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Short communication

Chromatographic behavior of the enantiomers of 2,2,2-trifluoro-1-(9-anthryl)ethanol on a quinidine-carbamate chiral stationary phase

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Abstract

The enantioseparation of 2,2,2-trifluoro-1-(9-anthryl)ethanol on silica-bonded quinidine carbamate was examined under linear chromatographic conditions. The significant impact of nonselective adsorption on the retention was demonstrated. The influences of a polar additive in the mobile phase on the retention, the selectivity and the thermodynamic quantities of the retention were measured. A small effect of the pressure on the selectivity and on the accuracy of the thermodynamic measurements was observed.

Keywords: Chiral stationary phase; Quinidine carbamate; Enantiomer separation; 2,2,2-Trifluoro-1-(9-anthryl)ethanol

1. Introduction

Chiral stationary phases (CSPs) based on the use of quinidine and quinine carbamate derivatives are a relatively new chiral anion-exchangers. These CSPs are advantageous for the enantioseparation of chiral acids and particularly of N-derivatized amino acids [1–3]. They were also shown to separate the enantiomers of binaphthols under NPLC conditions [2], which suggests a new field of applications of chinconan carbamate bonded CSPs, the separation of the enantiomers of neutral compounds. The enantioseparation of 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) on a quinidine carbamate based CSP was previously demonstrated [4]. The adsorption of these enantiomers from a toluene–acetonitrile (98:2, v/v) solution under conditions of nonlinear chromatography was studied in detail [5]. However, there were no data on the adsorption of TFAE under linear conditions, making incomplete this thermodynamic study and there were no data either on the influence of the mobile phase composition. This work deals with these issues.

2. Experimental

2.1. Equipment and materials

All measurements made in this work were made with the HP 1100 liquid chromatograph (Agilent Technologies, Palo Alto, CA) described earlier [5]. Toluene–acetonitrile solutions, with an acetonitrile concentration of 1, 2 and 3% (v/v) were used as the mobile phase. Both solvents were HPLC grade from Fisher Scientific (Fair Lawn, NJ, USA). (*R*)- and (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol and 1,3,5-tri-*tert*-butylbenzene (TtBB) were from Aldrich (Milwaukee, WI, USA). All the chemicals were used as supplied. The column used was a 150 mm × 4 mm *Chiris* Chiral AX:QD1 column, from Iris Technologies (Lawrence, KS, USA). It was packed with 5 μm silica particles on the surface of which quinidine carbamate was immobilized. The structure of this ligand is illustrated in Fig. 1.

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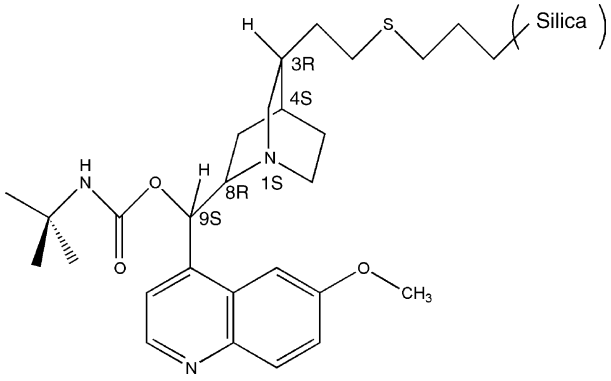

Fig. 1. Structure of the quinidine carbamate chiral selector.

2.2. Measurement of experimental data

All experimental data were measured at a 1 ml/min mobile phase flow-rate, at 15, 22, 30 and 40 °C. The bands of TFAE were recorded at 330 nm, the peaks of TtBB at 280 nm. The sample volume was 2 μl, the sample concentration 0.9 g/l for each pure enantiomer, 1.8 g/l for the racemic mixture. The hold-up volume was derived from the retention time of TtBB. The influence of the average column pressure on the retention of TFAE was measured with a mobile phase containing 2% acetonitrile at 22 °C. The inlet pressure was adjusted by adding pieces of 0.0025 in. I.D. capillary restrictors cut to the desired length downstream the UV detector. The pressure was monitored at the pump outlet with the gauge of the HP 1100 pump module.

3. Results and discussions

The retention of a compound in HPLC depends on both the stationary and the mobile phases. Under such experimental conditions that the adsorption isotherm is linear, the retention factor (k) does not depend on the amount of compound injected. Preliminary experiments showed that the sample amount used in this study fulfills this condition. The values of k', the theoretical plate number (N), the selectivity (α) and the resolution factor (R_s) are listed in Table 1 at different temperatures. The column efficiency is modest, which is common for similar columns [3]. Yet, plate numbers of 4000–5000 (Table 1) and the absence of peak tailing (Fig. 2) prove that the mass-transfer kinetics is reasonably fast. Fig. 2 illustrates the separation of the TFAE enantiomers at different temperatures. (*S*)-TFAE is the more retained isomer. Despite the small separation factor, the resolution is nearly complete with mobile phases containing 1 and 2% acetonitrile at low temperatures. It is notably worse at higher temperatures or with a higher acetonitrile concentration.

