Thermodynamic Properties of Mixtures Containing Precursors of Vitamin B5

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Thermodynamic properties of different organic solvents dissolved in precursors of vitamin B5 are determined at infinitely dilute concentrations by using gas−liquid chromatography. From an analysis of experimental data and using the Peng−Robinson equation of state, the thermodynamic properties of the mixtures in the whole range of concentration were predicted.

Introduction

Ketopantolactone (KPL), *R*-pantolactone (*R*-PL), and the racemic mixture of pantolactone (*RS*-PL) are intermediates in the synthesis of pantothenic acid, known as vitamin B5 and used in many different pharmaceutical applications ranging from food integrators to neurotropic drugs.[1]

Presently, oxidation of racemic pantolactone to ketopantolactone followed by an enantioselective hydrogenation of this last compound to *R*-pantolactone is one of the most promising process alternatives to the often applied resolution procedures carried out at the step of the open chain hydroxy-acid form,[2−4] as shown in Figure 1.

Enantioselective hydrogenation is preferred to the resolution processes because of its short and clean operations and its competitive costs of production, basic requirements in the pharmaceutical industry. The aim of the present work is the characterization of ketopantolactone, *R*-pantolactone, and the racemic mixture and the investigation of the properties of organic mixtures containing these compounds.

Chromatographic Methods

Infinite dilution activity coefficients are an important property from a theoretical point of view, since they represent the macroscopic evidence of the properties of a solution constituted by a single solute molecule surrounded by the solvent. Chromatographic techniques have been used extensively for the direct measurement of activity coefficients at infinite dilution. The reason for their popularity is the wide availability of chromatographic apparatus for analytical purposes and that only minor modifications to the commercial devices are usually necessary to perform fast and accurate physical−chemical measurements.[5−7] The chromatographic key factors for the determination of the activity coefficients are the evaluation of the retention time of the solutes and of the amount of stationary phase (KPL, *R*-PL, and *RS*-PL in this work) contained in the column. The thermodynamic properties of the binary mixtures of KPL, *R*-PL, or *RS*-PL with organic solvents were studied using the inverse liquid−gas chromatographic technique (IGC) to focus the attention on the behavior of the stationary phase. This chromatographic method has the advantages of having a rigorous theoretical background and a great operative simplicity.

Helium was used as carrier gas, and different organic compounds were used as solutes to be injected into the column. Thus, the retention properties of several organic solutes in lactones were determined at different temperatures using the following equation:

$$V_g^\circ = \frac{F_m}{w} j \frac{p_o - p^\circ_{H_2O}}{760} \frac{273}{T_m}(t_r - t_a) \tag{1}$$

where V_g° is the specific retention volume, F_m is the carrier flow rate, w is the weight of stationary phase in the column, p_o is the pressure at the outlet of the column, $p^\circ_{H_2O}$ is the vapor pressure of the water at the temperature T_m of the soap flow meter, t_r is the retention time of the injected solute, t_a is the retention time of the unretained solute (dead time), and j is the James−Martin factor that introduces a correction for the pressure drop in the column.

From the retention equation (eq 1), assuming that in the column equilibrium conditions are reached, the activity coefficient of the injected solute at infinite dilution in the stationary phase is given by

$$\gamma_i^\infty = \frac{273R}{V_g^\circ f_i^\circ M} \tag{2}$$

where γ_i^∞ is the activity coefficient of the solute i at infinite dilution in the stationary phase, f_i° is the fugacity of the liquid solute in a standard state (in this context the actual temperature and pressure of the pure liquid), and M is the molecular weight of the stationary phase.

