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Experiments on tracer diffusion in aqueous and non-aqueous solvent combinations

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Forced Rayleigh scattering is used to study the tracer diffusion of an azobenzene in binary combinations of polar solvents, including water. In the absence of water, the tracer diffusion coefficient D in the mixture lies between the diffusion coefficients within the pure solvents, on a curve that is reasonably close to the prediction of free-volume theory. If water is present, on the other hand, the diffusion coefficient displays a minimum that is less than the smaller of the two pure-solvent values. We attempt to understand the different behavior in water by concentrating on the fairly hydrophobic nature of the solute, leading to a first solvent shell that is hydrophobic on the inside and hydrophilic on the outside. We also believe that clusters of amphiphiles explain the observation that, in aqueous combinations, D is nearly constant above a certain amphiphile mole fraction. © *2014 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4896303]

I. INTRODUCTION

Combinations of organic solvents with water continue to be important in many technological, biological, and medical applications.[1–6] Of particular relevance is the disruption of the water hydrogen-bonding structure generated by molecules possessing hydrophobic sections.[1,3,7–16] The change with concentration of the diffusion coefficient of either water or the organic molecule has provided insight in a large number of experimental and simulation studies.[4,9,10,17–22] In many cases, however, one is concerned with the motion and reactions of a solute molecule within the solvent combination.[7,8,23–27] In the present effort we wish to study the changes with solvent concentration of the diffusion of a largely (though not completely) hydrophobic tracer molecule comparable in size to many drug molecules.

For solvents, in addition to water (pH 10), we employ the amphiphiles acetone, dimethyl sulfoxide (DMSO), and acetonitrile. To understand the effects of water, we study the tracer motion in both aqueous and non-aqueous binary combinations. We are interested in DMSO/water combinations because DMSO is readily transported without harm through the skin; this has been used to produce medications.[28,29]

II. EXPERIMENTAL APPROACH

The experimental and analysis aspects of our forced Rayleigh scattering apparatus have been previously documented.[30,31] Briefly, two coherent pulsed "pump" laser beams interfere within the sample to produce temporary gratings of wavevector q. The pump beams are absorbed by the tracer molecule and create excited states within the bright fringes. The ground and excited states have different refractive indices so that "complementary" phase gratings are produced, in which the ground (unperturbed) and excited regions are 180° out of phase. The diffusion-driven grating decay is monitored using a "probe" laser beam at a different wavelength, sensitive to the refractive-index difference, that diffracts from the sample. If the ground-state and excited-state grating amplitudes are, respectively, A_g and A_{ex}, the homodyne-detected diffracted intensity falls off with time as

$$\frac{I}{I(0)} = [A_g \exp(-q^2 D_g t) - A_{ex} \exp(-q^2 D_{ex} t)]^2, \qquad (1)$$

where D_g and D_{ex} are the ground and excited-state diffusion coefficients. The desired geometric mean diffusion coefficient $D = \sqrt{D_g D_{ex}}$ can be obtained from a combination of the first two cumulant rates.[30,31] As a tracer molecule we employed the azobenzene derivative known as methyl red (MR) at 7 × 10^{-4} M (Fig. 1), so that the ground and excited states are, respectively, *trans* and *cis*. Azobenzenes are very useful because of the very long *cis* lifetime, permitting grating decay via diffusion instead of excited-state decay. The pump and probe wavelengths were 488 and 633 nm, respectively. For a protic tracer such as methyl red, the difference between D_g and D_{ex} is largest for hydrogen-bonding solvents, where it does not exceed 20%.[30] We confirmed that the grating decay was indeed due to diffusion by measuring the diffraction decay rate at different grating spacings, and we saw the decay rate was proportional to q^2. Most of the data was acquired at room temperature; however, we found that the solvent dependences detailed below did not depend on temperature.

III. RESULTS AND DISCUSSION

The diffusion constant D of MR is shown at different solvent concentrations in Figs. 2 and 3. It is seen that in the non-aqueous combinations (Fig. 2), D lies between the diffusion constants within the pure solvents. In the aqueous combinations (Fig. 3), however, the diffusion constant has a minimum value that is smaller than either pure-solvent value. The minimum is fairly pronounced, being around 1/6 of the pure

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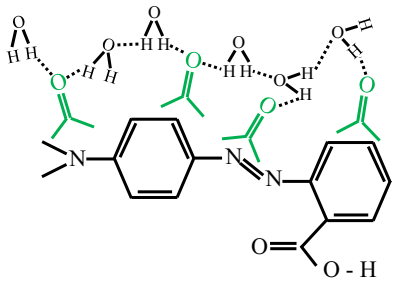

