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Report

Cosolvency and Deviations from Log-Linear Solubilization

Joseph T. Rubino[1] and Samuel H. Yalkowsky[2]

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The solubilities of three nonpolar drugs, phenytoin, diazepam, and benzocaine, have been measured in 14 cosolvent–water binary mixtures. The observed solubilities were examined for deviations from solubilities calculated by the equation $\log S_m = f \log S_c + (1 - f) \log S_w$, where S_m is the solubility of the drug in the cosolvent–water mixture, S_c is the solubility of the drug in neat cosolvent, f is the volume fraction of cosolvent, and S_w is the solubility of the drug in water. When presented graphically, the patterns of the deviations were similar for all three drugs in mixtures of amphiprotic cosolvents (glycols, polyols, and alcohols) and water as well as nonpolar, aprotic cosolvents (dioxane, triglyme, dimethyl isosorbide) and water. The deviations were positive for phenytoin and benzocaine but negative for diazepam in mixtures of dipolar, aprotic cosolvents (dimethylsulfoxide, dimethylformamide, and dimethylacetamide) and water. The source of the deviations could not consistently be attributed to physical properties of the cosolvent–water mixtures or to alterations in the solute crystal. Similarities between the results of this study and those of previous investigations suggest that changes in the structure of the solvent play a role in the deviations from the expected solubilities.

KEY WORDS: cosolvency; solvent mixtures; deviations; log-linear solubility equation; crystal changes; water structure.

INTRODUCTION

It has been shown previously that a log-linear increase in solubility with increasing volume fraction of cosolvent, f, generally occurs for three compounds (phenytoin, diazepam, and benzocaine) studied in each of 14 cosolvent–water systems (1–3). In almost all cases, some positive or negative deviation from the predicted linear behavior occurs. The curvature has been observed previously in propylene glycol–water systems. Hagen and Flynn (4) reported a sigmoidal shape to the log S_m vs f plots for hydrocortisone esters in propylene glycol–water mixtures. Yalkowsky and Rubino (5) reported a similar curvature for a mixture of solutes in propylene glycol–water mixtures. In this report Eq. (1) can be considered as the expression which describes the expected solubility of a drug in a water–cosolvent mixture:

$$\log S_m = f \log S_c + (1 - f) \log S_w \qquad (1)$$

where S_m is the solubility of the drug in the cosolvent–water mixture, f is the volume fraction of cosolvent, S_c is the solubility of the drug in neat cosolvent, and S_w is the solubility in water.

Deviations from the predicted solubilities are a result of interactions which take place in the solute–cosolvent–water mixture which do not take place in mixtures of the drug with the individual solvents alone. These deviations can result from interactions involving cosolvent–water, solute–solute, or solute–water–cosolvent (6–9).

In addition, Eq. (1) assumes that the crystal form of the drug remains the same in water, cosolvent, and the solvent mixtures. A change in the crystalline form of the drug either by polymorphism or by formation of solvates will result in a change in the amount of energy required to destroy the crystal structure. Such changes have been reported for caffeine (10), cholesterol (11), and dextropropoxyphene napsylate (12) in solvent mixtures.

In order to examine the deviations from log-linear solubility in the cosolvent–water mixtures studied, plots were constructed of log (observed solubility) minus log [solubility predicted from Eq. (1)]. This was performed for the three drugs studied, i.e., phenytoin, diazepam, and benzocaine. Various other properties of the solvent mixtures were examined for deviations from a log-linear mixing rule and compared to the deviations in the solubility data.

METHODS

The solubilities of phenytoin, diazepam, and benzocaine in cosolvent–water mixtures were determined as described previously (1–3). The cosolvents included propylene glycol (PG), glycerin (GLYC), dimethylformamide (DMF) (Fisher Scientific Co., Fairlawn, N.J. 07410), 1,3-butanediol (BUTDIOL) (M.C.B., Manufacturing Chemists, Inc., Cincinnati, Ohio 45212), ethanol (ETOH) (U.S. Industrial Chemicals Co., New York, N.Y. 10016), methanol (MEOH), dimethylsulfoxide (DMSO) (Burdick & Jackson Laboratories, Inc., Muskegan, Md. 49442), dimethylacetamide (DMA) (Matheson, Coleman, & Bell, Cincinnati, Ohio 45212), triglyme (TRIG), polyethylene glycol (PEG) 200 &

[1] School of Pharmacy, Beard Hall 200H, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27514.

