Influence of 2-Propanol on Adsorption Equilibria of α- and *δ*-Tocopherol from Supercritical Carbon Dioxide on Silica Gel

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Knowledge of thermodynamic functions describing adsorption isotherms is of much importance for the design and optimization of adsorption processes. This work deals with the investigation of the adsorption behavior under the influence of a modifier. The experimental setup consisted of two supercritical fluid chromatography units. Adsorption isotherms of α- and *δ*-tocopherol were determined at a pressure of 20 MPa and a temperature of 313 K. The stationary phase was an unmodified silica gel, and supercritical carbon dioxide was used as the mobile phase. The modifier 2-propanol was added to the mobile phase in contents of 4.6, 5.5, and 6.5 % mass fraction. The experimental results of pure substances were described with cubic Hill isotherms. The adsorption equilibria of the mixture were predicted with the ideal adsorbed solution theory and verified with experimentally determined data.

Introduction

The separation of mixtures by thermal separation processes plays a decisive role in many areas of the chemical and pharmaceutical industries. High-pressure adsorption processes like supercritical fluid chromatography (SFC) rank among these processes. They take advantage of the distribution of different components between a solid and a fluid. The stationary phase usually consists of porous solid particles that have a high surface area. In the case of SFC, the mobile phase is a supercritical fluid like carbon dioxide, which can be modified with an organic solvent (modifier) to improve selectivity and separation performance. Since SFC processes are of increasing interest, the optimization of process conditions in terms of production rate, yield, and costs is of particular importance especially for preparative applications.[1] In general, it is a big challenge to optimize such processes.

An adequate simulation of chromatographic processes requires knowledge of the distribution of a mixture between the stationary and the mobile phase. This information is included in the adsorption isotherms, which have to be determined individually for each separation problem.[2] They describe the behavior of the adsorption equilibria and, as such, the dependence of stationary phase loading on the concentration of the same component in fluid phase at equilibrium conditions. Since usually adsorption isotherms cannot be determined theoretically, experimental determination is required.

Adsorption equilibria have been determined for different systems like naphthalene from carbon dioxide on silica gel,[3] salicylic acid on activated carbon,[4] or terpenes from carbon dioxide on silica gel.[5] Lübbert and co-workers[6,7] determined the adsorption equilibria of α- and *δ*-tocopherol from supercritical carbon dioxide on two unmodified silica gels (Nucleosil 100-5 and Kromasil KR60-10-SIL) at pressures from (16 to 26) MPa and a temperature of 313 K. The carbon dioxide was modified with a constant content of 5 % mass fraction 2-propanol. Their research was done with regard to the pressure dependence of the adsorption equilibria.

On one hand, polar substances in SFC with supercritical carbon dioxide have very broad elution peaks with long retention times or do not elute at all if no modifier is added. On the other hand, high amounts of organic solvents are undesired and lead to poor resolutions or even to inseparability.[8] Therefore, it is necessary to optimize the content of the modifier for each separation problem. As such, the aim of this work is to determine adsorption equilibrium data of α- and *δ*-tocopherol on an unmodified silica gel from a mixture of carbon dioxide and 2-propanol in terms of the 2-propanol content in the mobile phase to give a basis for the optimization of the usage of 2-propanol as a modifier in SFC processes.

Theoretical Background

Supercritical Fluids and Modifier. The mobile phase used in this work is supercritical carbon dioxide that is modified with 2-propanol. The density of this mixture is assumed to be identical to the density of pure carbon dioxide.[6] To calculate the density from pressure and temperature data, the empirical equation of state from Span and Wagner[9] is applied. To determine the volume flow inside the column, mass flows of all components are calculated from pump flow rates and densities taking into account the temperature and pressure. The small pressure drop over the column allows the use of the mean value for pressure and density.[7] The applied temperature and pressure allow the dissolution of $\geq 8\ \mathrm{mg{\cdot}mL^{-1}}$ of α- and *δ*-tocopherol in pure carbon dioxide.[10] Since a modifier is used in this work, the maximum solubility is not exceeded.