FIG. 1. Ortho methyl red and parts of the first two proposed solvation shells, using acetone as an example. The first shell is mostly acetone, shown in green, and the second shell is mostly water. Some of the hydrogen bonds are shown as dashed lines.

acetone value in acetone/water, and 1/6 of the pure water value in DMSO/water. It should be noted that minima have been observed in the diffusion constant of either solvent in a number of studies.[4,10,17,18] In addition, Chowdhuri and Chandra[27] have used simulations to observe a minimum in D for a much smaller solute—a neutral Cl atom—in a mixture of DMSO and water. Our results seem to be qualitatively consistent with those of Chandra *et al*, although the changes we see in D are more dramatic: we observe a maximum/minimum ratio of up to about 6, while for Cl, Chandra *et al.* see a bit more than 3.

To predict the expected dependence of the MR diffusion constant on the solvent mole fraction, we require a general theory of diffusion in liquids. The Cohen-Turnbull free-volume theory[32] has been more successful than the textbook pure-Arrhenius approach.[33] The Cohen-Turnbull free-volume diffusion coefficient of a tracer is given by

$$\mathrm{D} = A\sqrt{T}\exp(-\gamma v^*/v_\mathrm{f}), \tag{2}$$

where A is a constant, v_f is the average free volume per solvent molecule, obtained through thermal expansion, at temperature T, and v^* is the minimum void volume required for tracer motion, expected to be about the size of the solvated tracer molecule. The coefficient γ accounts for free-volume overlap, and should be between $\frac{1}{2}$ and 1. If two solvents are present and the molecules are uniformly dispersed, we expect

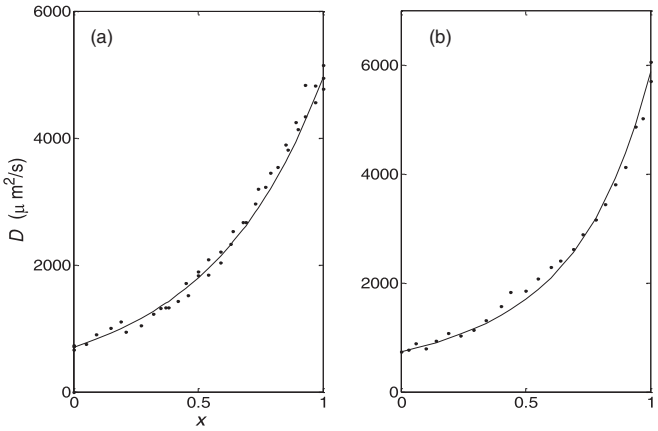

FIG. 2. The MR diffusion coefficient in binary mixtures of DMSO with (a) acetone, and (b) acetonitrile at 25 °C. x represents the mole fraction of acetone or acetonitrile. The fits are described in the text.

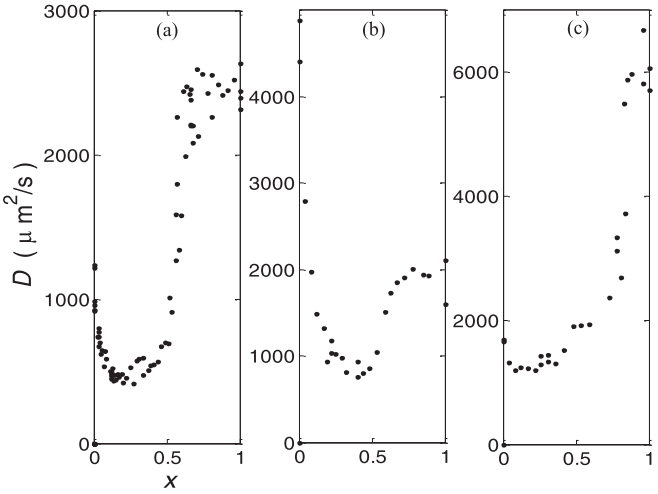

FIG. 3. The MR diffusion coefficient measured in three aqueous combinations, with (a) acetone, (b) DMSO, and (c) acetonitrile. In each case x is the mole fraction of the amphiphile.

the total free volume to be equal to the molar sum of the individual free volumes. From Eq. (2), $v_\mathrm{f} = -\gamma v^*/ln(D/A\sqrt{T})$, so the free-volume prediction of a tracer diffusion coefficient D in a binary solution is

$$\frac{1}{\ln(D/A\sqrt{T})} = \frac{x_1}{\ln(D_1/A\sqrt{T})} + \frac{1-x_1}{\ln(D_2/A\sqrt{T})}, \tag{3}$$

where the pure-solvent diffusion coefficients are D_1 and D_2, and x_1 is the mole fraction of solvent 1. In the non-aqueous cases of Fig. 2, we show fits to Eq. (3) using $A\sqrt{T}$ as the single adjustable parameter. The fit values of $A\sqrt{T}$ are $10^{-7\pm1}$ μm^2/s for DMSO/acetone (Fig. 2(a)), and $10^{1\pm1}$ μm^2/s for DMSO/acetonitrile (Fig. 2(b)). The error bars on $A\sqrt{T}$ are so large because, in view of Eq. (3), the dependence of D on $A\sqrt{T}$ is rather weak for a given D_1 and D_2.

