Enthalpies of Transfer of Theophylline and Caffeine from Water to Aqueous Alcohols at 25 °C

J. H. Stern* and E. Lowe

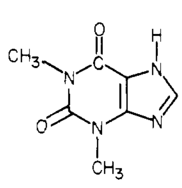
Department of Chemistry, California State University at Long Beach, Long Beach, California 90840

Enthalpies of transfer ($\Delta\bar{H}_3$) of the xanthines theophylline and caffeine at very low concentrations (m_3) from water to m_2 molal aqueous alcohols and sucrose were determined calorimetrically. The initial limiting slopes $(\partial\Delta\bar{H}_3/\partial m_2)m_3$ in ethanol (m_2 = 1, 2, 3) are 0.65 and 0.88 kcal kg mol^{-2} for theophylline and caffeine, respectively, with the latter value appearing to be the largest reported for a nonelectrolyte in aqueous ethanol. Transfer of theophylline to the homologous series methanol, ethanol, 1-propanol, and 2-propanol (m_2 = 1) increases regularly by 0.3 kcal kg mol^{-2}. All results are attributed in part to the energy difference of cavity formation in water and in the more structured aqueous alcohols, respectively, and depend on the size of the transferred nonelectrolyte. The enthalpies of transfer of theophylline and caffeine to 1 *m* sucrose are each 0.7 kcal/mol lower than in 1 *m* ethanol, and this constant difference shows that the transfer between two different equimolal solutions in the limiting region is independent of these related solutes.

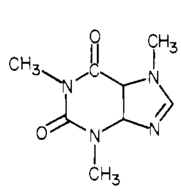
Introduction

There is a lack of thermodynamic data for transfer of nonelectrolytes from water to mixed solvents such as aqueous alcohols and sucrose. These ternary systems are of general importance, with the cosolvents inducing poorly understood changes on the solvent properties of water. Enthalpies of transfer $\Delta\bar{H}_3$ are sensitive variables for examining these changes and have been reported for a few smaller nonelectrolyte solutes sufficiently soluble for calorimetric measurements. Free energies of transfer $\Delta\bar{G}_3$ for larger nonelectrolytes have been reported for various systems (*1*); however, the compensation effect of $\Delta\bar{H}_3$ and $T\Delta\bar{S}_3$ frequently tends to minimize and smooth out $\Delta\bar{G}_3$. Enthalpies for larger solutes would complement the data and qualitatively test theoretical models invoked to explain observed interaction differences in water and in the mixed solvents. For example, the scaled particle theory includes as a major term the energy of formation of a cavity in the solvent capable of accommodating the solute (*2*). Thus if $\Delta\bar{H}_3$ reflects in part the energy difference between the formation of a cavity in the mixed solvent and in pure water, respectively, one would expect a dependence on the size of the transferred molecule. This dependence has been suggested (*3*); however, the available data are not conclusive, since trends in $\Delta\bar{H}_3$ have been restricted to smaller molecules and are frequently not discernible.

Theophylline and caffeine are two large polar molecules which have received some thermodynamic attention. Both form complexes with aqueous, polar, aromatic ligands (*4*, *5*) and at higher concentrations tend to dimerize (*6*, *7*). Theophylline is an important broncho-dilating drug (*8*) with diuretic properties (*9*), frequently formulated in aqueous ethanol or in aqueous solutions containing sugar. Caffeine has similar pharmacodynamic effects and is commonly ingested in the presence of aqueous ethanol and sucrose. The magnitude and nature of interaction of each of these two xanthines, which differ only by one methylene group, is not known in the above solutions.



theophylline



caffeine

This contribution describes enthalpies of transfer of theophylline and caffeine to 1, 2, and 3 *m* ethanol and to 1 *m* sucrose, and theophylline to methanol, 1-propanol, and 2-propanol (all 1 *m*) at 25 °C. Previous related studies in this laboratory include the thermodynamics of the aqueous caffeine-salicylate complex (*4*), partial molal heat capacities of theophylline and caffeine in pure water (*10*), and enthalpies and heat capacities of transfer of some simpler electrolytes and nonelectrolytes in the above mixed solvents (*11*–*13*).

Experimental Section

Theophylline (Nutritional Biochemical) was dried at 90 °C prior to use. Caffeine (Calbiochem) was resublimed under vacuum and used in glass ampules which were filled and sealed under dry nitrogen. All other materials were high-purity commercial products. The water was distilled and deionized. The calorimeter and calorimetric procedure were described elsewhere (*14*). The overall range was 0.0013–0.0037 mol of theophylline and 0.0014–0.0053 mol of caffeine dissolved in 450–500 g of solution, with the majority of runs ranging from ca. 0.002 to 0.003 mol per run.