Using basic definitions, a similar equation is obtained for the fugacity coefficient of component i in the mixture

$$\hat{\varphi}_i^\infty = \frac{273R}{V_g^\circ P M} \tag{3}$$

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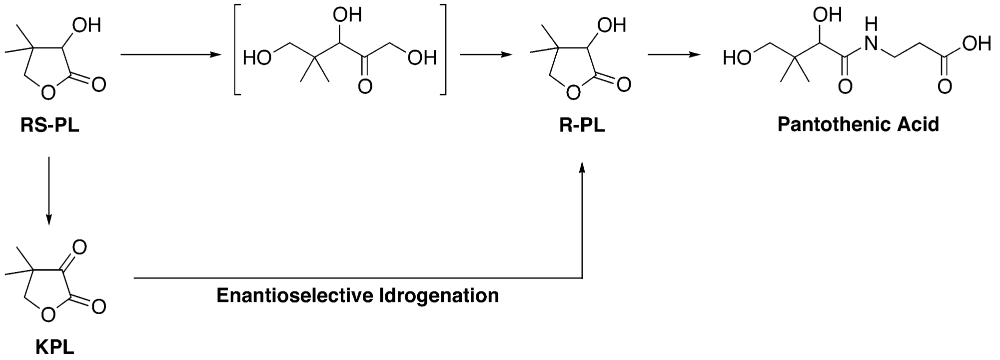

Figure 1. Synthesis of pantothenic acid.

The experimental values of the activity coefficients at infinite dilution and of the fugacity coefficients at infinite dilution can be used for the determination of the binary interaction parameters needed in different thermodynamic models.

The determination of the amount of stationary phase under normal conditions does not represent a problem except when the vapor pressure of the stationary phase is very high, as for the pantolactones. In this case the determination of the retention volumes has to be carried out evaluating the real amount of stationary phase very carefully, as follows: (a) the column is accurately weighed before the measurements with an electronic balance; (b) the chromatographic apparatus is equilibrated with a column containing a stable stationary phase; (c) when the apparatus is ready to start measurements, the column containing the given pantolactone is put in the apparatus and the time of analysis is registered; (d) the injection times of the solutes are registered continuously, and (e) after the tests, the column is again weighed to quantify the loss of stationary phase, assuming that this parameter is linear with time. To quantify the loss of stationary phase and to determine the vapor pressures of the lactones, a gas saturation method was used in the same temperature range of the chromatographic experiments. These results were compared with the ones obtained by evaluating the losses of stationary phase during the IGC tests. An average deviation of less than 5% in the values of the vapor pressures confirmed the good agreement between them.

A recent approach called “non-steady-state gas chromatography” (NSGC)[8,9] can be used as an alternative method to calculate the activity coefficients at infinite dilution when volatile stationary phases are analyzed. In this process, uncoated open tubular columns or columns packed only with a deactivated support are used.

In the NSGC method, the solvent that constitutes the stationary phase is injected and (due to its volatility) is allowed to coat the walls or the packing support. The carrier gas entering the column becomes saturated with the solvent vapors. As a consequence, the solvent is thus steadily depleted from the wetted walls or packing of the column starting at the inlet of the column. When a steady baseline is achieved, small samples of a solute (that should be more volatile than the solvent) are injected. Due to the losses of solvent from the column, the retention time (and the retention volume) of the solute decreases during the lifetime of the column. The change in the retention times of the solutes is linear with time.

Finally, infinite dilution activity coefficients are related to the decrease of the solute’s retention time and to the solvent and solute vapor pressures by a simple equation.[8,9]

Assuming an ideal vapor phase and a solution that is sufficiently diluted to be considered in the Henry’s law region, the following relationship is retained

$$\Delta V_{\mathrm{N}} = \frac{RT}{p_i^{\circ}\gamma_i^{\infty}}\Delta n^{\mathrm{S}} \tag{4}$$

where ΔV_{N} is the variation of the net retention volume due to a loss of solvent Δn^{S} and p_i° is the vapor pressure of the solute.