[2] College of Pharmacy, University of Arizona, Tucson, Arizona 85721.

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400 (Aldrich Chemical Co., Milwaukee, Wis. 53201), dioxane (Eastman Kodak Co., Rochester, N.Y. 14650), sorbitol (70%, w/w) (sorb), and dimethylisosorbide (DMI) (I.C.I. America, Wilmington, Del. 19897).

Observed minus expected solubility plots were prepared by calculating

$$\log (S_m/S_i) = \log (\text{observed solubility}) - [f \log S_c + (1 - f) \log S_w]$$

where S_i is the solubility calculated by Eq. (1). These calculations were performed using the Statistical Package for the Social Sciences (13) and plotted using Subroutine Plot.

Data for the various solution properties of the cosolvent–water mixtures, including vapor pressure (VP) density (d), surface tension (γ), viscosity (η), specific heat (SpHt), boiling point (BP), and refractive index (RI) were taken from literature sources (see tables for references) when available or determined experimentally. Surface tensions were determined using the Cenco-DuNuoy tensiometer (Model 70535, Central Scientific Co., Chicago, Ill. 60623).

Observed minus predicted properties for the cosolvent–water mixtures were calculated for each property in a manner analogous to that used for the solubility data:

$$\log (P_m/P_i) = \log P_m - [f \log P_c + (1 - f) \log P_w]$$

where P_m is the observed or experimental measurement, P_i is the expected value calculated in a manner analogous to Eq. (1), P_c is the value of the property for neat cosolvent, and P_w is the value of the property for water.

Crystal changes were examined by equilibrating excess drug with water, cosolvent, or cosolvent–water mixtures in a manner similar to that used for the solubility determinations. The remaining solid was collected on filter paper and dried by passing a gentle, constant stream of air through the powder by use of a buchner funnel and vacuum flask. Thermograms were obtained for each crystal using a DuPont Model 1909 differential scanning calorimeter (DuPont Co., Analytical Instrument Division, Wilmington, Del. 19898).

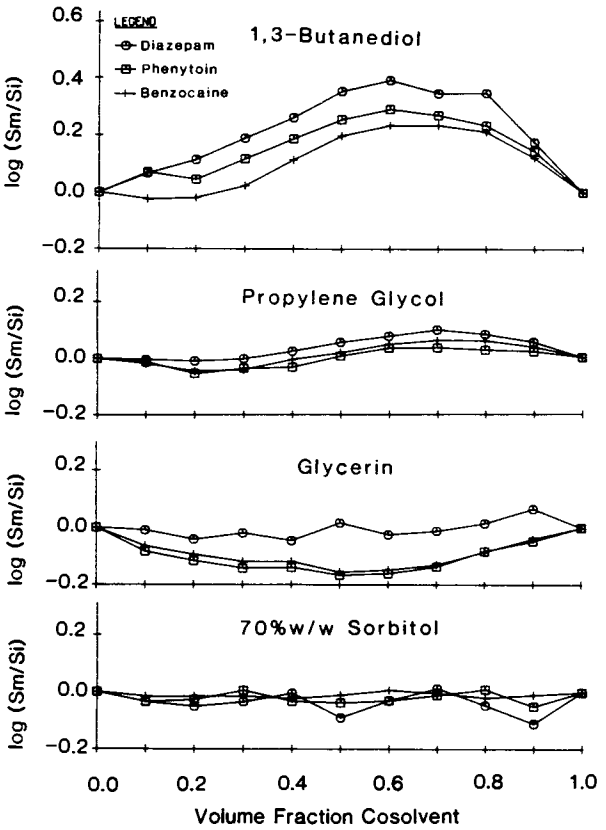

Fig. 1. Excess solubilities in polyhydroxy cosolvent–water mixtures.

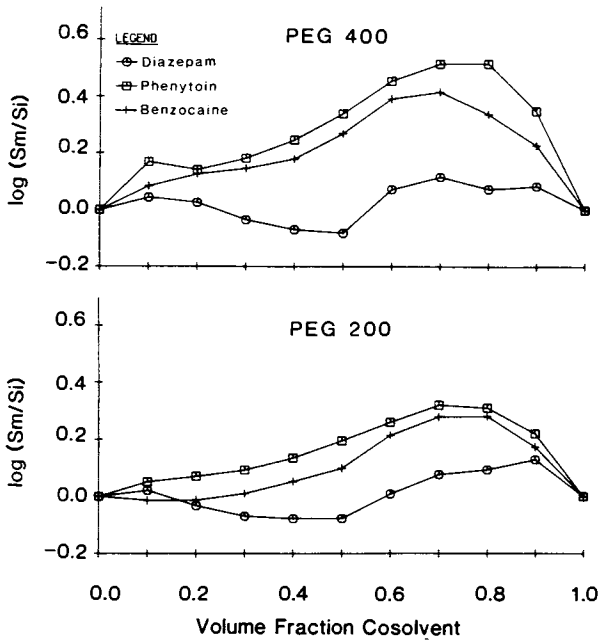

Fig. 2. Excess solubilities in PEG–water mixtures.