Results and Discussion

Enthalpies of solution, ΔH_3 and $\Delta H_3°$, in the mixed solvents and in pure water, respectively, and the enthalpy of transfer of theophylline and caffeine, $\Delta\bar{H}_3 = \Delta H_3 - \Delta H_3°$, are shown in Tables I and II. All uncertainty intervals are standard deviations of the means. The value of $\Delta H_3°$ of theophylline agrees within 2% with an earlier study (*10*). It may be noted that $\Delta H_3°$ of resublimed caffeine is 8% lower than that for caffeine recrystallized from benzene. The present value is in satisfactory agreement with that for resublimed caffeine reported elsewhere recently (*15*). The dependence on method of purification (*16*) may be due to different crystalline modifications of anhydrous caffeine, whose crystal structure has not yet been reported.

Figure 1 shows $\Delta\bar{H}_3$ for theophylline and caffeine plotted against ethanol molality m_2. Both curves resemble those for smaller molecules and electrolytes, generally characterized by approximately linear positive $\Delta\bar{H}_3$ at low m_2, followed by an inflection region with increasing alcohol concentration. Slopes $(\partial\Delta\bar{H}_3/\partial m_2)_{m_3}$ taken from the initially linear portions of the curves are of interest because they represent limiting solute–solvent interaction differences and should allow meaningful comparison between various solutes. Table III shows values of $(\partial\Delta\bar{H}_3/\partial m_2)_{m_3}$ for theophylline, caffeine, and several amino acids (*17*) in aqueous ethanol. It may be noted that complex formation

Table I. ΔH_3 and $\Delta\bar{H}_3$ of Theophylline at 25 °C

system	m_2, mol kg^{-1}	no. of runs	ΔH_3, kcal/mol	$\Delta\bar{H}_3$, kcal/mol
pure water	0.0	12	4.74 ± 0.04 ($\Delta H_3°$)	
ethanol	1.0	8	5.39 ± 0.04	0.65
ethanol	2.0	6	6.01 ± 0.06	1.27
ethanol	3.0	6	6.58 ± 0.02	1.84
methanol	1.0	4	5.01 ± 0.02	0.27
1-propanol	1.0	8	5.60 ± 0.03	0.86
2-propanol	1.0	4	5.61 ± 0.16	0.87
sucrose	1.0	9	4.66 ± 0.03	−0.08

Table II. ΔH_3 and $\Delta\bar{H}_3$ of Caffeine at 25 °C

system	m_2, mol kg^{-1}	no. of runs	ΔH_3, kcal/mol	$\Delta\bar{H}_3$, kcal/mol
pure water	0.0	11	3.30 ± 0.03 ($\Delta H_3°$)	
ethanol	1.0	6	4.18 ± 0.04	0.88
ethanol	2.0	6	4.82 ± 0.05	1.52
ethanol	3.0	6	5.23 ± 0.04	1.93
sucrose	1.0	6	3.51 ± 0.04	0.21

Table III. Limiting Slopes $(\partial\Delta\bar{H}_3/\partial m_2)_{m_3}$ in Aqueous Ethanol

nonelectrolyte	$(\partial\Delta\bar{H}_3/\partial m_2)_{m_3}$, kcal kg mol^{-2}
caffeine	0.88
theophylline	0.65
valine	0.36
aminobutyric acid	0.30
alanine	0.27
glycine	0.23

between the xanthines and these mixed solvents is unlikely since large negative enthalpies would be expected.

Limiting slope values for all four amino acids increase with increasing size. In addition to size, polarity must also be an important factor. For example, acetic acid is 0.12 kcal kg mol^{-2} higher than glycine (*12*). The size effect with theophylline and caffeine is evident, especially since the latter appears to be the largest molecule with correspondingly the highest value reported in aqueous ethanol. If $\Delta\bar{H}_3$ is in part the energy difference of cavity formation in pure water and in the more structured aqueous ethanol (*18*), then it should indeed be positive for all solutes, with the largest value for caffeine.

Theophylline transfer to the homologous series methanol, ethanol, 1-propanol and 2-propanol increases by 0.3 kcal kg mol^{-2}. In comparison, acetic acid in the series methanol, ethanol, and 1-propanol increases by 0.15 kcal kg mol^{-2} (*12*). The incremental changes for each of the two systems remains constant and the difference in values could again be attributed to a size effect.