The application of different modifiers in SFC with carbon dioxide has already been investigated in terms of selectivity and resolution.[8,11−13] Increasing modifier content increases the solubility of polar substances, thereby decreasing the retention factor. On the other hand, the resolution of peaks increases up to a maximum and then decreases. The modifier not only influences the solubility but also competes for active sites on the stationary phase. This influences both selectivity and retention especially at small modifier contents.[14]

Adsorption Isotherms. The general way to describe adsorption equilibria is the application of adsorption isotherms. They

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represent the loading of the adsorbent with a component relative to the concentration of this component in the fluid phase. Single-component equilibria can usually be described by standard isotherm models like the Langmuir and BET models. A very flexible equation for describing nonlinear isotherms of various systems is the Hill isotherm (eq 1), which is here applied in its cubic form (eq 2). It was derived by Hill[15] from statistical thermodynamics and can be fitted to a wide range of adsorption equilibria:

$$q = \frac{q_s}{n} \frac{b_1 c + 2b_2 c^2 + 3b_3 c^3 + ... + n b_n c^n}{1 + b_1 c + b_2 c^2 + b_3 c^3 + ... + b_n c^n} \tag{1}$$

$$q = \frac{q_s}{3} \cdot \frac{b_1 c + 2b_2 c^2 + 3b_3 c^3}{1 + b_1 c + b_2 c^2 + b_3 c^3} \tag{2}$$

Ideal Adsorbed Solution Theory (IAST). To describe the adsorption behavior of mixtures, the interactions between the different components and their competition for free sites has to be taken into account. This can be done for instance by modifications to single-component isotherm models. In this work, the IAST developed by Myers and Prausnitz[16] is applied for the prediction of competitive adsorption behavior from single-component adsorption equilibrium data.

With the assumption of an ideal adsorbed solution, isotherms can be calculated using single-component isotherms (eq 3) to solve the following system of equations (eqs 4 to 8):

$$q_i^0 = f(c_i^0) \tag{3}$$

$$\pi_{\text{mix}} = \pi_i(\tilde{c}_i^0) = \int_0^{\tilde{c}_i^0} \frac{q_i^0}{c_i^0} \mathrm{d}c_i^0 \tag{4}$$

$$\sum_{i=1}^{K} \frac{c_i}{\tilde{c}_i^0} = 1 \tag{5}$$

$$z_i = \frac{c_i}{\tilde{c}_i^0} \tag{6}$$

$$\sum_{i=1}^{K} \frac{z_i}{q_i^0(\tilde{c}_i^0)} = \frac{1}{q_{\text{tot}}} \tag{7}$$

$$q_i = z_i q_{\text{tot}} \tag{8}$$

π_i represents the modified spreading pressure, which specifies the equilibrium. The reference state for adsorption is the adsorption of single components at an equal spreading pressure.[7,17] The index 0 characterizes the single-component state. The $\tilde{c}_i^0$ are fictitious concentrations for the pure components at which these components would possess the same spreading pressure π_{mix} as the mixture. q_{tot} indicates the loading relating to the total volume of adsorbent. The molar fraction of the adsorbate is indicated by z_i.

One major advantage of the IAST is the adaptability of single-component isotherm models without restrictions in structure to predict the behavior of the mixture.[18] Disadvantages are the necessary tests for each system and the calculation complexity.[6]

Perturbation Chromatography. Perturbation chromatography (which is also known as the minor disturbance method (MDM), step and pulse method, concentration pulse chromatography, or impulse response chromatography) is based on the application of very small perturbations to an equilibrated system. It was primarily developed for analysis in gas chromatography by Reilley et al.[19] and Helfferich and Peterson[20] and later also adapted to other areas.

To execute perturbation experiments, the stationary phase has to be equilibrated with all components of interest. Therefore, a solution with a defined concentration of the components is continuously passed through the column that contains the stationary phase. After equilibrium is reached, small amounts of solvent are injected into the solvent stream in order to perturb the equilibrium. The perturbations have to be small so that the column does not reach a new state of equilibrium.

Depending on the amount of components, perturbation leads to one or several response peaks. Each component except for the mobile phase creates one characteristic peak. Retention times of these peaks are recorded and can be used as basic data for the calculation of the equilibrium by applying the equilibrium theory of chromatography as defined by

$$t_{R,i}(\bar{c}) = t_M \left(1 + \frac{1-\epsilon}{\epsilon} \left.\frac{\mathrm{d}q}{\mathrm{d}c}\right|_{\bar{c}}\right) \tag{9}$$

The equilibrium theory, which is also known as the ideal model, neglects all conceivable kinetic resistances and acts on the assumption of a permanent equilibrium between mobile and stationary phases.[18] The derivative $\mathrm{d}q/\mathrm{d}c$ (eq 9) can be replaced by an isotherm model in its derivative form. Thus, isotherm parameters can be determined:

$$\left.\frac{\mathrm{d}q_i}{\mathrm{d}c_i}\right|_{\bar{c}} = \sum_{j=1}^{N} \left.\frac{\partial q_i}{\partial c_j}\right|_{\bar{c}} \left.\frac{\mathrm{d}c_j}{\mathrm{d}c_i}\right|_{\bar{c}}, \quad i = 1, ..., N \tag{10}$$