RESULTS

The $\log S_m/S_i$ vs f plots for the three drugs are shown for each individual cosolvent–water mixture in Figs. 1–5. It can

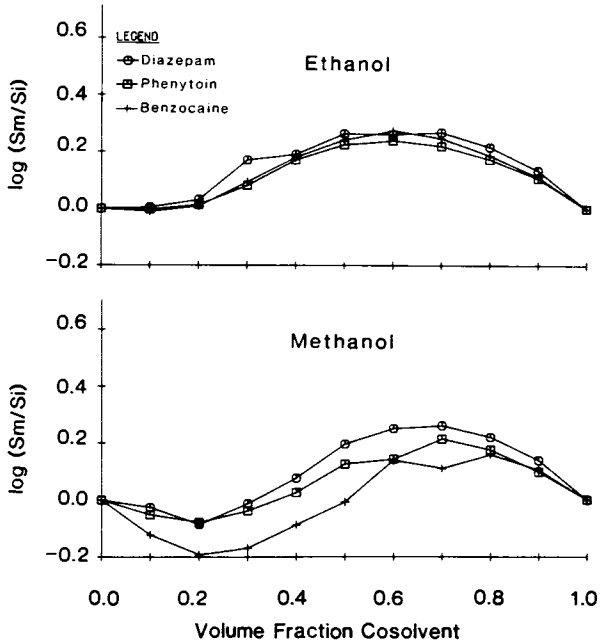

Fig. 3. Excess solubilities in alcohol–water mixtures.

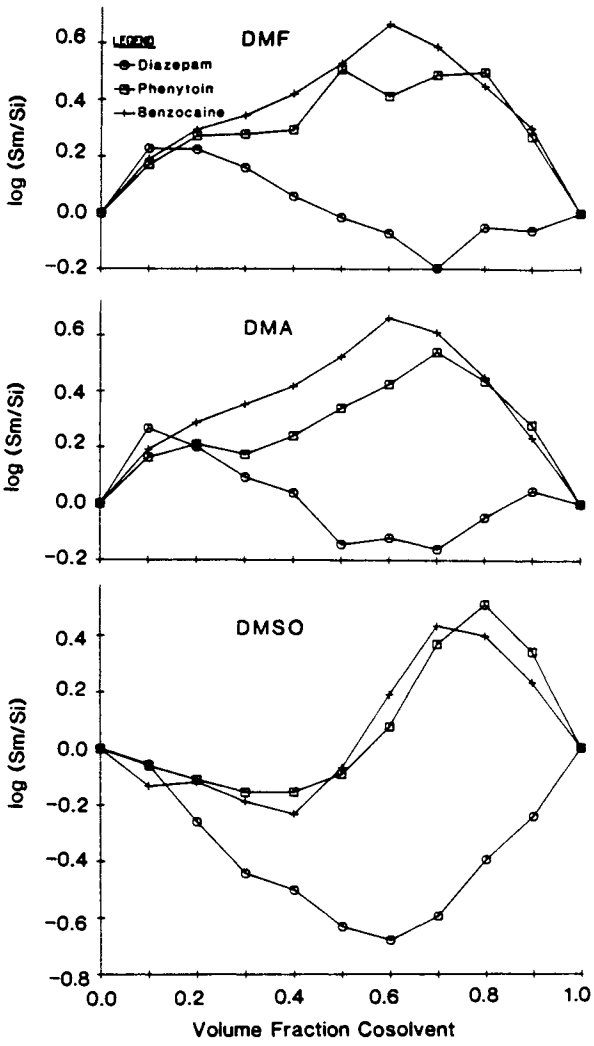

Fig. 4. Excess solubilities in DMSO, DMA, and DMG–water mixtures.

