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Report

Thermodynamics in the Prediction of the Solubilities of Binary Mixtures of the Diastereoisomers and Enantiomers of Ephedrine

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Equations derived from the Clausius–Clapeyron and Prigogine–Defay equations were used to determine the free energy of mixing for diastereoisomers and enantiomers from heats of fusion and transition temperature data. These equations are applied to the thermodynamics of mixing of the six binary equimolar combinations of (1*R*,2*S*)-ephedrine, (1*S*,2*R*)-ephedrine; and (1*R*,2*R*)- and (1*S*,2*S*)-pseudoephedrine isomers. The relative equilibrium solubility of the binary mixtures in water is consistent with thermodynamic calculations.

KEY WORDS: solubility; enantiomers; diastereoisomers; thermodynamics; ephedrine.

INTRODUCTION

Significant differences in the chromatographic, biological and spectroscopic, properties of (1*R*,2*S*)-, (1*S*,2*R*)-, (1*R*,2*R*)-, and (1*S*,2*S*)-ephedrine and of binary mixtures have been reported (1–12). Differences in interactions on mixing may be related to fundamental thermodynamic differences between the enantiomers and the diastereoisomers on mixing. Changes in free energy on mixing for enantiomers have been reported from calorimetric data but no predictions on the interactions of diastereoisomers were made (13–16). Research efforts have been conducted in the thermodynamics of mixing related to predicting solute–solvent interactions from various fundamental physical properties (17–26). This suggests that ephedrine solute–solute stereoisomeric interactions which are manifested as solubility differences may also be predictable from fundamental thermodynamic properties.

EXPERIMENTAL

Differential thermal analysis curves were generated with a Mettler TA2000 differential thermal analysis system (DTA) using capped aluminum crucibles previously calibrated for melting point and heat capacity. Individual isomers and binary mixtures were melted and allowed to resolidify prior to collection of thermodynamic data.

A total of 1.00 g isomer of each individual ephedrine isomer or 0.50 g of each of two isomers was weighed into a sealable glass vial and, after adding deionized water, was sealed and immersed in a circulating water bath at 30.0 ± 0.5°C. The concentration of total isomers was determined directly from their relative UV absorbance in 0.1 *N* HCl (Perkin Elmer UV-vis Model 559A spectrophotometer). The ratio of (1*R*,2*R*)- and (1*S*,2*S*)-pseudoephedrine to (1*R*,2*S*)- and (1*S*,2*R*)-ephedrine was determined by nine integrations of the alpha-methine doublet protons at 4.17 and 4.75 ppm, respectively, using NMR spectroscopy (Bruker WP-2000). The ratio of mixed enantiomers was determined by optical rotation in water (Perkin Elmer Model 241 polarimeter with 10-cm cell at 589 nm).

SOLUBILITIES

From the Clausius–Clapeyron and Prigogine–Defay equations activity ratios for diastereoisomers and enantiomers can be calculated from heats of fusion and temperatures of transition data (Appendix A). Thus,

$$\ln \frac{a_A}{0.5\, a_{AB}} = \frac{T_{AB}\Delta H_A + T_A \Delta H_{AB}}{RT_A T_{AB}} - \frac{\Delta H_A + \Delta H_{AB}}{RT_A} \tag{1}$$

where T_A, T_B, and T_{AB} are the transition temperatures of the individual isomers and that of the equimolar mixture, and ΔH_A, ΔH_B, and ΔH_{AB} are the heats of fusion of the individual isomers and the equimolar mixtures, respectively. The activity ratio compares that of A by itself versus the activity of the same amount of A in the presence of an equal amount of B. The chemical activity of A may thus increase, decrease, or remain the same on mixing.

For enantiomers the change in free energy and change in entropy on mixing can be calculated directly from Eq. (1). Thus,

$$\Delta G_{AB} = -RT \ln \frac{a_A}{0.5\, a_{AB}} \tag{2}$$

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And

$$\Delta S^{A}_{AB} = R \ln \frac{a_A}{0.5\, a_{AB}} \tag{3}$$

Since at equimolar concentrations $\Delta S^{A}_{AB} = \Delta S^{B}_{AB}$ and $\Delta S^{A}_{AB} + \Delta S^{B}_{AB} = \Delta S_T$,

$$\ln \frac{0.5 a_{AB}}{a_A} = \frac{-\Delta S_T}{2R} \tag{4}$$

or

$$\frac{a_A}{0.5 a_{AB}} = \exp\left[\frac{\Delta S_T}{2R}\right] \tag{5}$$

Thus,

$$\frac{a_A}{a_{AB}} = 2 \exp\left[\frac{-\Delta S_T}{2R}\right] \tag{6}$$

The solubility of A relative to the solubility of AB can be calculated from the activity ratio. Thus,

$$C_T = C_A * \frac{a_A}{a_{AB}} \tag{7}$$

where C_T is the concentration of both isomers and C_A is the concentration of either enantiomer.