If more than one component is present, the analysis is substantially more complicated because of interactions between the components. Quantification is only possible if an isotherm model is given.[21]

Experimental Section

Experimental Setup. The experimental setup shown in Figure 1 consists of two SFC units A and B and was conceived and built by Lübbert.[7] Liquid carbon dioxide is compressed by a pneumatic pump (30 MPa) and delivered into the two chromatographic units. Unit A is used for the perturbation experiments. During experimental analysis, unit A is supplied with carbon dioxide by a syringe pump (260D, ISCO, Lincoln, NE) to adjust a constant volume flow rate. The modifier is added to unit A by a second syringe pump (260D, ISCO, Lincoln, NE). A feed solution can be supplied by a HPLC pump (K1001, Knauer, Berlin, Germany). Perturbations are detected by a UV detector (SPD-10A, Shimadzu, Kyoto, Japan). The pressure in unit A is adjusted by a controlled valve V31. Samples for perturbation are injected manually through an injection valve.

Unit B is used to analyze the concentration plateau in unit A by a switching valve V23. The modifier is added by a HPLC pump (HPP M300, Gynkotek, Germering, Germany). Pressure is controlled by back pressure valve V15. The flow rate is controlled by a depressurisation unit V27 and V28. The concentration is detected by a UV detector (LCD 503, GAT, Bremen, Germany).

Materials. Carbon dioxide (CO_2) was obtained from YARA Industrial (Bad Hönningen, Germany) and had a purity of ≥ 99.95 % (grade 3.5). 2-Propanol with a purity of ≥ 99 % (GC analysis) was donated by BASF (Ludwigshafen, Germany), and *n*-hexane with a purity of ≥ 99 % was obtained from Merck

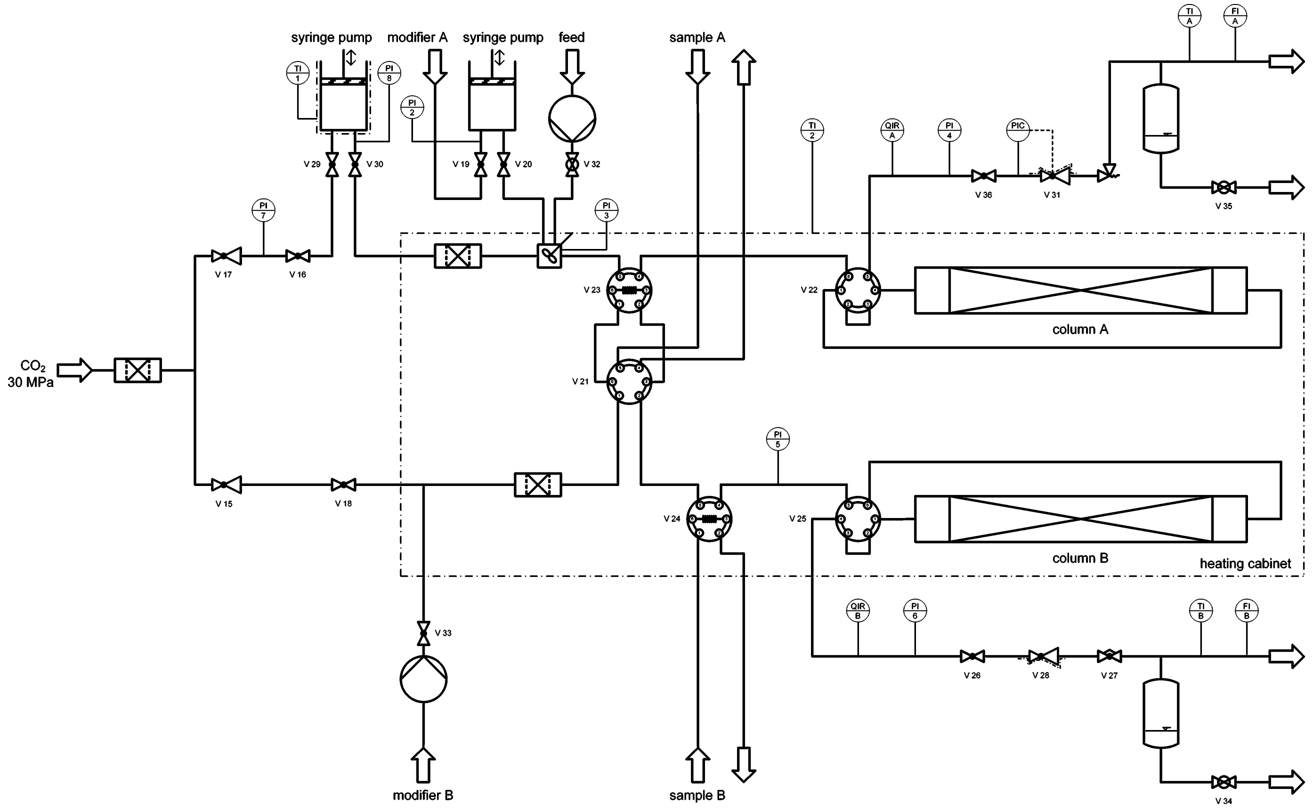

Figure 1. Experimental setup.