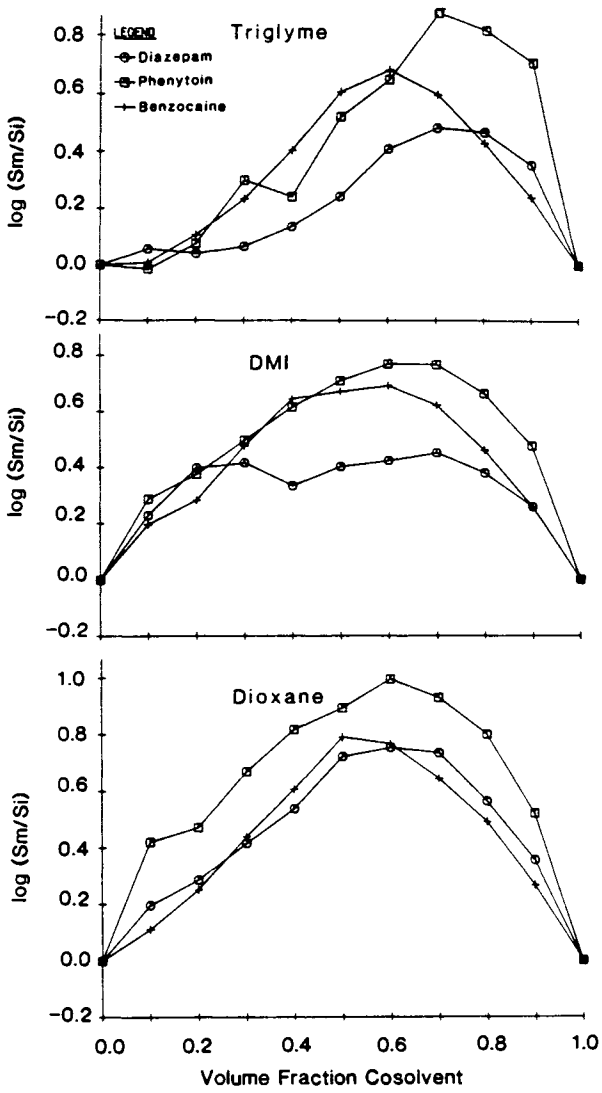

Fig. 5. Excess solubilities in dioxane, DMI, and triglyme–water mixtures.

be seen that for the amphiprotic cosolvents, the glycols and alcohols, the same general shape of the plots exist for all three drugs. The log S_m/S_i vs f plots in DMSO, DMA, and DMF–water mixtures show similar patterns for phenytoin and benzocaine but a different pattern is seen for diazepam.

In only one drug–cosolvent–water system, DPH in DMA–water mixtures, was any sign of a crystal change evident. This is illustrated in Fig. 6, where an endothermic peak is evident at about 90°C. Fig. 7 presents the results of a thermogravimetric analysis (TGA) of DPH which was equilibrated with DMA. The loss of weight at 90°C suggests that the additional peak seen in the thermogram is due to the liberation of solvent from the crystal and is thus not a polymorphic transition.

Table I contains a summary of the observed minus predicted properties of several of the cosolvent–water mixtures. These are presented as the volume fraction of cosolvent at which the maximum (+) or minimum (−) of the log P_m/P_i vs f plots occurs. The point of maximum deviation of the log S_m/S_i vs f plots are also presented for comparison. The maxima or minima in the cosolvent–water properties generally agree for groups of structurally related solvents for each individual property. For example, the maximum deviation in the density plots for the glycols occur around the same range, $f = 0.5$ to 0.7, as does the maximum deviation in the viscosity, etc. However, not all the properties have extrema at the same point for a given cosolvent–water mixture. This is especially true for the amphiprotic cosolvents. The agreement between the various properties is generally better for the aprotic cosolvent–water mixtures.

Similarities in the shapes of the log S_m/S_i vs f plots for the three different drugs suggested cosolvent–water interactions as the primary reason for their deviations. Thus, physical properties of the solvent mixtures were examined for evidence that this was the case. Of the various properties examined, none consistently predicts the extrema in the log S_m/S_i vs f plots, although density corresponds in several cases. The sigmoidal shape seen in some of the solubility plots was not evidence in any of the plots of the various solvent mixture properties. In addition, the sign of the deviation for the various properties does not always give a consistent prediction as to whether a maximum or a minimum in the solubility plot occurs. For example, in most cases a positive deviation in vapor pressure corresponds