If the carrier flow rate and the temperature of the column are constant, the loss of solvent is directly proportional to time. Considering a time interval $\Delta t_i = t_1 - t_2$ between two successive solute injections, the following equation is obtained

$$\gamma_i^{\infty} = -\frac{p_{\mathrm{S}}^{\circ}}{p_i^{\circ}}\left(\frac{\Delta t_{\mathrm{R}i}}{\Delta t_i}\right)^{-1} \tag{5}$$

where $\Delta t_{\mathrm{R}i}/\Delta t_i$ is the rate at which the retention time of a solute decreases with its injection time and p_{S}° is the vapor pressure of the solvent phase.

Compared with the IGC method, this method presents, since a difference of retention times is measured, the advantages that there is no need to know the amount of solvent and that solid support adsorption probably tends to be canceled.

Experimental Section

Apparatus. A thermal-conductivity chromatograph (Fractovap Model B, Carlo Erba, Italy) was used. The column was prepared by dissolving a weighed amount of KPL, *R*-PL, and *RS*-PL, respectively, in chloroform and by adding Chromosorb WHP 100/200 mesh (Supelco) and then evaporating chloroform.

Materials. KPL (CAS no. 13031-04-4, molecular weight 128.11), *R*-PL (CAS no. 599-04-2, molecular weight 130.15), and *RS*-PL, racemic mixture of *R*-PL and *S*-PL (CAS no. 5405-04-3), were supplied by Hoffman-La Roche. All the organic solvents (Sigma Aldrich) were used without any further treatment. Carbon dioxide was obtained from S.I.A.D.

Results. The volatility revealed by KPL, *R*-PL, and *RS*-PL during gas saturation tests that determine the vapor pressures of these substances (0.0074 bar at 373.4 K for *R*-PL and *RS*-PL) suggested the possibility of trying the nonstationary gas chromatographic approach to determine the activity coefficients at infinite dilution.

Working with a column of *R*-PL at 368.42 and 373.40 K for 3 h and with flow rates that were less than 0.5 mL·s^{-1}, the results in Tables 1 and 2 were obtained.

Table 1. Activity Coefficients at Infinite Dilution in *R*-PL Determined with NSGC and with IGC at T = 368.42 K

	$\gamma^{\infty}_{\mathrm{NSGC}}$	$\gamma^{\infty}_{\mathrm{IGC}}$	difference of γ^{∞}/%
DEE	2.73	2.80	2.5
Eac	1.65	1.63	1.2
T	3.65	3.48	4.8

Table 2. Activity Coefficients at Infinite Dilution in *R*-PL Determined with NSGC and with IGC at T = 373.40 K

	$\gamma^{\infty}_{\mathrm{NSGC}}$	$\gamma^{\infty}_{\mathrm{IGC}}$	difference of γ^{∞}/%
DEE	2.76	2.83	2.5
Eac	1.67	1.65	1.2
T	3.69	3.52	4.7

Table 3. Fugacity Coefficients at Infinite Dilution in KPL

	ln $\hat{\varphi}_i$			
	T = 343.61 K	T = 353.52 K	T = 363.43 K	T = 373.41 K
C5	3.65	3.73	3.86	4.09
C6	2.95	3.17	3.24	3.47
C7	2.34	2.51	2.75	2.84
CyC6	2.12	2.28	2.50	2.64
DEE	2.54	2.70	2.91	3.09
THF	0.26	0.56	0.86	1.10
EtOH	−0.25	0.21	0.63	1.00
Eac	0.05	0.41	0.74	1.00
A	0.33	0.60	0.88	1.15
Bz	0.53	0.78	1.04	1.30
T	−0.16	0.13	0.42	0.71
ACN	−0.58	−0.30	−0.01	0.29
CO_2	5.60	5.62	5.70	5.74