(Darmstadt, Germany). DL-α-Tocopherol was purchased from EMD Biosciences (San Diego, CA) with a purity of ≥ 99 % (GC analysis) and used for single-component experiments. The DL-α-tocopherol used for competitive adsorption experiments was provided by AppliChem (Darmstadt, Germany) and had a purity of ≤ 98 % (GC analysis). D-δ-Tocopherol obtained from MP Biomedicals (Aurora, OH) had a purity of ≥ 90 % mass fraction.

The chromatographic columns (250 × 4.6 mm) were packed in this laboratory with the nonmodified spherical silica gel Kromasil KR60-10-SIL from EKA Chemicals (Bohus, Sweden) applying the slurry method. The silica gel has a particle size of 10 μm and a pore size of 8 nm.

Experimental Conditions and Procedure. All experiments were carried out at a temperature of 313 K (± 1.5 K) and a pressure of 20 MPa (± 0.25 MPa) in both chromatographic units. The flow rate in unit A was set to 3 mL·min^{-1} (± 0.015 mL·min^{-1}). The modifier content was varied from 4.6, 5.5, to 6.5 % mass fraction (± 0.3 % mass fraction) in unit A while the content in unit B was set constant to 6.5 % mass fraction (± 0.3 % mass fraction).

Experiments were carried out for both pure substances α- and δ-tocopherol as well as for mixtures of the two tocopherols in ratios of 1:1, 1:3, and 3:1, respectively. Feed mixtures were prepared in 2-propanol. The perturbations were caused by injection of small amounts of pure 2-propanol to unit A. The concentration level was changed by adjusting the feed flow rate. To counteract the effect of decreasing peak heights at higher concentration levels, the detection wavelength was decreased, starting from $\lambda_A = 290$ nm to $\lambda_A = 250$ nm, and the perturbation volume was increased by changing the injection loop (5 μL, 10 μL, and 20 μL). The plateau concentration was analyzed by means of unit B ($\lambda_B = 290$ nm).

The linear region of the isotherms at low concentration levels was analyzed by individual injections of small amounts of pure substance α- or δ-tocopherol dissolved in *n*-hexane. Hold-up volumes were determined by manual injections of tocopherol in *n*-hexane while the column was displaced by a pipe adapter (VICI, Schenkon, Switzerland) with a negligible volume. The porosities were analyzed by injections of pure *n*-hexane, which is not retained by the silica packing.

Table 1. Linear Adsorption Coefficients for α- and *δ*-Tocopherol at Different Modifier Contents *X*

	mass fraction		
	$X = 4.6$ %	$X = 5.5$ %	$X = 6.5$ %
linear adsorption coefficient α, K_α^H	10.8	9.0	7.7
linear adsorption coefficient δ, K_δ^H	19.8	15.1	11.9

Results and Discussion

The system parameters were determined by manual injections. The hold-up volume of the setup (without column) was determined using 11 chromatograms. The average value for unit A is $V_{ext} = 0.850$ mL. The porosity of each column was determined from 10 chromatograms at varying experimental conditions of pressure and temperature. The values for the units are $\epsilon_A = 0.768$ and $\epsilon_B = 0.763$.

To describe the isotherm slope at zero concentration, the linear adsorption coefficients were derived from 10 analytical chromatograms. Solutions of both substances in n-hexane were injected at the three different modifier levels. The results are shown in Table 1.

Single-Component Adsorption. The slopes of the different isotherms were calculated from measured retention times. Parameters of the cubic Hill isotherm in its derivative form were fitted to the measured data by iteration. The iteration succeeded for both tocopherols and all different modifier contents. The determined parameters are shown in Table 2; graphical representations of the fitting can be seen in Figures 2 and 3. The

Table 2. Isotherm Parameters and Coefficient of Determination

X/%	b_1/kg^{-1}·m^3	b_2/kg^{-2}·m^6	b_3/kg^{-3}·m^9	q_s/kg·m^{-3}	r^2
		α-Tocopherol			
4.6	1.800e−3	1.500e−5	6.854e−6	1.800e+4	0.98
5.5	4.050e−3	5.383e−5	8.808e−6	6.696e+3	0.98
6.5	7.857e−4	1.463e−5	2.931e−7	2.921e+4	0.99
		δ-Tocopherol			
4.6	6.149e−4	1.464e−5	2.793e−6	9.655e+4	0.98
5.5	2.209e−2	6.148e−4	9.957e−5	2.043e+3	1.00
6.5	1.990e−3	2.094e−5	4.688e−6	1.797e+4	0.99

adjustment of the cubic Hill isotherm to the measurement data turned out to be very suitable. The isotherms based on the parameters are shown in Figures 4 and 5. They show an unusual anti-Langmuir behavior as already mentioned by Lübbert and Johannsen.[6] The solid line indicates the region where the fitted isotherms are based on measured data.

