

Extent of Hydration of Dimethyl Sulfoxide in Aqueous Solution

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Abstract □ The maximum hydration of dimethyl sulfoxide (DMSO) in aqueous solution at 25° was investigated by the deviation of experimental values of fluidity, dielectric constant, refractive index, density, and molar refraction from values calculated by linear interpolation between the values of the two pure liquids as a function of mole fraction. The maximum deviation in fluidity and dielectric constant occurred at the ratio of three water molecules per DMSO molecule; this is the maximum hydration. The magnitude of the maximum deviation was 203% for fluidity and 4% for dielectric constant. The maximum deviation in refractive index and molar refraction occurred at water-DMSO molar ratios of 2:1 and 1:1. These two values are shown to be low.

Keyphrases □ Dimethyl sulfoxide hydration—aqueous solution □ Viscosity—dimethyl sulfoxide-water mixtures □ Density—dimethyl sulfoxide-water mixtures □ Refractive indexes—dimethyl sulfoxide-water mixtures

Dimethyl sulfoxide (DMSO) is a powerful solvent for inorganic (1, 2) and organic compounds including high polymers (3), and is therefore often used as a medium for conducting reactions (2-4). In the pharmaceutical field, DMSO is unique as a skin penetrant and greatly improves the percutaneous absorption of many drugs (5). During a study of solutions of organic compounds in DMSO-water mixtures, it became necessary to know the extent of hydration of DMSO, *i.e.*, the maximum number of water molecules associated with a DMSO molecule at room temperature. A review of the physicochemical literature on the DMSO-water system revealed the need for additional data. Pertinent old and new data and their interpretation are presented here.

THEORETICAL

Association in a binary liquid system can usually be detected by the deviation of the experimental values of an intensive property of the mixtures from the additive values of the property. The latter is calculated by linear interpolation between the two values of that property of the two pure components as a function of composition. The stoichiometric composition of a complex formed between the two components is often that composition at which this deviation Δ reaches a maximum:

$$\Delta p = p_{12 \text{ exptl.}} - p_{12 \text{ calcd.}} = p_{12 \text{ exptl.}} - (x_1 p_1 + x_2 p_2) \quad (\text{Eq. 1})$$

Here, p is the property (density d , refractive index n , or dielectric constant D), x is the mole fraction, and Subscripts 1, 2, and 12 refer to water, DMSO, and to their mixtures.

Molar refractions of the mixtures were obtained from measured densities and refractive indexes by

$$[R]_{12 \text{ exptl.}} = \left(\frac{n_{12}^2 - 1}{n_{12}^2 + 2} \right) \left(\frac{x_1 M_1 + x_2 M_2}{d_{12}} \right) \quad (\text{Eq. 2})$$

Calculated molar refractions were obtained by

$$[R]_{12 \text{ calcd.}} = x_1 \left(\frac{n_1^2 - 1}{n_1^2 + 2} \right) \left(\frac{M_1}{d_1} \right) + x_2 \left(\frac{n_2^2 - 1}{n_2^2 + 2} \right) \left(\frac{M_2}{d_2} \right) \quad (\text{Eq. 3})$$

where M represents the molecular weights (6).

The most reliable and sensitive property for obtaining the composition of association complexes is the fluidity ϕ , which is the reciprocal of viscosity. Fluidity deviation has been applied successfully not only to the study of strong association complexes (7, 8) but also to weaker ones, such as those formed through hydrogen bonding (9-11). The Kendall equation (12)

$$\log \phi_{12 \text{ calcd.}} = x_1 \log \phi_1 + x_2 \log \phi_2 \quad (\text{Eq. 4})$$

is obeyed by ideal or nearly ideal solutions (7). Association between the two liquid components causes the observed fluidity of their mixture to be smaller than that calculated by Eq. 4 (7-9).

This is readily visualized in terms of Eyring's model, according to which a liquid consists of solid-like domains and vacancies or holes. Flow occurs when a flow unit moves into a hole under the action of an applied shear force (13). Single molecules are the flow units in nonassociated liquids. Associated liquids have greater flow units and require greater holes to flow, which results in increased viscosity or smaller fluidity. In the DMSO-water system, the greatest flow unit exists in the mixture where the greatest number of water molecules is associated with each DMSO molecule. This is the composition for which viscosity and deviation from the Kendall equation are the greatest.

In order to obtain positive Δ values for fluidity and molar refraction, Δ was obtained by subtracting the experimental values from those calculated, contrary to what was done for density, refractive index, and dielectric constant (Eq. 1).

For ideal solutions, Δ values are usually zero. In the case of fluidity, the magnitude of Δ may be a measure of the magnitude of the interaction between the two components (14).

EXPERIMENTAL

Materials—DMSO (Crown Zellerbach Corp.) was given three fractional crystallizations, followed by prolonged refluxing over calcium hydride, and by fractional distillation from calcium hydride under reduced pressure in an atmosphere of dry nitrogen. Thorough drying was important because traces of moisture affected the viscosity strongly. The properties of the purified solvent, $MP = 18.53^\circ$, $n_D^{25} = 1.4768$, $d_4^{25} = 1.0957 \text{ g./cm.}^3$, and $\phi = 50.0 \text{ poise}^{-1}$ based on the value of 0.8903 cp. for the viscosity of water at 25°, are in good agreement with published values (4, 15-17).