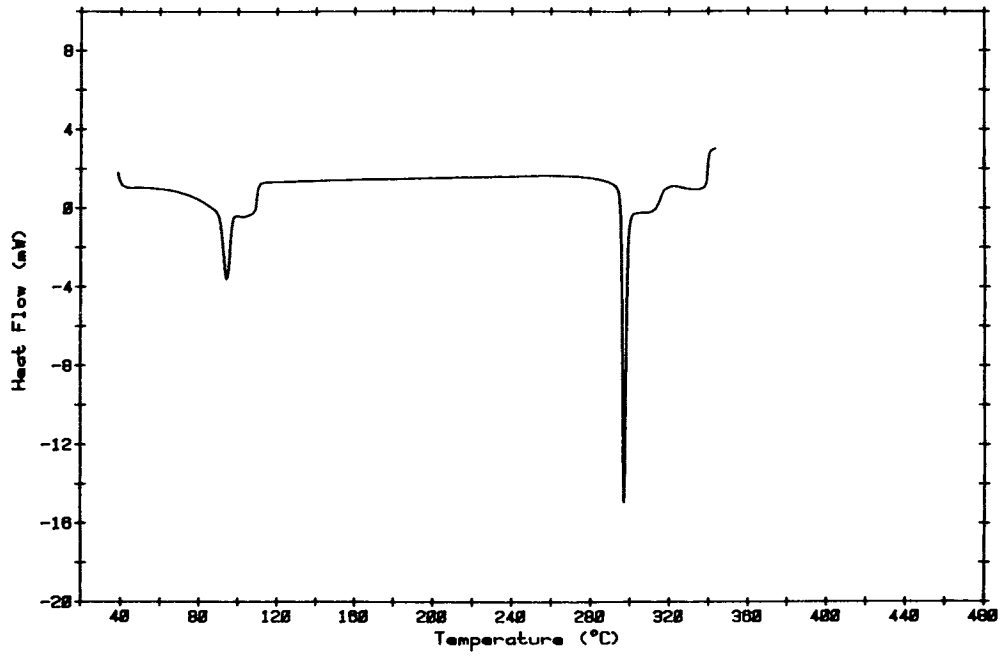

Fig. 6. Thermogram of phenytoin crystals after equilibration with DMA.

with a positive deviation in solubility, but this is just the opposite in the case of glycerin.

DISCUSSION

The results of the DSC analysis of the drug crystals which were equilibrated with the various solvents show that crystal structure changes occur in only one drug–solvent system, i.e., phenytoin in the DMA–water system. Although crystal changes have been shown to correspond to changes in solubility–cosolvent composition plots (10), they apparently are not the reason for the unpredicted behavior seen in these drug–solvent systems. In the case of DPH in DMA–water mixtures, the deviations from Eq. (1) seem to be similar to those in the DMF and DMSO–water systems, where no apparent changes in the drug crystal occurred. Thus, the crystal changes may not provide contributions to the large deviations from the expected solubilities in the DMA–water system. The possibility exists that the conditions used in drying the drug crystals may be severe enough to remove solvent that is loosely bound to the crystals (14). A number of the crystals were allowed to dry without the aid of a vacuum and no abnormal phenomena were observed for these crystals.