The dashed line indicates an isotherm measured by Lübbert[7] for a modifier content of 5 % mass fraction. Differences in progressions can be ascribed to small differences in the experimental setup, for example different packing of the columns. The decrease of the slope with increasing modifier content is related to an increased solubility of the components in carbon dioxide caused by the modifier. As shown in Figures 4 and 5, the influence of the modifier on the slope of the isotherms decreases with increasing modifier content. Thus the influence of the modifier on the adsorption equilibrium decreases. A comparison between the slopes of the isotherms of both tocopherols indicates that δ-tocopherol adsorbs stronger than α-tocopherol at equal modifier content. Furthermore δ-tocopherol is more affected by the modifier than α-tocopherol. This is indicated by the variation in slope at different modifier contents. With increasing modifier content the adsorption

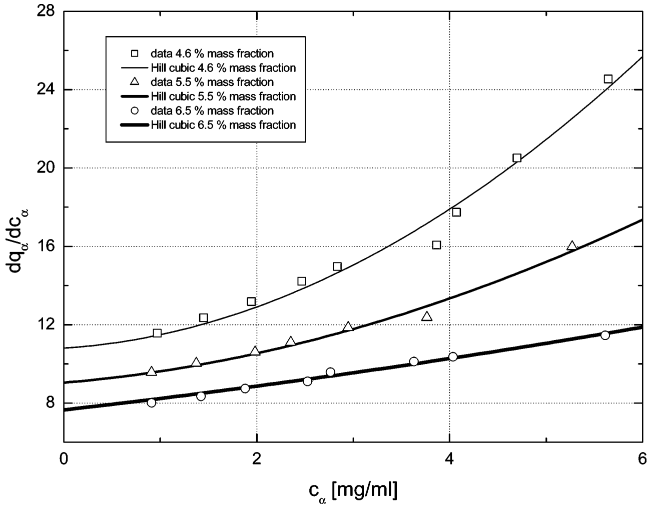

Figure 2. Isotherm slope fitting α-tocopherol for different modifier contents (P = 20 MPa, T = 313 K).

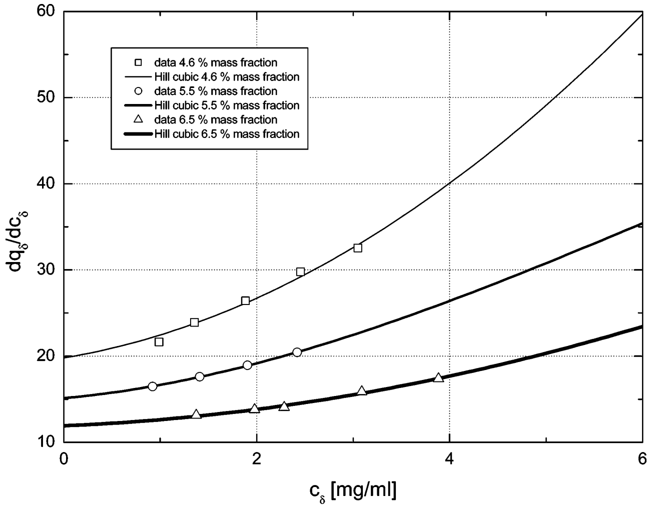

Figure 3. Isotherm slope fitting δ-tocopherol for different modifier contents (P = 20 MPa, T = 313 K).

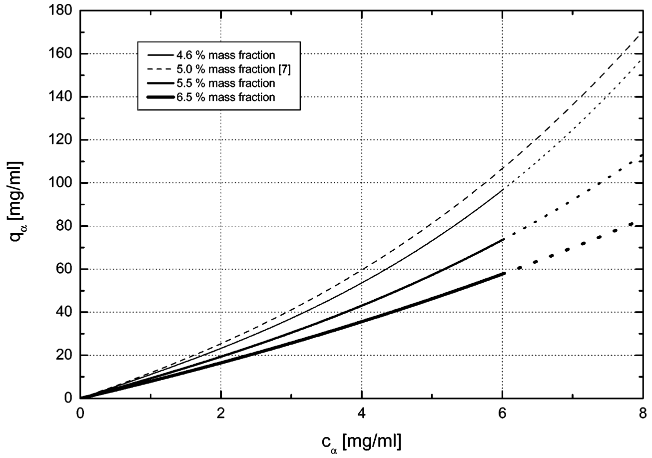

Figure 4. Isotherms of α-tocopherol for different modifier contents (P = 20 MPa, T = 313 K).