Table 4. Fugacity Coefficients at Infinite Dilution in *R*-PL

	ln $\hat{\varphi}_i$		
	T = 368.49 K	T = 373.36 K	T = 378.27 K
C5	4.27	4.47	4.63
C6	3.68	3.71	3.77
C7	3.10	3.20	3.29
C8	2.62	2.66	2.83
CyC6	2.83	2.89	2.94
EtCyC6	1.92	2.03	2.13
MCyC6	2.58	2.66	2.82
DEE	2.83	2.89	2.99
DPEE	2.09	2.12	2.36
THF	0.76	0.96	1.09
EtOH	0.73	0.90	1.00
Eac	1.06	1.17	1.31
Pac	0.57	0.68	0.86
A	1.02	1.12	1.23
Bz	1.35	1.51	1.68
T	0.87	0.98	1.10
ACN	0.35	0.44	0.59
CO_2	5.61	5.64	5.71

Table 5. Fugacity Coefficients at Infinite Dilution in *RS*-PL

	ln $\hat{\varphi}_i$		
	T = 368.48 K	T = 373.33 K	T = 378.25 K
C5	4.39	4.56	4.63
C6	3.68	3.85	3.93
C7	3.21	3.30	3.32
C8	2.61	2.65	2.82
CyC6	2.88	2.95	3.00
EtCyC6	1.96	2.04	2.15
MCyC6	2.54	2.69	2.76
DEE	2.80	2.89	3.00
DPEE	2.11	2.22	2.33
THF	0.84	0.99	1.10
EtOH	0.74	0.89	1.06
Eac	1.06	1.20	1.33
Pac	0.55	0.69	0.84
A	1.05	1.13	1.27
Bz	1.40	1.57	1.71
T	0.89	1.00	1.13
ACN	0.37	0.47	0.59
CO_2	5.94	6.00	6.02

Table 6. Binary Interaction Parameters for KPL-Containing Systems

solute	k_{ij} for KPL	solute	k_{ij} for KPL
C5	0.0934	A	−0.0313
C6	0.0855	Bz	0.0369
C7	0.0774	T	0.0414
CyC6	0.1144	ACN	−0.0300
DEE	0.0357	EtOH	0.0154
THF	0.0015	CO_2	0.1209
Eac	−0.0075		

Table 7. Binary Interaction Parameters for *R*-PL- and *RS*-PL-Containing Systems

	k_{ij}			k_{ij}	
solute	*R*-PL	*RS*-PL	solute	*R*-PL	*RS*-PL
C5	0.1163	0.1211	THF	−0.0185	−0.0155
C6	0.0895	0.0965	Eac	−0.0075	−0.0062
C7	0.0818	0.0859	Pac	−0.0076	−0.0079
C8	0.0731	0.0728	A	−0.0376	−0.0354
CyC6	0.1200	0.1224	Bz	0.0512	0.0545
EtCyC6	0.0802	0.0814	T	0.0531	0.0546
MCyC6	0.1067	0.1054	ACN	−0.0219	−0.0210
DEE	0.0114	0.0110	EtOH	0.0070	0.0089
DPEE	−0.0187	−0.0169	CO_2	0.0826	0.1418

Tables 1 and 2 show the good agreement between the experimental values obtained with traditional chromatography and the nonstationary approach. Tables 3−5 report the experimental results obtained with the IGC for the fugacity coefficients in KPL, *R*-PL, and *RS*-PL at different temperatures. Usually the uncertainty of the experimental ln $\hat{\varphi}_i$ values varies from 2 to 5%, but in the presence of volatile stationary phases, the uncertainty clearly increases and particularly when the interactions with less soluble solutes, the paraffins in this case, are considered. The solvents were chosen on the basis of their dielectric constants in order to cover a broad range of values and to study the influence of their polarity in the enantiodifferentiation[10] (hydrogenation). The number of solutes was limited to shorten the tests and consequently to reduce losses of the stationary phase.

