shifts measured in the gas phase [11]. The parameters O_j and H_j were obtained by fitting quantum mechanical values of shielding (relative to free Xe atom) for Xe in clathrate hydrates in which the structures of the cages of water molecules which form around the Xe atoms are well established from neutron diffraction studies. The universality of the Xe–O and Xe–H chemical shift functions used here has been established by accurate predictions of Xe chemical shifts in 12 types of clathrate hydrate cages from quantum mechanical calculations in only two types of cages [12].

The Xe–Xe chemical shift contributions are not included in the averaging, thereby resulting in an average appropriate to the infinite dilution limit. The low solubility of Xe in water also means that this limit holds for the experimental value as well. During the simulation we also calculated the solubility of xenon in water (x_i) from the density profiles, since this is simply related to the Henry's constant via the equation

$$H_{i,j} = \lim_{x_i \to 0} \{P_{\text{gas}}\phi_{\text{gas}}/x_i\}, \qquad (3)$$

where P_{gas} and ϕ_{gas} are, respectively, the pressure and experimental fugacity coefficient of xenon in the gas compartment. By comparing the statistical accuracies of the average chemical shift and the solubility obtained in our simulations, we can directly

Table 2
Parameters for the chemical shift function (Eq. (2)). All parameters are in units of ppm × jth power of Å

	$j = 6$	$j = 8$	$j = 10$	$j = 12$
O_j	-0.13684×10^5	0.71463×10^6	-0.204210×10^7	-0.58507×10^7
H_j	-0.77387×10^3	0.116762×10^6	-0.58205×10^6	0.71436×10^6

compare the efficiency of evaluating intermolecular potential models using average chemical shifts against other traditionally used dilute solution properties such as solubility or Henry's constant.

3. Results

The average chemical shift of xenon in water obtained using the method outlined above at 298 K is shown in Fig. 2. For the results shown in Fig. 2, the initial system configuration consisted of a solution section with 15 molecules of xenon and 465 molecules of water. Equilibrium is obtained more rapidly in general if the solution has an excess of xenon. This is because expulsion of xenon from the solution is more rapid than diffusion of xenon into the solution from the gas phase. The gas compartment had 80 molecules of xenon. The results shown are for a case when the results converged somewhat slower than typical. As will be shown later, in many cases they converged within 100 000 time steps. The experimental value for the chemical shift at 298 K is reported to be 196 ppm [13]. Even in the somewhat slower converging case it has converged quite well in less than 0.1 ns to the known experimental value (not the goal here, but of interest). The results shown are for the SPC potential for water and Xe–O parameters of $\sigma = 3.4$ Å, and $\varepsilon = 0.651$ kJ/mol. The results are quite sensitive to the potential parameters. For example, using the SPC model for water and $\sigma = 3.255$ Å and $\varepsilon = 0.753$ kJ/mol, the chemical shift was 239, while using the same parameters for Xe–O, but TIPS4P for water the value obtained for chemical shift was 259. These results clearly indicate that chemical shift is relatively easy to obtain in MD and that it is sensitive to the potential model; both are highly desirable features.

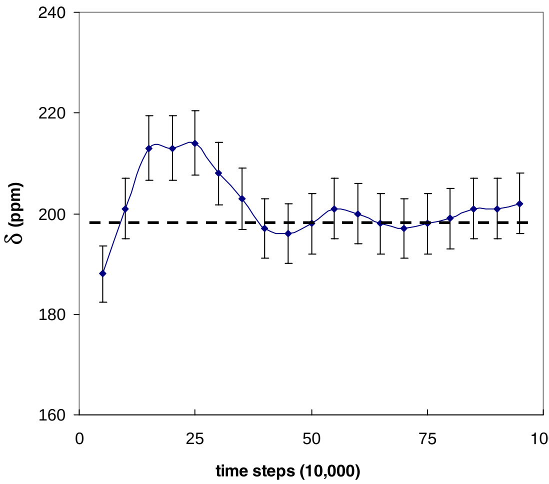

Fig. 2. Average Xe chemical shifts as a function of time in molecular dynamics simulations at 298 K. The solid lines guide the eye. The dashed line is the experimental value at 298 K.