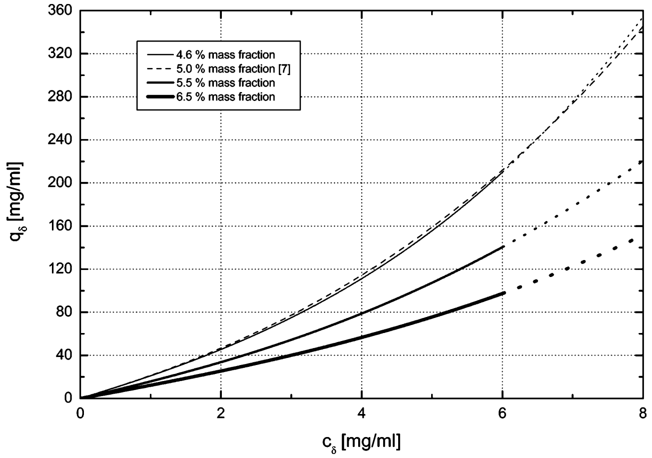

Figure 5. Isotherms of δ-tocopherol for different modifier contents (P = 20 MPa, T = 313 K).

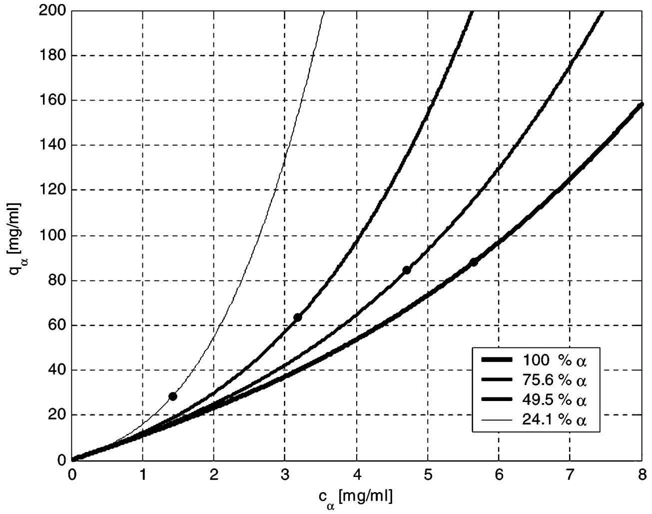

Figure 6. Mixture isotherms for α-tocopherol (P = 20 MPa, T = 313 K, X = 4.6 % mass fraction).

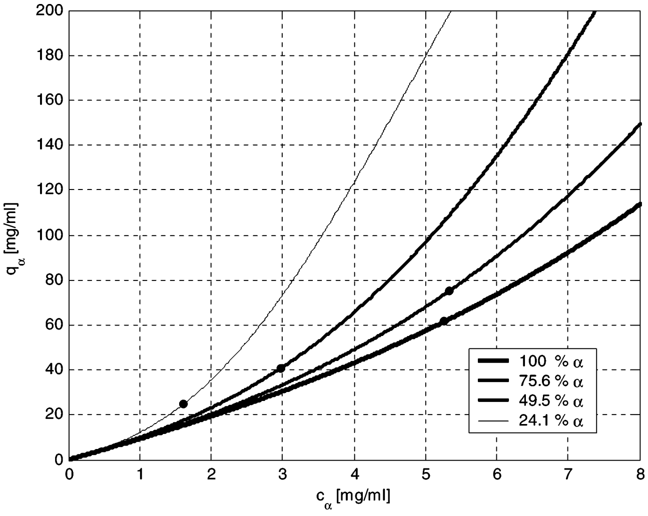

Figure 7. Mixture isotherms for α-tocopherol ($P = 20$ MPa, $T = 313$ K, $X = 5.5$ % mass fraction).