For diastereoisomers the mole fraction of A at the eutectic concentration can be calculated extending the same derivation as for the interaction of enantiomers (Appendix B). For $X_A > X_B$,

$$X_{AU} = \frac{S_A}{S^{A}_{AB}} * \frac{S^{B}_{AB}}{S_B} \tag{8}$$

The solubility of the more soluble isomer at the eutectic concentration can be calculated directly from the product of the solubility of the individual isomer and its mole fraction X_A present in the mixture,

$$C^{A}_{T} = C_A * X_{AU} \tag{9}$$

where C_A is the solubility of the more soluble isomer alone and C^{A}_{T} is the solubility of the same isomer in the eutectic mixture. Since $X_B = 1 - X_{AU}$ and since $C^{B}_{T} = C_T - C^{A}_{T}$,

$$C^{B}_{T} = C_A * (1 - X_{AU}) \tag{10}$$

The relative solubility of the individual isomers can also be related empirically to the following equation:

$$C_A = \frac{3.00}{S_A} - 0.038 \tag{11}$$

for $n = 4$ with a correlation coefficient of $r = 0.989$, where C_A is the solubility concentration of the individual isomers and S_A is simply ΔH_A divided by the transition temperature.

RESULTS AND DISCUSSION

The stereoisomers of ephedrine differ structurally only in absolute configuration. Thus differences in properties on mixing should be directly related to only interaction between isomers. Thermodynamic data are presented in Table I. Solubility data are presented in Table II. The solubility of mixtures of ephedrine isomers was performed with equal amounts of the individual isomers and not with a recrystallized portion of a combined mixture to assure that differences in solubility are not due to differences in crystal lattice energy between individual and mixed isomers. Solutions were maintained at a constant temperature for 7 days to assure that the particle size of the solids would not significantly affect the solubility.

Table I. Thermodynamic Data[a] Ephedrine Isomers

Isomer[b]	ΔH_n (kcal/mol)	T_n (K)	S_A (e.u.)	ΔS^{A}_{AB} (e.u.)	S^{A}_{AB} (e.u.)	ΔS_T (e.u.)
−E	3.14	306.7	10.2	1.3	11.5	
+E	3.41	307.2	11.1	1.4	12.5	
±E	6.00	350.9		0.5	12.0	1.0
+U	7.33	392.9	18.7	0.0	18.7	
−U	7.51	392.9	19.1	0.0	19.1	
±U	8.10	393.1		−0.2	18.9	−0.4
−E/+U	2.41	326.6	10.2	0.6	10.8	
+U/−E	2.41	326.6	18.7	−3.8	14.9	−4.1
−E/−U	1.99	329.4	10.2	0.7	10.9	
−U/−E	1.99	329.4	19.1	−3.7	15.4	−4.5
+E/+U	1.82	322.8	11.1	0.6	11.7	
+U/+E	1.82	322.8	18.7	−3.6	15.1	−3.4
+E/−U	1.51	321.9	11.1	0.5	11.6	
−U/+E	1.51	321.9	19.1	−4.1	15.0	−3.4

[a] ΔH_n is the heat of fusion of the individual isomer or equimolar mixture. T_n is the temperature of transition from solid to liquid of the same isomer or mixture. S_A is the entropy of isomer A, ΔS^{A}_{AB} is the change in entropy of the isomer in the equimolar mixture, and S^{A}_{AB} is the sum resulting entropy of the isomer in the equimolar mixture. The value ΔS_T is the difference in entropy between A and B in the equimolar mixture.

[b] Ephedrine isomers refer to (1*S*:2*R*)-ephedrine [+E], (1*R*:2*S*)-ephedrine [−E], (1*R*:2*R*)-pseudoephedrine [+U], and (1*S*:2*S*)-pseudoephedrine [−U]. Thermodynamic data are the averages of duplicate determinations.