Water was doubly distilled. Water-DMSO mixtures were prepared in 100-g. batches by weighing out the two liquids to the nearest milligram.

Methods—The temperatures during the measurements were maintained constant within $\pm 0.01^\circ$. Viscosities were measured with

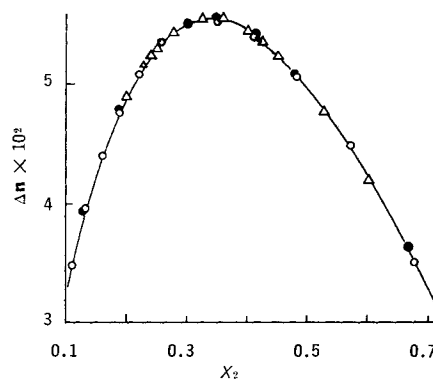


Figure 1—Differences between experimental and calculated refractive indexes of DMSO-water mixtures. Key: ●, Ref. 15; ○, Ref. 17; ▲, Ref. 16; △, this work.

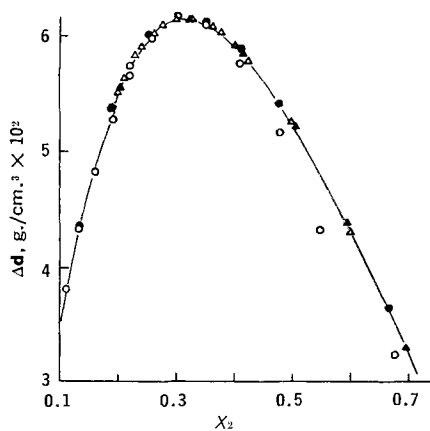


Figure 2—Differences between experimental and calculated densities of DMSO-water mixtures. Symbols as in Fig. 1.

a viscometer (Cannon-Fenske) which had the flow time of 286.4 sec. for water. The kinetic energy correction was too small to be taken into account. Duplicate measurements, made on fresh portions of the solutions, agreed within 0.2 sec. Densities were determined with a pycnometer (Sprengel-Ostwald) of 25-ml. capacity. Refractive indexes for the sodium D line were measured with a refractometer (Abbé).

RESULTS

Figures 1 and 2 are plots of the differences between measured refractive indexes (n_D^{25}) and densities (d_4^{25}) of DMSO-water mixtures published in the literature (15-17) and in this paper, and those interpolated by means of Eq. 1. The compositions employed in this work were chosen to be in the range where this difference goes through a maximum, because it is the composition corresponding to the maximum difference that is being sought.

There is good agreement between the three sets of experimental refractive indexes, but one of the four sets of experimental density values (17) is consistently lower than the other three. This results

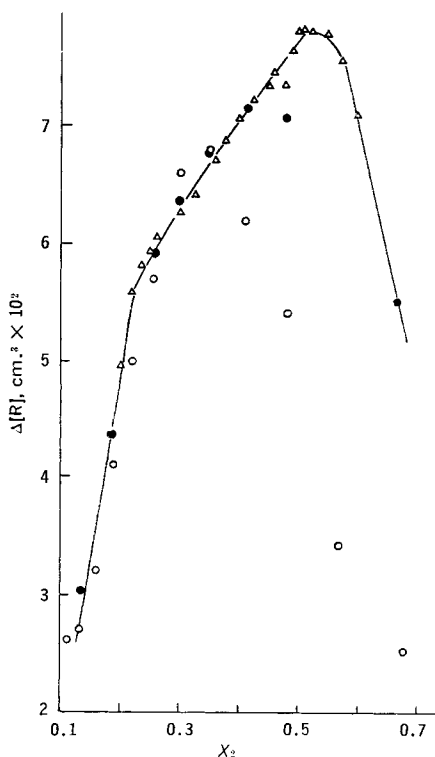


Figure 3—Differences between calculated and experimental molar refractions of DMSO-water mixtures. Symbols as in Fig. 1.

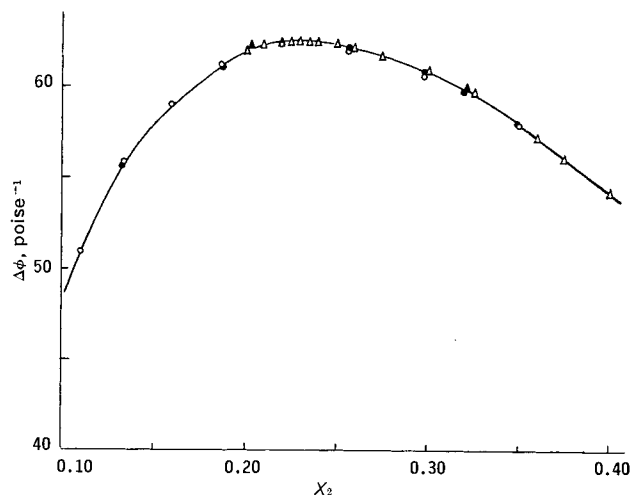


Figure 4—Differences between calculated and experimental fluidities of DMSO-water mixtures. Symbols as in Fig. 1.

in high molar refractions $[R]_{12 \text{ exptl.}}$ and low $\Delta[R]$ values (see Fig. 3).