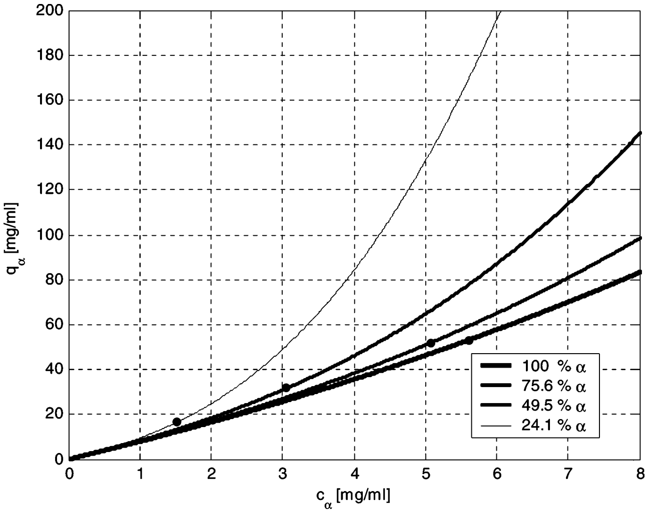

Figure 8. Mixture isotherms for α-tocopherol ($P = 20$ MPa, $T = 313$ K, $X = 6.5$ % mass fraction).

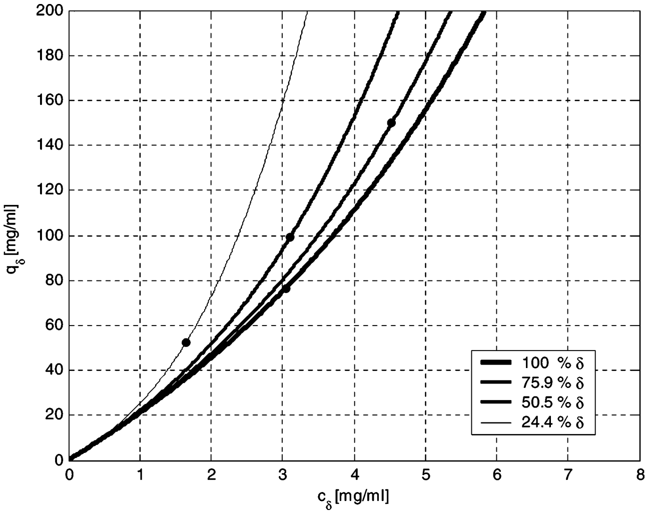

Figure 9. Mixture isotherms for δ-tocopherol ($P = 20$ MPa, $T = 313$ K, $X = 4.6$ % mass fraction).

behavior of both tocopherols converges, which was also reflected in peak resolution.

Competitive Adsorption. To determine competitive adsorption equilibrium the IAST was applied. Isotherms were predicted from single-component equilibrium data for the three different concentration ratios of both tocopherols for all different modifier contents. Predicted isotherms of α- tocopherol can be seen in Figures 6 to 8, and those for δ-tocopherol are shown in Figures

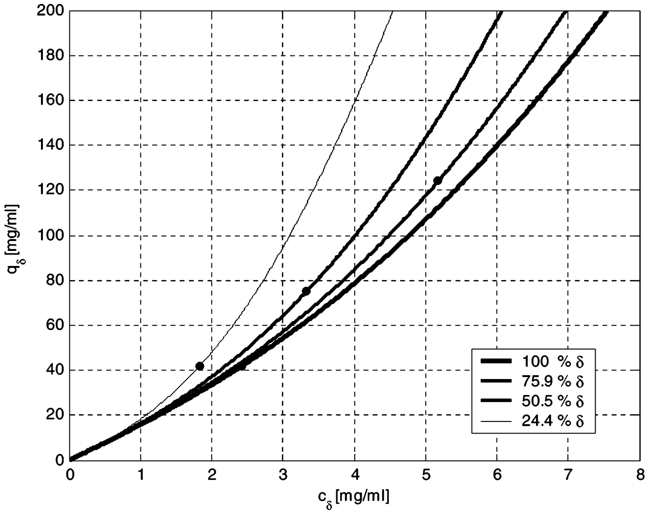

Figure 10. Mixture isotherms for δ-tocopherol ($P = 20$ MPa, $T = 313$ K, $X = 5.5$ % mass fraction).

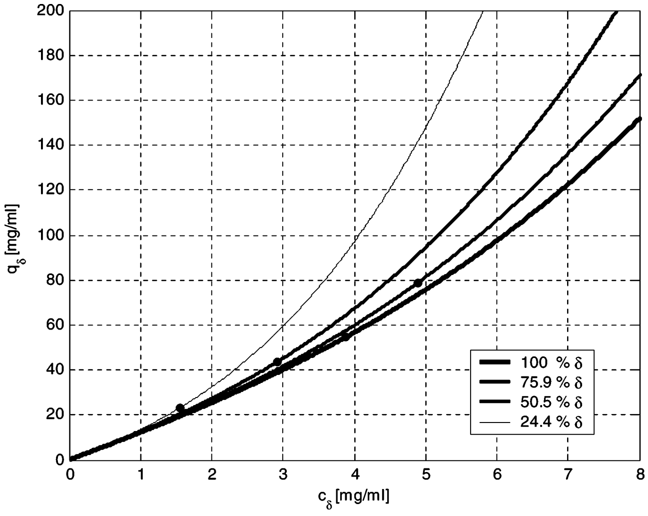

Figure 11. Mixture isotherms for δ-tocopherol ($P = 20$ MPa, $T = 313$ K, $X = 6.5$ % mass fraction).