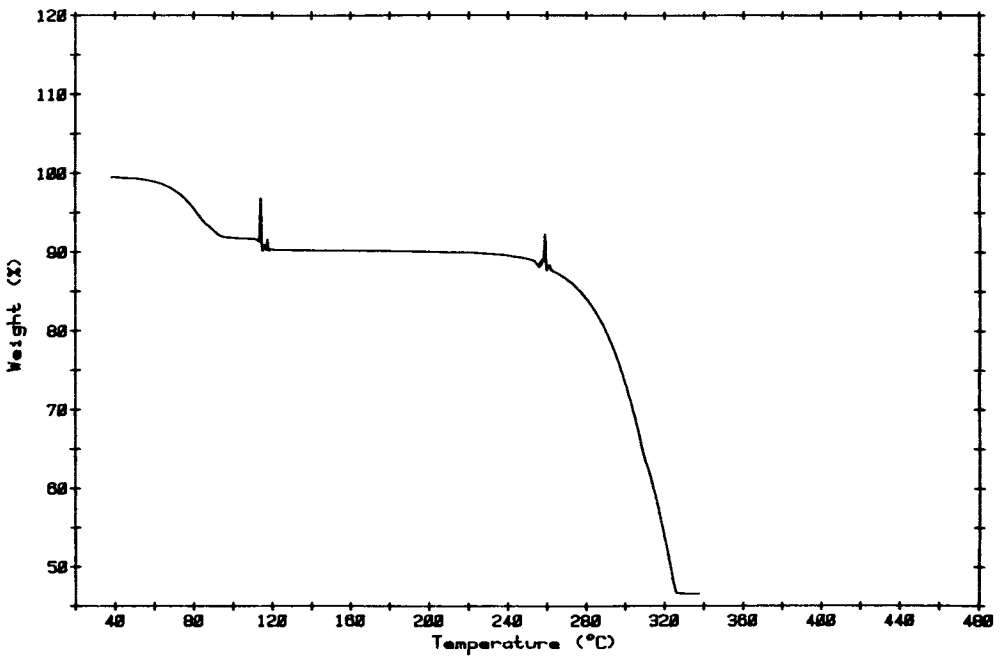

Fig. 7. TGA of phenytoin crystals after equilibration with DMA.

Table I. Position (Volume Fraction) of Maximum (+) or Minimum (−) of Excess Properties of Cosolvent–Water Mixtures

Cosolvent	VP	d	γ	RI	η	SpHt	BP	DPH	BENZ	DIAZ
PG	0.9; +[a]	0.5; +[a]	0.3; −[b]	0.5; +[b]	0.8; −[b]	0.5; +[b]	0.8; −[b]	0.7; +	0.7; +	0.7; +
								0.2; −	0.2; −	0.2; −
Butdiol		0.7; +[c]		0.6; +[d]	0.7; −[d]			0.6; +	0.7; +	0.6; +
GLYC	0.9; +[e]	0.5; +[f]	0.3; +[g]	0.5; +[h]	0.7; −[i]	0.5; +[j]	0.8; −[k]	0.5; −	0.5; −	0.5; −
ETOH	0.3; +[l]	0.6; +[l]	0.4; −[g]	0.5; +[h]	0.5; +[i]	0.5; +[j]	0.3; −[k]	0.6; +	0.6; +	0.6; +
MEOH	0.3; +[d]	0.6; +[f]	0.3; −[g]	0.6; +[h]	0.6; +[i]	0.5; +[j]	0.3; −[k]	0.7; +	0.8; +	0.7; +
DMSO	0.7; +[m]	0.6; +[n]	0.9; −[o]	0.6; +[n]	0.7; +[n]	0.4; +[o]		0.8; +	0.7; +	0.6; −
								0.4; −	0.4; −	
DMA		0.6; +[p]			0.6; +[p]	0.7; −[q]		0.7; +	0.6; +	0.7; −
DMF		0.7; +[d]			0.6; +[r]	0.7; −[s]		0.6; +	0.6; +	0.7; −
Dioxane	0.7; +[t]	0.6; +[u]	0.3; −[v]	0.6; +[u]				0.6; +	0.5; +	0.6; +
TRIG		0.6; +[w]		0.6; +[d]	0.6; +[w]			0.7; +	0.6; +	0.7; +

[a] Source: Ref. 22. [b]Source: Ref. 23. [c]Source: Ref. 40. [d]Source: Ref. 30. [e]Source: Ref. 17. [f]Source: Ref. 31. [g]Source: Ref. 25. [h]Source: Ref. 26. [i]Source: Ref. 27. [j]Source: Ref. 28. [k]Source: Ref. 29. [l]Source: Ref. 24. [m]Source: Ref. 32. [n]Source: Ref. 33. [o]Source: Ref. 34. [p]Source: Ref. 20. [q]Source: Ref. 37. [r]Source: Ref. 38. [s]Source: Ref. 39. [t]Source: Ref. 35. [u]Source: Ref. 36. [v]Source: this work. [w]Source: Ref. 41.

The results of the examination of the various properties of the cosolvent–water mixtures suggest that simple measures of solvent cohesiveness or hydrogen bond density do not always predict deviations from log-linear cosolvency in these aqueous systems. Additional insight into the reasons for the deviations from log-linear behavior of solutes in cosolvent–water mixtures can be gained from previous thermochemical data. Arnett and McKelvey (15) observed that the partial molal heat of the solution ($\overline{\Delta H}_s$) for several electrolytes at infinite dilution showed maxima at the same solvent composition for t-butyl alcohol–water systems. Further measurements in other cosolvent–water mixtures led to the conclusion that the position of the maxima relative to the cosolvent composition is the same for all solutes in a given cosolvent system. This observation parallels the results seen in most of the log S_m/S_i vs f plots.