For the investigation of thermodynamic properties of KPL−organic solvent mixtures, pentane (C5), hexane (C6), heptane (C7), cyclohexane (CyC6), diethyl ether (DEE), acetone (A), tetrahydrofurane (THF), ethyl acetate (Eac), toluene (T), ethanol (EtOH), acetonitrile (ACN), and carbon dioxide (CO_2) were used.

In the case of *R*-PL and *RS*-PL, octane (C8), ethylcyclohexane (EtCyC6), methylcyclohexane (MCyC6), dipropyl ether (DPEE), and propyl acetate (Pac) were added to the previous solvents to compare the behavior of these solutes toward *R*-pantolactone and the racemic mixture, which contains it. There is a slight increase in the fugacity coefficients in the experimental values obtained at 373.1 K for KPL, *R*-PL, and *RS*-PL; this demonstrates the relative higher solubility of these solvents toward the ketopantolactone.

Polar substances that are characterized by elevated dielectric constants have lower fugacity coefficients than the others, especially the paraffins. Toluene is an exception to the rule, and for this reason it is used as solvent in enantioselective hydrogenation.[10]

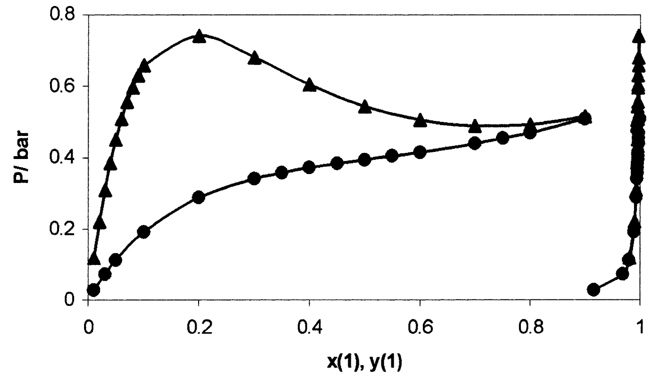

Figure 2. Vapor−liquid equilibrium data predictions for the system heptane (1) + KPL (2) at 353.1 K (curve with the symbols ● refers to $k_{ij} = 0$).

Discussing the experimental data, it is important to underline the linear tendency of the natural logarithm of the fugacity coefficient as a function of the inverse of the temperature of analysis: this confirms the direct correlation between temperature and the fugacity coefficients.

The fugacity coefficients at infinite dilution have been correlated using the Peng−Robinson equation of state

$$P = \frac{RT}{V-b} - \frac{a}{V(V+b)+b(V-b)} \qquad (6)$$

where a and b are positive constants defined as a function of the critical parameters T_c and P_c of the different solvents[11] and V is the molar volume.

Consequently, using eq 6, the fugacity coefficient is defined as follows:

$$\ln \hat{\phi}_i = \frac{B_i}{B}(z-1) - \ln(z-B) - \frac{A}{2B\sqrt{2}}\left(\frac{2\sum x_j A_{ij}}{A} - \frac{B_i}{B}\right)\ln\left(\frac{z+2.414B}{z-0.414B}\right) \qquad (7)$$

where

$$A = \frac{aP}{(RT)^2} \qquad A_{ij} = \frac{a_{ij}P}{(RT)^2}$$

$$B = \frac{bP}{RT} \qquad B_i = \frac{B_iP}{RT}$$

$$z = \text{compressibility factor}$$

From the experimental values of the fugacity coefficients, and on the basis of the pure component properties, it is possible to evaluate the binary interaction parameter k_{ij} between each solvent and the different lactones. In Tables 6 and 7, the k_{ij} values obtained for the three lactones are reported. Due to the narrow range of temperatures investigated, the temperature dependency of the interaction parameters has not been considered.

On the basis of the numerical values of the binary interaction parameters, it is possible to predict the thermodynamic properties of the different mixtures at different temperatures and pressures and in particular to calculate the phase behavior. As an example, in Figure 2 vapor−liquid equilibrium data calculated for the system heptane−KPL at 353.1 K are reported.