It was previously shown that there are two types of adsorption sites on this CSP, high-energy enantioselective and low-energy nonselective sites [5]. The number of selective sites is 30–40 times lower than that of nonselective ones. The simultaneous decrease of retention and selectivity with increasing acetonitrile concentration shows that both types of sites are affected. The relative contribution of the selective adsorption sites to the equilibrium constant, estimated from the data previously published [5], shows that the contribution is ∼30% and does not differ much for the two enantiomers.

The influence of the acetonitrile concentration on the two types of sites suggests that at least part of the nonselective sites are segments of the selector molecule that can take part in polar interactions (e.g., donor–acceptor, H-bonding, dipole–dipole) that are achiral. The low-energy of these sites can be explained by two causes. First, there are strong interactions between these sites and the solvent molecules. The important effect of solvation on the adsorption energy on the surface of the stationary phase was assumed earlier [5]. Second, the highly energetic interactions involved with adsorption on the high-energy sites require that favorable steric

Table 1
Temperature dependence on the retention, separation and efficiency

T (K)	p[a] (bar)	$k_{(R)}$	$k_{(S)}$	α	$N_{(R)}$[b]	$N_{(S)}$	R_s[c]
1% acetonitrile							
288	67	15.32	17.70	1.16	3790	3930	2.09
295	62	12.05	13.70	1.14	4050	4210	1.89
303	58	9.33	10.42	1.12	4410	4510	1.67
313	53	7.04	7.74	1.10	4770	4790	1.44
2% acetonitrile							
288	60	10.76	12.35	1.15	4090	4220	2.01
295	55	8.91	10.08	1.13	4410	4520	1.85
303	53	7.24	8.08	1.12	4670	4760	1.67
313	49	5.67	6.25	1.10	4940	5000	1.45
3% acetonitrile							
288	68	9.80	11.07	1.13	3900	3980	1.74
295	63	7.94	8.86	1.12	4310	4370	1.62
303		6.32	6.95	1.10	4730	4710	1.44
313	59.5	4.86	5.29	1.09	5120	5070	1.25

[a] Inlet pressure.
[b] $N = 5.45(t_R/w_{0.5})^2$; t_R is retention time, $w_{0.5}$ is width on half of height of a chromatographic peak.
[c] The theoretical expression: $R_s = (\sqrt{N}/2)((k'_1 + k'_2)/(2 + (k'_1 + k'_2)))((\alpha - 1)/(\alpha + 1))$ was used, see ref. [6].

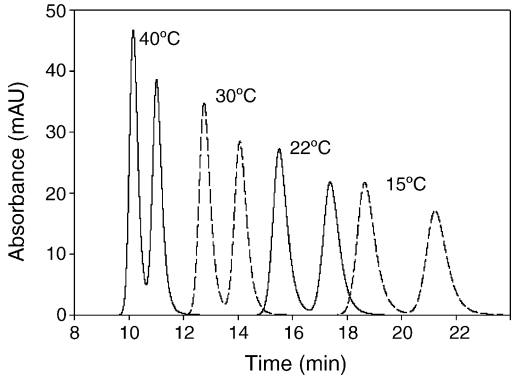

Fig. 2. Chromatograms of racemic 2,2,2-trifluoro-1-(9-anthryl)ethanol, solid and dashed lines, respectively, at different temperatures. Mobile phase: toluene–acetonitrile (99:1, v/v).

Table 2
Enthalpies and entropies of TFAE at different acetonitrile concentrations

Acetonitrile content (%, v/v)	$\Delta H_{(R)}$ (kJ/mol)	$\Delta H_{(S)}$ (kJ/mol)	$\Delta\Delta H$ (kJ/mol)	$\Delta S_{(R)}$ (J/(mol K))	$\Delta S_{(S)}$ (J/(mol K))	$T\Delta\Delta S$[a] (kJ/mol)	$\Delta\Delta G$[b] (kJ/mol)
1	−23.4	−24.8	−1.4	−54	−58	−1.09	−0.32
2	−19.2	−20.4	−1.2	−42	−46	−0.90	−0.30
3	−21.0	−22.2	−1.2	−49	−52	−0.93	−0.27

[a] $T\Delta\Delta S = \Delta\Delta H - \Delta\Delta G$; $T = 295$ K.
[b] $\Delta\Delta G = -RT\ln(\alpha)$; $T = 295$ K.

conditions take place, which might not be possible with some of the selector conformers.