The differences in thermodynamic and solubility properties between individual isomers themselves and among the binary mixtures cannot be attributed to impurities within the samples themselves. No interferences were detected with mass spectroscopy, NMR, and IR and UV spectroscopy. Optical rotations of enantiomers were equal with opposite signs. The same isomers were used in the mixtures as in the individual isomers.

CONCLUSIONS

The equilibrium solubility of each two-component system in the six-binary combination of ephedrine mixtures is predicted within ±7% of the experimentally determined values from the thermodynamic data even though the solubilities of the binary mixtures vary over a range of a factor of five. Interestingly the total solubility of ephedrine and pseudoephedrine in binary mixtures is consistently lower than that of (1*R*:2*S*)-ephedrine alone. The solubility decrease for enantiomeric mixtures compared to the individual compounds is even more marked than that for diastereoisomeric mixtures.

Solubilities of diastereoisomeric mixtures of ephedrine

Table II. Ephedrine Solubility (mol/liter in Water at 30.0°C)[a]

Isomer[b]	C_A	C_{AB}^{A} Calc.	C_{AB}^{A} Exp.	C_{AB}^{B} Calc.	C_{AB}^{B} Exp.	C_T exp.
−E/+U	0.257	0.193	0.189			0.249
+U/−E				0.064	0.060	
−E/−U	0.257	0.194	0.189			0.249
−U/−E				0.063	0.060	
+E/+U	0.227	0.174	0.181			0.244
+U/+E				0.053	0.063	
+E/−U	0.227	0.171	0.175			0.237
−U/+E				0.056	0.062	
−E/+E	0.257	0.073	0.075			0.151
+E/−E	0.227			0.073	0.075	
−U/+U	0.131	0.025	0.024			0.047
+U/−U	0.110			0.025	0.024	

[a] C_A is the experimental solubility of the *A* isomer alone and C_T is the total solubility of both isomers together. C_{AB} is the solubility of an individual isomer in the presence of the second isomer.

[b] Ephedrine isomers refer to (1*S*:2*R*)-ephedrine [+E], (1*R*:2*S*)-ephedrine [−E], (1*R*:2*R*)-pseudoephedrine [+U], and (1*S*:2*S*)-pseudophedrine [−U], Thermodynamic data are the averages of duplicate determinations.

and pseudoephedrine at the eutectic concentration can be calculated with reasonable accuracy only from three points on the freezing point depression curve, i.e., for each of the pure compounds and for the equimolar quantity (see Fig. 1). The calculations of solubility assume the inflection point where $dT/dX = 0$ for diastereoisomers is at the equimolar concentration. A higher accuracy should be obtained if the actual inflection point of diastereoisomers in the freezing point depression curve can be calculated from fundamental principles or experimentally measured with precision. Heats of fusion and temperatures of transition can then be obtained at the mole fraction corresponding to this inflection point.

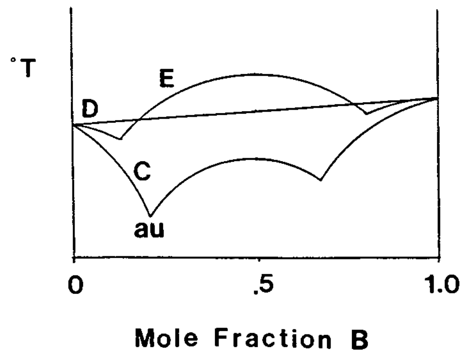

Fig. 1. Representative freezing point depression curve for enantiomers and diastereoisomers where *T* is the temperature of transition from solid to liquid and X_B is the mole fraction *B*. T_A, T_{AB}, and T_B are the of *T* at X_B = 0, 0.5, and 1.0, respectively. At $X_B = 0.5$, T_{AB} can be less than (C), greater than (E), or equal to (D) the average of T_A and T_B, respectively. Except in Case D, an inflection point occurs at $X_B = 0.5$ for enantiomers and at or near $X_B = 0.5$ for diastereoisomers. The value X_{AU} is the mole fraction of *A* at the eutectic concentration. For enantiomers T_A should equal T_B.

The solubility of the two dextrorotatory compounds differs by one-half and the entropy ($\Delta H/T$) differs by a factor of two; the levorotatory compounds' solubility likewise is inversely proportional to their entropy. In each case the pseudoephedrine isomer had the larger entropy and lower solubility.