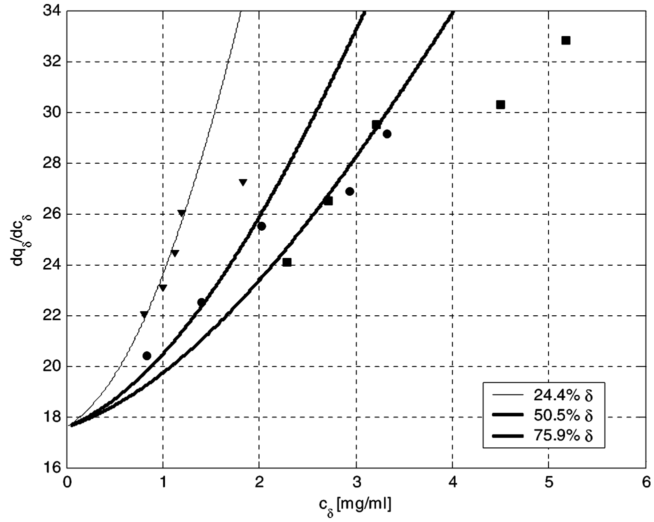

Figure 12. Predicted and measured isotherm slope for δ-tocopherol in mixture ($P = 20$ MPa, $T = 313$ K, $X = 5.5$ % mass fraction).

9 to 11. The range, which is related to experimental data, is confined by marker points.

To compare predicted and measured data, isotherm derivatives were calculated from retention times like for single-component adsorption. These data were plotted together with the total differentials of the predicted isotherms. Figure 12 shows one example of comparison between measured (symbols) and predicted (lines) data. The results show that the IAST can be used for prediction in this adsorption system. The deviations of measured data in the region of higher concentrations depend on decreasing accuracy in the measurement with increasing concentrations. Concerning the behavior at different modifier content, the isotherms for competitive adsorption resemble those for single-component adsorption. Due to this, the slope is decreasing with increasing modifier content. The competition of both tocopherols can be recognized by the slopes. The lower the concentration of one component in the mixture, the sharper is the increase of its isotherm in comparison to the increase of the single-component isotherm.

Conclusions

The aim of this work was to determine the adsorption equilibria of α- and δ-tocopherol with respect to its dependence on modifier content in the mobile phase. Experiments were performed for both tocopherols as pure substances and as mixtures at three different modifier contents. The experimentally determined data were successfully fitted to the cubic Hill isotherm for single-component adsorption. The IAST was applied to predict comparative adsorption isotherms and was verified with experimental data. The theory was shown to be suitable to describe mixture isotherms for this system. Acquired data can be used for simulations of adsorptive separation processes to improve the use of this modifier in terms of selectivity, retention, and cost.

Glossary

b_1	coefficient of Hill isotherm ($m^3 \cdot kg^{-1}$)
b_2	coefficient of Hill isotherm ($m^6 \cdot kg^{-2}$)
b_3	coefficient of Hill isotherm ($m^9 \cdot kg^{-3}$)
c	concentration in fluid phase ($kg \cdot m^{-3}$)
$\bar{c}$	plateau concentration ($kg \cdot m^{-3}$)
$\tilde{c}_i^0$	fictitious concentration (IAST) ($kg \cdot m^{-3}$)
K^H	linear adsorption coefficient (Henry coefficient) (−)
M	molar mass ($kg \cdot kmol^{-1}$)
N	counter (−)
n	counter (−)
P	pressure (Pa)
q	loading of pore-free adsorbent volume ($kg \cdot m^{-3}$)
q_{tot}	loading relating to total volume of adsorbent ($kg \cdot m^{-3}$)
q_s	saturation loading ($kg \cdot m^{-3}$)
T	temperature (K)
t_M	hold-up time (s)
t_R	retention time (s)
V_{ext}	hold-up volume of experimental setup (column excluded) (m^3)
$\dot{V}$	volume flow ($m^3 \cdot s^{-1}$)
X	modifier content in mass fraction (%)
z_i	molar fraction in adsorbate (−)

Greek Letters

ϵ	overall porosity (−)
λ	wavelength (m)
π	spreading pressure ($J \cdot m^{-3}$)

Indices

0	comparison system
i,j	component
mix	value for mixture
n	counter

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