The thermodynamics of this separation were studied through van't Hoff equation

$$\ln k' = \left(\frac{-\Delta H^\circ}{RT}\right) + \left(\frac{\Delta S^\circ}{R}\right) + \ln \beta \quad (1)$$

where ΔH° and ΔS° are the standard enthalpy and entropy of transfer of the solute from the mobile to the stationary phase, or adsorption enthalpy and entropy. β is phase ratio.

The $\ln k$ versus $1/T$ plots (not shown) for both enantiomers and for all mobile phase compositions are linear, with correlation factor $R > 0.999$. The solute distribution process between the mobile and the stationary phases is exothermic (Table 2). The absolute value of the adsorption enthalpy is larger in the 1% acetonitrile solution than in the 2 and 3% solutions, which supports the assumption that the adsorption sites are solvated by the polar modifier. The differences $\Delta\Delta H = \Delta H^\circ_{(S)} - \Delta H^\circ_{(R)}$ are small (Table 2). Such low values indicate that the separation does not take place because there is a different number of interactions between the two enantiomers and the chiral center. Rather, it suggests that the enantioseparation is the result of minor differences in the stability of the adsorption complexes, differences that are caused by steric factors.

Both the enthalpy and entropy of adsorption have the same sign, thus they give opposite contributions to the free energy of adsorption, the enthalpy contribution being prevalent. However, the entropy term is relatively high, 66–70% of the enthalpy term ($T\Delta S$). The physical explanation is obvious, the energy released by the formation of an adsorption complex is partially consumed in processes of structural changes of the bulk solution and the surface layer. The contributions of the enthalpy and entropy terms to the free energy difference, $\Delta\Delta G$, are of the same order and have the same sign (Table 2). Thus, the entropy term hampers the separation which the enthalpy term assists. The correlation between ΔH° and ΔS° shows that the stronger the adsorption complex formed, the more ordered the adsorption layer.

In order to estimate the pressure dependence of k, experiments were carried out (see Section 2). As could be expected from the relatively small size of the TFAE molecule [7,8], the pressure has almost no influence on the retention of TFAE nor on the separation of its enantiomers. As the inlet pressure changes from 59 to 186 bars, the retention factor decreases linearly by 2.3 and 2.5% for (R)- and (S)-TFAE respectively, resulting in a drop of α of about 0.2%.

A change of the column temperature at constant flow rate leads to a change of the inlet pressure due to the temperature dependence of the eluent viscosity (Table 1). But Eq. (1) is valid only at constant pressure and thermodynamic quantities derived from the data in the table are apparent values. The influence of the pressure on the retention factor is complex, involving thermodynamic, hydrodynamic, and experimental aspects. The nature of this effect was comprehensively discussed in [8,9]. Assuming that k is a function of only the pressure (p) and the temperature one can write

$$\frac{\mathrm{d}\ln k'}{\mathrm{d}T} = \left(\frac{\partial \ln k'}{\partial T}\right)_p + \left(\frac{\partial \ln k'}{\partial p}\right)_T \frac{\mathrm{d}p}{\mathrm{d}T} \quad (2)$$

The total derivative $\mathrm{d}\ln k'/\mathrm{d}T$ can be measured experimentally but only the partial derivative $(\partial \ln k'/\partial T)_p$ has a clear physical meaning. The data presented permit an evaluation of the second term of Eq. (2). It is of the order of $0.0001\ \mathrm{K}^{-1}$ at 22 °C, in the interval of pressure studied. The estimate of the total derivative on the left-hand side of Eq. (2) is around $-0.03\ \mathrm{K}^{-1}$. Hence, the derivative $(\partial \ln k'/\partial T)_p$ is less than the experimental value measured by only ∼0.3%.

4. Conclusions

Although originally developed for the separation of chiral acids in ion-exchange chromatography, the quinidine carbamate CSP separates chiral arylcarbinols in the normal-phase mode. Thermodynamic measurements show that adsorption is slightly exothermic, with a value of the heat of adsorption typical of retention processes taking place in the liquid phase and accompanied with the formation of hydrogen bonds. The small differential adsorption enthalpy suggests that the chiral separation is due to small differences in steric interactions between either enantiomer and the selector. The adsorption mechanism is influenced by solvation. Both the enantioselective and the nonselective sites are affected by a change in the concentration of the mobile phase modifier, acetonitrile. Surface solvation by toluene is also important, apparently on account of the shielding of the nonselective adsorption sites [5]. The driving force for the transfer of the analyte from the liquid phase to the surface of the CSP is the difference between the energy of the eluate in the bulk solution and in the adsorption complex whereas the ordering processes of

the system result in a loss of free energy that hampers the adsorption.

The enantioselectivity is not seriously affected by the pressure and the errors introduced in the calculation of the thermodynamic quantities of adsorption due to the dependence of the inlet pressure on the temperature, are negligible.

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