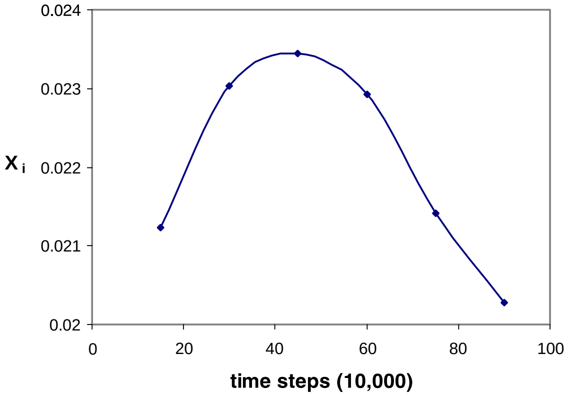

Fig. 3. Solubility of xenon in water (mole fractions) as a function of time in molecular dynamics simulations. The solid lines guide the eye. The estimated solubility at this state condition (T, P) is approximately 0.017 (assuming xenon to be an ideal gas in the gas compartment – see Fig. 1).

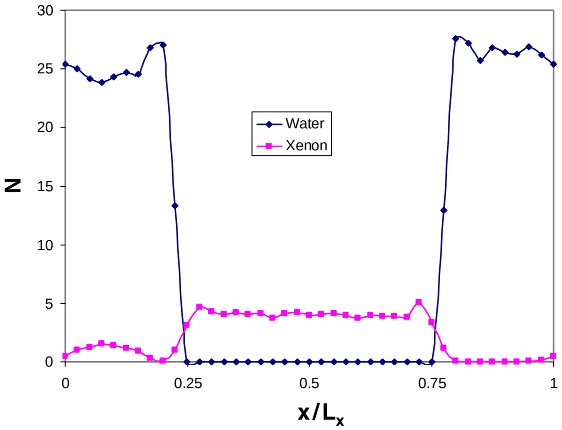

Fig. 4. The density profile of water, and xenon at the end of a typical MD simulation with 10^6 steps. N represents the number of molecules in a slit 0.025 L_x thick in the x-direction. The two membranes are at $x = 0.25\ L_x$ and $0.75\ L_x$ (see Fig. 1).

In Fig. 3, we show the solubility of xenon (in mole fractions) in water obtained from the same simulation (cf. Fig. 2) as a function of time. It is clear from the results that the solubility of xenon in water has not converged at all in the length of the simulation (1 million time steps). The reason for this lack of convergence can be understood by examining the density profiles shown in Fig. 4. For converged solubility results, the density profiles must be symmetric with respect to the two membranes. The density profiles show that while for water the results are somewhat symmetric, for xenon in the gas phase quite satisfactory, they are rather poor for xenon in the solution phase. This explains the difficulty in obtaining converged results from molecular dynamics for solubility. The