It is interesting to note the different shapes of the curves obtained with $k_{ij} = 0$ and $k_{ij} = 0.0774$: using the experimental value of k_{ij}, it is possible to show the incipient instability of the liquid phase. The presence of two liquid phases was also confirmed experimentally in a visual cell with a mixture of 50% mass heptane and KPL at 343.1 K.

Conclusions

This work made it possible to thermodynamically characterize precursors of vitamin B5, because of their fundamental importance in the pharmaceutical industry. Using chromatographic approaches, the behaviors of KPL, *R*-PL, and *RS*-PL in binary mixtures were completely defined. During gas saturation tests that were performed to determine vapor pressure, the stationary phases were shown to be volatile, providing an opportunity to try the NSGC method, a different way to determine activity coefficients at infinite dilution.

By analyzing the results obtained with NSGC, it is evident that the utility and the effectiveness of this approach are preferable to those of the stationary approach in the case of volatile solutes and solvents. Nevertheless, this method cannot be applied when the volatility of the solutes is lower than that of the solvent and when the ratio $\Delta t_{Ri}/\Delta t_i$ is too low or too high. Comparison between the experimental data obtained with NSGC and IGC showed a good agreement between the two chromatographic techniques. The IGC approach was chosen, and it certainly guaranteed simplicity, quick operation, and use of small quantities of sample. These characteristics allow the application of IGC to determine activity coefficients at infinite dilution and fugacity coefficients, which are an index of the interactions in the liquid phase. Moreover, the experimental chromatographic data allowed the evaluation of the binary interaction parameters k_{ij} for the Peng−Robinson equation used for calculation of vapor−liquid equilibrium.

Literature Cited

(1) Karaev, A. L. Patent Number 5.705.687, 1998, January 6.
(2) Schmid, R. Homogeneous Catalysis with Metal Complexes in Pharmaceuticals' and Vitamins' Company: Why, What for and Where to Go? *Chimia* **1996**, *50*, 110−113.
(3) Schürch, M.; Schwalm, O.; Mallat, T.; Weber, T.; Baiker, A. Enantioselective Hydrogenation of Ketopantolactone. *J. Mol. Catal.* **1997**, *169*, 275−286.
(4) Schürch, M.; Künzle, N.; Mallat, T.; Baiker, A. Enantioselective Hydrogenation of Ketopantolactone: Effect of Stereospecific Product Crystallization during Reaction. *J. Mol. Catal.* **1998**, *176*, 569−571.
(5) Eckert, C. A.; Sherman, S. R. Measurement and Prediction of Limiting Activity Coefficients. *Fluid Phase Equilib.* **1996**, *116*, 333−342.
(6) Sandler, S. L. Infinite Dilution Activity Coefficients in Chemical, Environmental and Biochemical Engineering. *Fluid Phase Equilib.* **1996**, *116*, 343−353.
(7) Kikic, I.; Alessi, P. The application of gas−liquid chromatography to the determination of the temperature dependence of the excess partial molar enthalpy of mixing at infinite dilution. *J. Chromatogr.* **1974**, *100*, 202−205.
(8) Belfer, A. J.; Locke, D. C. Non-Steady-State Gas Chromatography for Activity Coefficient Measurements. *Anal. Chem.* **1984**, *56*, 2485−2489.
(9) Belfer, A. J.; Locke, D. C.; Landau, I. Measurement of Limiting Activity Coefficients Using Non-Steady-State Gas Chromatography. *Ind. Eng. Chem. Res.* **1991**, *30*, 1900−1906.
(10) Bürgi, T.; Baiker, A. Conformational Behaviour of Cinchonidine in Different Solvents: a combined NMR and an Initio Investigation. *J. Am. Chem. Soc.* **1998**, *120*, 12920−12926.
(11) Tassios, D. P. *Applied Chemical Engineering Thermodynamics*; Springer-Verlag: Berlin, 1993.

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