Aqueous sucrose differs from alcohols in its effect on the solvent properties of water. For example, recent spectroscopic measurements show that water-water and water-sucrose interactions do not differ appreciably (*19*). Enthalpies of transfer of NaCl to aqueous sucrose are negative and are similar in magnitude to other hydrophilic cosolvents including hydrogen peroxide and urea (*20*). Direct comparison with other nonelectrolyte transfers in ethanol and sucrose is not possible since $\Delta\bar{H}_3$ data are not available; however, the enthalpies of pair-wise interactions obtained from dilution measurements also illustrate the difference. The values for urea-sucrose (*21*) are lower than for urea-*tert*-butyl alcohol (*22*), −0.14 and 0.17 kcal kg mol^{-2}, respectively, just as the values of $\Delta\bar{H}_3$ for theophylline and caffeine are each 0.7 kcal/mol lower in 1 *m* sucrose than in 1 *m* ethanol. The constancy of this difference is remarkable and shows that the transfer between two such diverse equimolal solutions in the limiting region is independent of the transferred solute, at least in this case of two such large molecules differing by one functional group only.

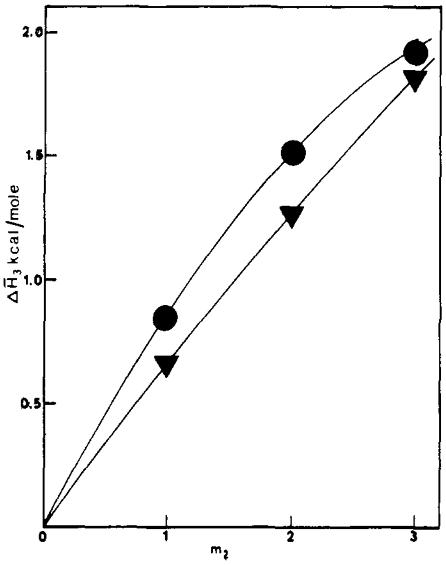


Figure 1. Enthalpies of transfer of theophylline and caffeine $\Delta\bar{H}_3$, from pure water to aqueous ethanol, m_2: ▼, theophylline; ●, caffeine.

Acknowledgment

The authors acknowledge Dr. C. de Visser for fruitful discussion.

Literature Cited

(1) M. Roseman and W. P. Jencks, *J. Am. Chem. Soc.*, **97**, 631 (1975).
(2) R. A. Pierotti, *Chem. Rev.*, **76**, 717 (1975).
(3) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. McC. Duggleby *J. Am. Chem. Soc.*, **87**, 1541 (1965).
(4) J. H. Stern, J. A. Devore, S. L. Hansen, and O. Yavuz, *J. Phys. Chem.*, **78**, 1922 (1974).
(5) P. Rohdewald and M. Baumeister, *J. Pharm. Pharmac.*, **21**, 867 (1969).
(6) S. J. Gill, M. Downing, and G. F. Sheats, *Biochemistry*, **6**, 272 (1967).
(7) A. L. Thakkar, L. G. Tensmeyer, and W. L. Wilham, *J. Pharm. Sci.*, **60**, 1269 (1971); D. Guttman and T. Higuchi *ibid.*, **60**, 1270 (1971).
(8) "Physicians Desk Reference", 31st ed, Medical Economics Co., Oradell, N.J., 1977.
(9) G. de Stevens, "Diuretics, Chemistry and Pharmacology", Academic Press, New York, N.Y., 1963.
(10) J. H. Stern and L. R. Beeninga, *J. Phys. Chem.*, **79**, 582 (1975).
(11) J. H. Stern and S. L. Hansen, *J. Chem. Eng. Data*, **16**, 360 (1971).
(12) J. H. Stern, O. Yavuz, and T. Swearingen, *J. Chem. Eng. Data*, **17**, 183 (1972).
(13) J. H. Stern, E. Lowe, and M. E. O'Connor, *J. Solution Chem.*, **3**, 823 (1974).
(14) J. H. Stern and C. W. Anderson, *J. Phys. Chem.*, **68**, 2528 (1964).
(15) A. Cesàro, E. Russo, and V. Crescenzi, *J. Phys. Chem.*, **80**, 335 (1976).
(16) A. Cesàro, private communication.
(17) C. A. Spink and M. Auker, *J. Phys. Chem.*, **74**, 1742 (1970).
(18) F. Franks and D. J. G. Ives, *Q. Rev., Chem. Soc.*, **20**, 1 (1966).
(19) D. W. James and R. L. Frost, *J. Phys. Chem.*, **73**, 2795 (1967).
(20) J. H. Stern and J. D. Kulluk, *J. Phys. Chem.*, **73**, 2795 (1967); J. H. Stern and W. R. Bottenberg, *ibid.*, **72**, 2229 (1971).
(21) J. J. Savage and R. H. Wood, *J. Solution Chem.*, **5**, 733 (1976).
(22) J. E. Desnoyers, G. Perron, L. Avédikian, and J. Morel, *J. Solution Chem.*, **5**, 631 (1976).

Received for review April 24, 1978. Accepted June 23, 1978. Financial support provided by the Long Beach Heart Association.