Kimura *et al.* (16) found two extrema in plots of the deviation from linearity of the heat of transfer of *N*-methyl pyrrolidone vs the mole fraction of alcohol. A maximum was evident at a mole fraction of about 0.2 (f = 0.45) for ethanol and 0.25 (f = 0.43) for methanol. A minimum was observed for ethanol at a mole fraction of 0.85 (f = 0.95) and was not apparent for methanol. The maximum excess enthalpy in the water-rich region is attributed to both hydrophobic hydration of the cosolvent and hydrogen bonding between water and alcohol, while the minimum in the alcohol-rich region is attributed to hydrogen bonding between water and alcohol. Hydrophobic hydration can be defined as the tendency of nonpolar molecules to be surrounded by structured water. Both phenomena alter the normal three-dimensional structure of water. Since in the present study the maximum in the log S_m/S_i vs f plots occurs between these two enthalpy extrema, it may be due to an optimum balance between the hydrophobic hydration of the cosolvent and cosolvent–water association through hydrogen bonding. At this point the solvent is most unstructured. This is supported by the maximum in the ethanol–water density data, which occurs at the point of most efficient packing of the solvent molecules. The implication of the breakdown in water structure is also supported by the partial vapor pressure data for alcohol–water mixtures (17), where the vapor pressure of water is changed more drastically than ethanol.

Plots of the excess enthalpies of solution vs the mole fraction of water show a single maximum for amide–water systems (18,19). This occurs at a mole fraction of DMF of about 0.25 (f = 0.59). This value is in general agreement with other properties such as density, viscosity, and specific heat. The maxima in the deviation of these properties from linearity have been attributed to complex formation between the cosolvent and water (20), however, the involvement of hydrophobic hydration cannot be overlooked as a contributing factor. Similarly, the deviations of the properties for the other aprotic cosolvent–water mixtures show maxima whose positions agree more closely with each other than with the amphiprotic cosolvent–water systems. Unlike amphiprotic cosolvents, the aprotic cosolvents are not self-associated through hydrogen bonding in the pure liquid state. Thus, the primary effect of the aprotic cosolvents is to break the three-dimensional structure of water through strong dipolar and hydrophobic effects without becoming self-associated at high volume fractions. Both phenomena occur maximally at the same concentration of cosolvent. The maximum deviation in the solubility plots occurs at this cosolvent composition as well.

Figures 1 to 5 show that positive deviation from the predicted solubility, as defined by Eq. (1), is generally seen at high volume fractions of cosolvent. The exception is diazepam at high volume fractions of DMSO, DMA, DMF, and the PEGs. One major difference between this solute and either phenytoin or benzocaine is the absence of proton donating groups on the diazepam molecule. Phenytoin and benzocaine possess secondary and primary amino groups, respectively. These are capable of interacting with these cosolvents in a hydrogen bond donor–acceptor-type interaction. Diazepam, which possesses only tertiary amino groups, is incapable of such interactions. The strong relative basicity of these cosolvents (21) makes the interaction with phenytoin and benzocaine more likely. Thus diazepam, which is incapable of participating in hydrogen bonding with the cosolvent, would be "squeezed out" of solution more effectively than phenytoin and benzocaine, which are able to compete with water for hydrogen bonding sites on the cosolvent molecule. This view is also supported by the fact that the degree of negative deviation in the diazepam solubility

was somewhat less in the PEGs. These compounds contain ether groups, which are less efficient proton acceptors than the double-bonded oxygen compounds (21). In addition, the PEGs possess amphiprotic hydroxyl groups as well as an aprotic ether portion, which places them in a category between purely amphiprotic cosolvents and purely aprotic cosolvents.

Despite these differences, similarities in the deviations from solubilities predicted by Eq. (1) for different solutes suggest that a single mathematical function may describe such phenomena for a given cosolvent water system. Further investigation of these observations will be performed.