Thermodynamic information on enantiomeric or diastereoisomeric interactions predicts relative solubility differences. Conversely the thermodynamic information could be calculated only from solubility data. This would be especially useful for thermally labile stereoisomeric compounds which can decompose on melting.

The thermodynamic and solubility results demonstrate that distinct physical properties of stereoisomers are related not only to the properties of the individual isomers but also to their interaction on mixing. In addition, the maximum interaction can occur not only at equimolar mixtures but also at mole ratios corresponding to their eutectic point concentrations. Physical properties from interactions related to the free energy of mixing may include determining the increased or decreased solubility of individual versus racemic drugs, predicting the difficulty of chromatographic resolution of chiral compounds on a chiral stationary phase, and investigating potentially enhanced or hindered transport of chiral isomeric mixtures through biological membranes.

APPENDIX A

From fundamental laws at constant pressure the free energy of mixing of two components changes with temperature by the formula

$$\frac{d(\Delta G_{\text{mix}})}{dT} = -\Delta S_{\text{mix}} \tag{A1}$$

Multiplying by the ratio dT/dX,

$$\frac{d(\Delta G_{\text{mix}})}{dX} = -\Delta S_{\text{mix}} \frac{dT}{dX} \tag{A2}$$

Plots of temperatures of transition versus mole fraction (Fig. 1) for both enantiomers and diastereoisomers indicate that as X_A approaches X_B, dT/dX_A approaches dT/dX_B and dT/dX_A approaches zero. (An unusual exception occurs when dT/dX is a constant with mole fraction and no freezing point depression is observed.) Therefore as X_A approaches the inflection point,

$$\frac{d(\Delta G_{\text{mix}})}{dX_A} = \frac{d(\Delta G_{\text{mix}})}{dX_B} \tag{A3}$$

i.e., $\Delta G_{\text{mix}_A} = \Delta G_{\text{mix}_B}$.

The Clausius–Clapeyron equation for the freezing point depression by an equimolar mixture to an individual stereoisomer is

$$\ln (0.5)X_{AB} = \frac{\Delta H_A}{R}\left[\frac{1}{T_A} - \frac{1}{T}\right] \tag{A4}$$

where ΔH_A is the heat of fusion of a single isomer, T_A and *T* are the melting points of one isomer and the mixture, respectively, and X_{AB} is the mole fraction of the equimolar mixture. The factor 0.5 is required because at low concentrations, adding a small amount of an equimolar mixture of isomers containing a common isomer is equivalent to adding half as much of the opposite isomer alone.

The Prigogine–Defay equation has been used to calculate enantiomeric excess by Fouquey and Jacques (13). This equation for the freezing point depression of an equimolar mixture by a common individual isomer contains the same variables of mole fraction, temperature of transition, and heats of fusion as the previous equation.

$$\ln \frac{X_A X_B}{0.25} = \frac{\Delta H_{AB}}{R}\left[\frac{1}{T_{AB}} - \frac{1}{T}\right] \tag{A5}$$

where ΔH_{AB} is the heat of formation of the equimolar mixture, T_{AB} and T are the melting points of the equimolar mixture and the actual mixture, respectively, and X_A and X_B are the mole fraction of the individual isomers, in which $X_A + X_B = 1$.

Replacing mole fraction by activity in Eqs. (A4) and (A5),

$$\ln \frac{(0.5a_{AB})}{a_A} = \frac{\Delta H_A}{R}\left[\frac{1}{T_A} - \frac{1}{T}\right] \tag{A6}$$

And

$$\ln \frac{a_A a_B}{0.25(a_{AB})^2} = \frac{\Delta H_{AB}}{R}\left[\frac{1}{T_{AB}} - \frac{1}{T}\right] \tag{A7}$$

And

$$\ln \frac{(0.5a_{AB})}{a_B} = \frac{\Delta H_B}{R}\left[\frac{1}{T_B} - \frac{1}{T}\right] \tag{A8}$$

Because for any nonzero values of a and b, $\ln a = \ln(a\,b) - \ln b$, from Eq. (A7),

$$\ln \frac{a_B}{(0.5a_{AB})} = \ln \frac{a_A a_B}{0.25(a_{AB})^2} - \ln \frac{a_A}{(0.5a_{AB})} \tag{A9}$$