We see that the fits in the non-aqueous cases are reasonable, so that one might hope we could also use Eq. (3) for the aqueous cases. In Eq. (3), however, D is always between D_1 and D_2, so we cannot describe the aqueous cases with Eq. (3). We think this is because the solvent molecules in the aqueous cases are not uniformly distributed. Except for its carboxylic acid group, MR is rather hydrophobic, so it is not surprising that water is a much poorer solvent than the others we have used. Based on this observation, we believe that in an aqueous combination, water will be largely absent from the first solvent shell, as shown in Fig. 1 for the case of acetone. For the amphiphilic solvent molecules under consideration, the hydrophobic and hydrophilic portions will lie, respectively, on the inside and outside of the first solvent shell. With the hydrophilic portion of the amphiphile pointing outward, water can readily hydrogen bond to form a second solvent shell (Fig. 1). Thus the first solvent shell is almost purely amphiphile, while the second solvent shell is nearly pure water. Hydrogen bonding in solvent shells has been discussed by Chowdhuri and Chandra.[27]

The first and second solvent shells so formed explain the minimum in the aqueous cases. If we start with pure water and add the amphiphile, D is reduced as the first solvent shell

forms. If we start with the pure amphiphile and add water, the diffusion constant is reduced as the second solvent shell forms. The formation of either solvent shell leads to an increase in the requisite free volume v^* in Eq. (2) and hence a smaller D. Since D is reduced, starting with either pure solvent, by adding the other solvent, there will necessarily be a minimum in D at some mole fraction.

In the non-aqueous cases we expect there to be single solvent shell with the methyl group(s) closer to the MR. DMSO and acetone present two methyl groups to MR, while acetonitrile provides only one. It is therefore not surprising that we found DMSO and acetone are better solvents than acetonitrile. We think this explains the observation that—the large error bars notwithstanding—there is a large difference in the fit values of $A\sqrt{T}$ for DMSO/acetone *vs*. DMSO/acetonitrile. In the latter, DMSO is preferred in the solvent shell, so that if acetonitrile is added to pure DMSO, D vs. x will be flatter at higher DMSO concentrations than DMSO/acetone, as observed. This results, for acetonitrile, in a $D(x)$ with a more rapidly increasing slope as we approach pure acetonitrile, and hence a larger fit value of $A\sqrt{T}$.

To understand the observation that, in the aqueous cases (Fig. 3), D is nearly constant above a certain amphiphile concentration, we turn to observations of transient aggregates in aqueous solutions of amphiphiles.[1,2,5,8,19,34–36] Following classic hydrophobe behavior,[5,37] the amphiphilic molecules tend to cluster together with their hydrophobic portions shielded from the water. For MR diffusion, starting with pure water, addition of the amphiphile forms a first solvent shell up to a certain amphiphile concentration, beyond which no additional amphiphile can be added to the shell. If more amphiphile is then added to the solution, the additional amphiphiles cluster away from the MR, so that further increases in amphiphile concentration do not affect the MR motion. We should note that the D = constant region is fairly evident in Fig. 3 for acetone and DMSO, but is only marginal for acetonitrile.

IV. CONCLUSIONS

We think our results show the utility of directly measuring solute diffusion constants in aqueous combinations. We have used the experimental results to understand aspects of both the first and second solvent shells, as well as amphiphile clustering. In the future we wish to carry out forced Rayleigh scattering and dynamic light scattering in the same experiment. If our thoughts are correct, we should observe larger, or a larger number of, amphiphile clusters as the amphiphile concentration increases in the region in which the MR diffusion coefficient is nearly constant. In addition, we need to study solute molecules with different sizes. Our postulate regarding the solvent shells means that more amphiphile solvent molecules are required for the first shell when the solute size increases, with the result that the minimum should move to higher amphiphile concentration. As a first consideration in this regard, we note that the minimum that we observe in DMSO/water occurs at a DMSO concentration that is about 20% larger than what Chowdhuri and Chandra[27] report for a small atomic solute. Finally, the DMSO/water results have medical implications, since the time required for a somewhat hydrophobic drug molecule comparable in size to MR to travel a given distance can apparently be changed rather significantly (a factor of 6) by varying the DMSO concentration.

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