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REFERENCES

1. J. T. Rubino, J. Blanchard, and S. H. Yalkowsky. *J. Parent. Sci. Technol.* 38:215–221, (1984).
2. J. T. Rubino and S. H. Yalkowsky. *J. Parent. Sci. Technol.* 39:106–111 (1985).
3. J. T. Rubino and S. H. Yalkowsky. *J. Parent. Sci. Technol.* (in press) (1985).
4. T. A. Hagen and G. L. Flynn. *J. Pharm. Sci.* 72:409–414 (1983).
5. S. H. Yalkowsky and J. T. Rubino. *J. Pharm. Sci.* 74:416–421 (1984).
6. N. A. Williams and G. L. Amidon. *J. Pharm. Sci.* 73:9–13 (1984).
7. N. A. Williams and G. L. Amidon. *J. Pharm. Sci.* 73:14–18 (1984).
8. N. A. Williams and G. L. Amidon. *J. Pharm. Sci.* 73:18–23 (1984).
9. J. Wisniak and A. Tamir. *Mixing and Excess Thermodynamic Properties,* Elsevier Scientific Publishing Co., New York, 1978, IXXXXXVIII.
10. J. B. Bogardus. *J. Pharm. Sci.* 72:837–838 (1983).
11. G. L. Flynn, Y. Shah, S. Prakongpan, K. H. Kwan, W. I. Higuchi, and A. F. Hofmann. *J. Pharm. Sci.* 68:1090–1097 (1979).
12. M. Nicklasson and A. Brodin. *Int. J. Pharm.* 18:149–156 (1984).
13. N. H. Nie, C. H. Hull, J. G. Jenkins, K. Steinbrenner, and D. H. Bent. *Statistical Package for the Social Sciences,* McGraw–Hill, New York, 1975.
14. R. R. Pfeiffer, K. S. Yang, and M. A. Tucker. *J. Pharm. Sci.* 59:1809–1814 (1970).
15. E. M. Arnett and D. R. McKelvey. *J. Am. Chem. Soc.* 87:1393–1394 (1985).
16. F. Kimura, S. Murakami, and R. Fujishiro. *J. Solut. Chem.* 4:241–247 (1975).
17. A. Klemenc. *Int. Crit. Tables* 3:284–292 (1928).
18. C. deVisser and G. Somsen. *J. Solut. Chem.* 3:847–855 (1974a).
19. C. deVisser and G. Somsen. *J. Phys. Chem.* 78:1719–1722 (1974b).
20. P. Assarsson and F. R. Eirich. *J. Phys. Chem.* 72:2710–2719 (1968).
21. R. W. Taft and M. J. Kamlet. *J. Am. Chem. Soc.* 98:377–383 (1976).
22. J. R. Verlinde, R. M. H. Verbeeck, and H. P. Thun. *Bull. Soc. Chem. Belg.* 84:1119–1130 (1975).
23. G. O. Curme and F. Johnston. *Glycols,* Reinhold, New York, 1952, Chap. 9.
24. H. J. E. Dobson. *J. Chem. Soc.* 2866 (1925).
25. F. G. Young and W. D. Harkins. *Int. Crit. Tables* 4:446–475 (1928).
26. R. H. Pickard, A. H. J. Houssa, and H. Hunter. *Int. Crit. Tables* 7:63–77 (1930).
27. G. Barr. *Int. Crit. Tables* 5:21–25 (1929).
28. J. H. Awbery. *Int. Crit. Tables* 5:115–117 (1929).
29. D. B. Keyes, D. B. Mason, and R. K. Taylor. *Int. Crit. Tables* 3:308–318 (1928).
30. J. Mellan. *Industrial Solvents Handbook,* Noyes Data Corp., Park Ridge, N.J., 1970.
31. H. W. Bearce, G. C. Mulligan, and M. P. Maslin. *Int. Crit. Tables* 3:115–124 (1928).
32. T. C. Chan, and A. Van Hook. *J. Solut. Chem.* 5:107–125 (1976).
33. R. G. Lebel and D. A. J. Goring. *J. Chem. Eng. Data* 7:100–101 (1962).
34. Y. Murakami and T. Yamada. *Kagaku Keogaku Kyeokai* 26:865–872 (1962).
35. A. M. Balcazar-Ortiz, R. B. Patel, M. M. Abbott, and H. C. Van Ness. *J. Chem. Eng. Data* 24:133–136 (1979).
36. H. Schott. *J. Chem. Eng. Data* 6:19–20 (1961).
37. C. deVisser, J. M. Heuvelsland, L. A. Dunn, and G. Somsen. *J. Chem. Soc. Farady Trans. I* 74:1159–1169 (1978).
38. S. Saphon and H. J. Bittrich. *Z. Phys. Chem. Leipzig* 252:113–124 (1973).
39. C. deVisser and G. Somsen. *Z. Phys. Chem. N.F.* 92:159–162 (1974c).