The agreement between the four sets of experimental fluidities (Fig. 4) is good. For DMSO mole fractions x_2 in the range of 0.50 to 0.95, there is a linear relationship between fluidity in poise^{-1} and x_2 . The least-squares equation is

$$\phi_{12 \text{ exptl.}} = 7.918 + 43.45x_2 \quad (\text{Eq. 5})$$

Table I lists the compositions at which the maximum differences between experimental and observed values occurred, together with the percent relative deviations calculated as

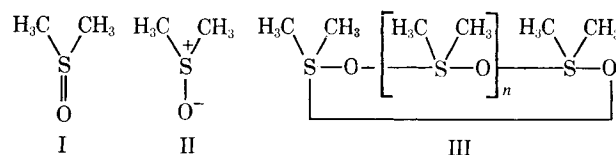
$$\text{rel. dev.} = 100 |p_{12 \text{ exptl.}} - p_{12 \text{ calcd.}}| / p_{12 \text{ exptl.}} \quad (\text{Eq. 6})$$

The data for dielectric constants D were taken from Reference 18.

By far the largest deviation was found for fluidity. The molar compositions corresponding to the maximum deviation range from one water molecule associated with each DMSO molecule to over three, depending on which property is considered.

DISCUSSION

IR evidence (19) indicates that the sulfur-oxygen link in sulfoxides is mainly a covalent double bond (Structure I) with a small proportion of the ionic Structure II.



Cyclic polymers like III have been proposed (2), especially below 40° . The formation of strong hydrogen bonds with water has been shown by IR spectroscopy (19). The high heat of mixing of water and DMSO (15, 20) indicates that the hydrogen bonds formed be-

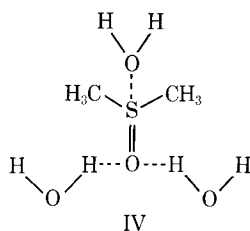
Table I—Compositions of Maximum Deviation between Experimental and Calculated Physical Properties in the DMSO-Water System at 25° , and Magnitude of the Deviations

Property p	x_2	$p_{12 \text{ exptl.}}$	Rel. Dev., ^a %
d_4^{25}	0.30	1.0881 g./ml.	5.6
n_D^{25}	0.34	1.4372	3.9
$[R]$	0.51	12.012 ml.	0.7
D	0.25	73.5	4.1
ϕ	0.23	30.79 poise^{-1}	202.8

^a Calculated by Eq. 6.

tween the two molecules are stronger than those formed between water molecules.

The heat of mixing *versus* composition curves went through a pronounced exothermic minimum at $x_2 = 0.37$, both at 25 and 70° (15, 20), and the excess free energy of mixing went through a shallower minimum at $x_2 = 0.4$. This does not imply that the maximum association between water and DMSO occurs at a molar ratio of 1.7:1, because water can be bound to DMSO not only by hydrogen bonding but also by interaction between the positive end of the sulfur-oxygen dipole and the negative end of the oxygen-hydrogen dipole (IV).



This latter interaction would make a small contribution to the heat of mixing relative to the formation of hydrogen bonds. Only if the functional groups interact with water almost exclusively through hydrogen bonding, like the ether group, does heat of mixing in the binary system with water give the correct composition of maximum interaction (9, 21).

The permanent dipoles of water and DMSO contribute only to D and not to n . D is measured at the low frequency of 10^6 cycles/sec., but n is measured with radiation of 10^{14} cycles/sec. A permanent dipole cannot line up quickly enough to follow an electric field alternating with such a high frequency, and therefore does not affect n (22).

For the same reason, the Lorenz-Lorentz equation (Eq. 2) does not reflect the true solution behavior because the total molar polarization contains a term which includes the square of the dipole moment in addition to the molar refraction term. Therefore, deviation from additivity of the dielectric constant rather than of the refractive index or of the molar refraction would be expected to give the composition of maximum interaction between DMSO and water.

As can be seen from Table I, dielectric constant and fluidity have maximum deviations at nearly identical compositions, which correspond to the maximum hydration of three water molecules per DMSO molecule. This could be represented by Structure IV.

In the case of water-miscible ethers, the maximum hydration was found to be two water molecules per ether group by deviation in fluidity. This is the value expected from considerations of electronic configurations. Molar refraction and refractive index deviations gave the maximum hydration as 1.2 water molecules per ether link (6, 9, 10). This is low for the same reason as discussed above.

In conclusion, deviation from additivity of dielectric constant and of fluidity indicated that the maximum hydration of DMSO in aqueous solution was three water molecules per DMSO molecule. Of the two techniques, fluidity measurements are to be preferred because they require only simple equipment and result in much larger deviations.

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