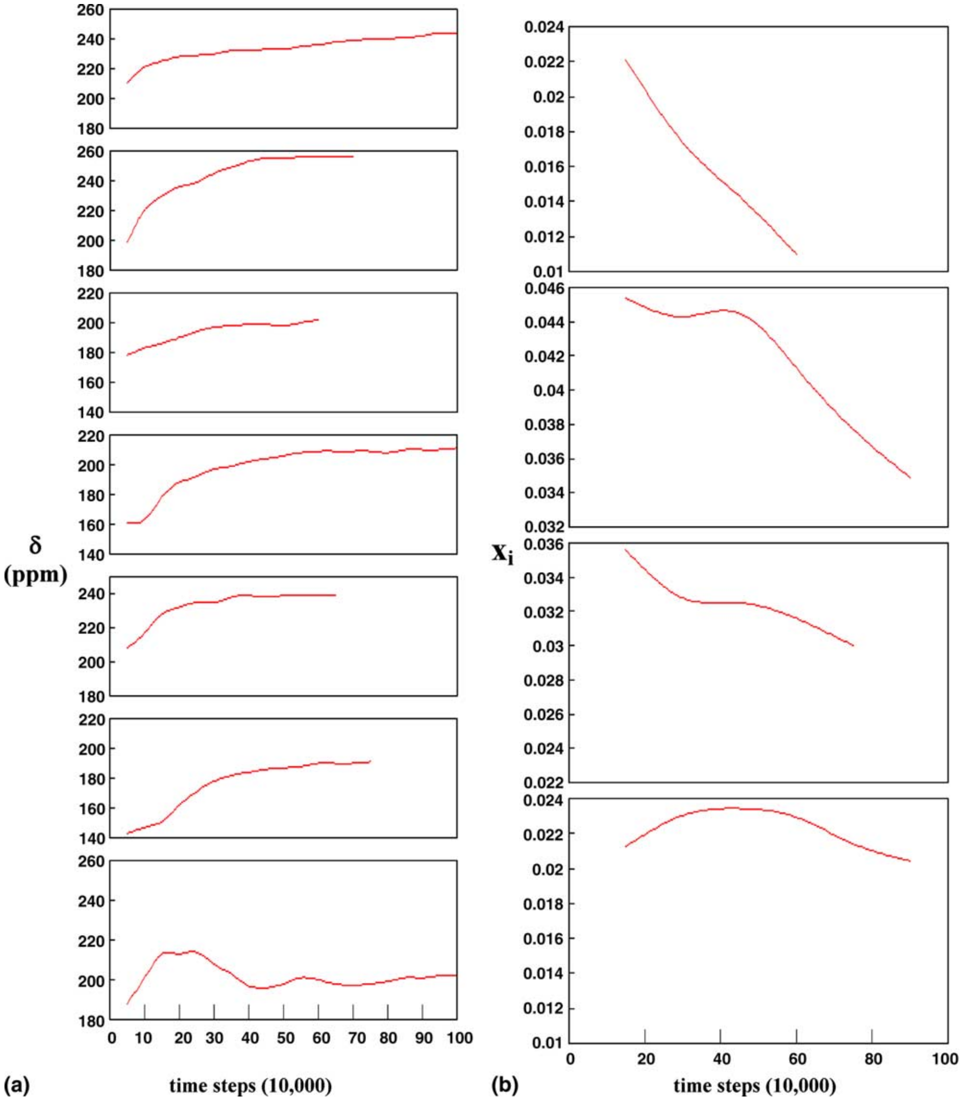

Fig. 5. Results in capsule form for (a) the chemical shift of Xe in H_2O (note expanded scale and discussion in text) and (b) solubility of xenon in water for several typical simulations using a range of potential models and parameters (see Table 1). Since solubility converges rather slowly only results for the four longer runs are included. For comparison purposes the results shown in Figs. 3 and 4 are at the bottom of each plot.

results are moving in the right direction, however. Assuming xenon to be ideal in the gas phase, the solubility of xenon in water at these conditions is approximately 0.017. Experimental data are available only at low pressures [14], but the solubility at such pressures is too small, $\sim 10^{-4}$, to simulate unless one includes over 100 000 molecules in the simulation, and carries out extremely long runs. Including non-ideality contributions for Xe (at $T = 298$ K and $\rho = 8.96$ mol/l) would lower these values somewhat. Thus an extrapolation of the results shown could very likely converge ultimately to the estimated solubility values. The solubility values obtained also appeared to be sensitive to the potential models used, although it is difficult to draw any definitive conclusions, since none of the simulations for the solubility actually converged.

Finally, results for the chemical shift and solubility for several other cases examined by us are shown in capsule form in Fig. 5. The results include both the SPC and TIPS4P potential models for water, a range of Xe–O parameters (see Table 1) and initial conditions and membrane characteristics. These results further confirm that the faster convergence of chemical shift compared to the gas solubility is quite general and not limited to any special cases. The results for the chemical shift shown are on a very expanded scale compared to the solubility. For instance the results shown at the top of Fig. 5a, which appear to be the slowest converging, in fact are within 3% of the final converged value in less than half the simulation length.

4. Conclusions

We have presented results for the average Xe chemical shift for xenon dissolved in water and shown that this property can be obtained more efficiently than other properties of dilute solutions of xenon in water. Furthermore, the average chemical shift appears to be quite sensitive to the potential models used. Both are desirable for evaluating the accuracy of proposed intermolecular potential models. The average chemical shift is particularly promising for systems with very low solubilities such as polar–nonpolar solutions, where equilibrium can otherwise be rather difficult to attain in a molecular dynamics simulation. Other molecular solutes and liquid solvents can be investigated in the same proposed way since nuclei with spin other than zero are ubiquitous.

Acknowledgements

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