Three equations relating the same variables results in unique solutions for the activity ratios $(a_A/0.5a_{AB})$ and $(a_B/0.5a_{AB})$. Selecting T as T_{AB} in Eqs. (A3) and (A5) and T as T_A and T_B, respectively, in two equations from Eq. (A4), the algebraic solution to the two equations is

$$\ln \frac{a_A}{0.5a_{AB}} = \frac{T_{AB}\Delta H_A + T_A\Delta H_{AB}}{RT_A\,T_{AB}} - \frac{\Delta H_A + \Delta H_{AB}}{RT_A} \tag{A10}$$

For enantiomers replacing A by B results in exactly equivalent activity ratios for the two isomers. For diastereoisomers replacing A by B will result in different activity ratios for the two isomers. The free energy of mixing then becomes simply

$$\Delta G_{AB} = -RT \ln \frac{a_A}{0.5a_{AB}} \tag{A11}$$

When the activity of A is equal to its activity in AB this reduces to the ideal free energy of mixing of $\Delta G = -RT \ln 2$.

And

$$\Delta S_{AB} = -R \ln \frac{a_A}{0.5a_{AB}} \tag{A12}$$

APPENDIX B

The eutectic solubility concentration $X_A > X_B$ can be obtained from adding diastereoisomer B to diastereoisomer *A*. Thus,

$$\frac{dS_A}{dX_A} = \frac{-dS_B}{dX_A} \tag{A13}$$

The same concentration can also be obtained from adding *A* to an equimolar mixture. Thus,

$$\frac{dS^A_{AB}}{dX_A} = \frac{-dS^B_{AB}}{dX_A} \tag{A14}$$

Therefore,

$$\frac{dS^A_{AB}}{dS_A} = \frac{dS^B_{AB}}{dS_B} \tag{A15}$$

Thus the change in concentration of *B* is

$$1 - X_A = 1 - \frac{dS^A_{AB}}{dS_B}\frac{dS_A}{dS^B_{AB}} \tag{A16}$$

At the eutectic concentration each $dS_A = dS_B = dS^A_{AB} = dS^B_{AB}$ with respect to X_A. Therefore,

$$X_{AU} = \frac{S_A}{S^A_{AB}} * \frac{S^B_{AB}}{S^A_B} \tag{A17}$$

where $S^A_{AB} = S_A + dS^A_{AB}$ and $S^B_{AB} = S_B + dS^B_{AB}$. The values for S_A and S_B are the entropy calculated from the pure isomers *A* and *B*. The values for dS^A_{AB} and dS^B_{AB} are calculated simply by multiplying Eq. (A10) by R or dividing Eq. (A11) by T.

NOMENCLATURE

ΔH_A	Heat of fusion of *A*
T_A	Temperature of transition of *A* from solid to liquid in degrees Kelvin
ΔH_{AB}	Heat of fusion of equimolar mixture of *A* and *B*
T_{AB}	Temperature of transition of equimolar mixture *A* and *B* from solid to liquid in degrees Kelvin
X_A	Mole fraction *A* in two-component mixture
R	Gas constant, 1.99 cal/mol K
S_A	Entropy of individual isomer *A* calculated from ˆ*H*/*T*
a_A	Chemical activity of *A*
a_{AB}	Chemical activity of an equimolar mixture of *A* and *B*
ΔG^A_{AB}	Change in free energy of mixing of *A* in equimolar mixture *AB*
ΔG^B_{AB}	Change in free energy of mixing of *B* in equimolar mixture *AB*
ΔG_{AB}	Change in solution free energy of mixing equimolar quantities of *A* and *B*
ΔS^A_{AB}	Change in entropy of mixing of *A* in equimolar mixture *AB*
ΔS_{AB}	Change in solution free energy of mixing equimolar quantities of *A* and *B*
ΔS_T	Change in solution entropy of mixing
C_A	Solubility concentration of isomer *A* alone
C_T	Solubility concentration of both isomers independent of absolute configurations

C_T^A	Solubility concentration of A in binary mixture
X_{AU}	Mole fraction of A at the eutectic concentration
S_{AB}^A	Entropy of A in an equimolar mixture of A and B
S_{AB}^B	Entropy of B in an equimolar mixture of A and B
dS_A	Incremental change in entropy of A on mixing
dS_{AB}^A	Incremental change in entropy of A in equimolar mixture on mixing
dS_B	Incremental change in entropy of B on mixing
dS_{AB}^B	Incremental change in entropy of B in equimolar mixture on mixing

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