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Improved apparatus for solid–liquid multi-stage counter-current extraction

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Abstract

An improved apparatus for solid–liquid multi-stage counter-current extraction (SLME) was developed. The apparatus has a set of 24 extraction vessels. Each extraction vessel unit is composed of a piston-cylinder in which the solid phase is placed, and a cup-cylinder in which the liquid phase is set. Of the 24 extraction vessels, 20 were used for the separation stage, and the other 4 were used for the back-extraction stage. (±)-Troger's base was selected as a racemic model compound for the continuous enantioseparation by the apparatus, and a cellulose derivative was used as the chiral separator. After 50 cycles of the operation (in 9 h), 0.1 g of (−)-enantiomer (85% in purity) was recovered from the solid phase by back-extraction with ethanol, whereas 1.1 g of (+)-isomer (75% in purity) was collected from the liquid phase (ethanol).

Keywords: Counter-current extraction; Extraction methods; True moving beds; Enantiomer separation; Instrumentation; Tröger's base

1. Introduction

We have developed a solid–liquid multi-stage dual-flow counter-current extraction (SLMCE) apparatus which can perform true moving bed chromatography, although it uses solid–liquid extraction vessels, and the process is stepwise [1]. Previously, using an apparatus with 12 extraction vessels, the continuous extractive separation of methyl- and propyl 4-hydroxybenzoate was accomplished using octadecyl-silica gel as the solid phase, and a mixture of water and 1-propanol (8:2) as the liquid phase. From a 1:1 mixture of methyl and propyl esters, methyl ester was extracted into the liquid phase at a purity of 98.8% and propyl ester was recovered from the solid phase by desorption at 95.9% purity. However, the previous apparatus has only 12 extraction vessels, and it is desirable to improve extraction efficiency by increasing the number of extraction vessels. We have designed a robot which can operate two sets of the previous apparatus in series while maintaining continuous counter-current motion in the vessels.

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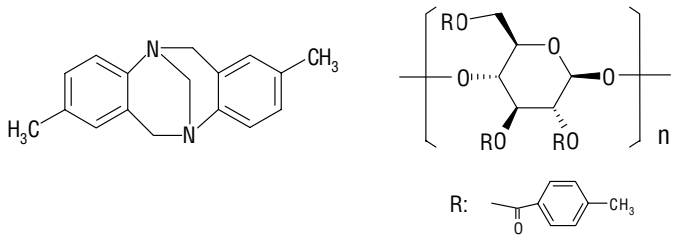

(±)-Troger's base (1) tris(4-methylbenzoyl) cellulose (2)

Fig. 1. The structure of Troger's base and the chrial separator used.

In this report, we describe the improved apparatus for SLMCE and its application to the continuous enantioseparation of (±)-Troger's base using tris(4-methylbenzoyl)cellulose as a chiral separator (Fig. 1).

1.1. An improved apparatus for solid–liquid multi-stage counter-current extraction

The structure of the unit extractor is similar to that reported previously [1]. Two extractors, each with 12 extraction vessels, are connected by a robot which can replace one of each cup-cylinder, or one of each piston-cylinder between the two extractors in such a manner that the dual-flow counter-current extraction movements are maintained (Figs. 2 and 3). This arrangement of two or more extractors being operated in series by the robot should provide a more efficient SLMCE apparatus. A unit vessel of the extractor has a syringe-like structure composed of a piston- and a cup-cylinder. A stainless steel piston-cylinder (128 mm × 49.95 mm o.d.) is inserted into a stainless steel cup-cylinder (120 mm × 50.15 mm i.d.). A sintered stainless steel filter (2 μm mesh) is welded on the bottom of the piston-cylinder in which the solid phase is set. A polyethylene piston-ring is set at a height 5 mm from the bottom.

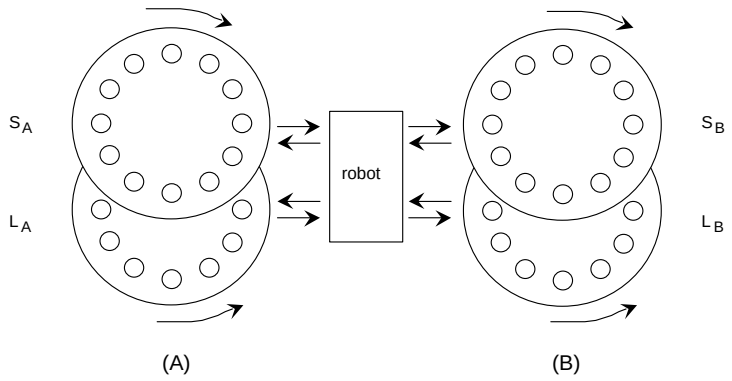

Fig. 2. A sketch of the improved apparatus. Two units of extractors (A and B, see [1] for a detailed description), each with 12 sets of extraction vessels were used. A robot was placed in-between the two extractors. The robot can remove piston-cylinders (solid phase, chiral separator) on S_A and S_B, or cup-cylinders (liquid phase) on L_A and L_B from both extractors at the same time, and then replace them in a dual-flow counter-current motion. Twenty vessels were used for the separation stage, and four vessels were used for the recovery stage (cf. Fig. 3).

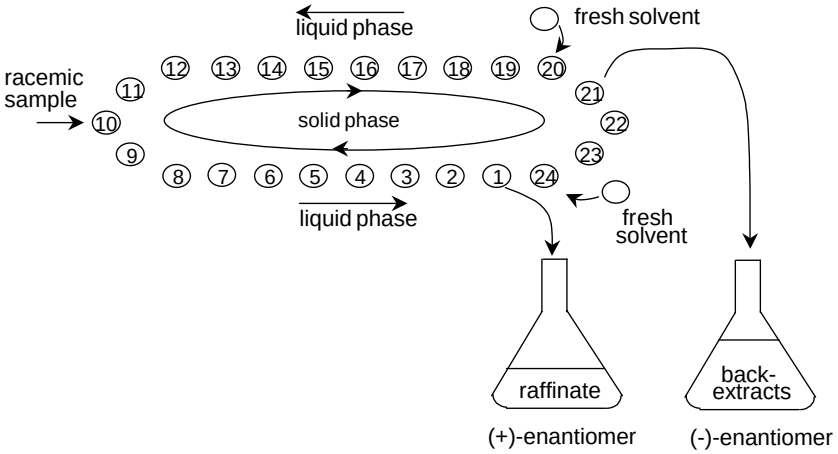

Fig. 3. Schematic diagram of the continuous enantioseparation. Only the liquid phase is shown (numbers in the circles indicate the position of the extraction process). The solid phase moves counter-currently to the liquid phase. Twenty (1st to 20th) sets of vessels were used for the separation stage, and the other four vessels (21st to 24th) were used for the back-extraction stage. A racemic sample was introduced as a liquid phase at the 10th position, and was enantiomerically separated into the raffinate and back-extract continuously.

Each unit extractor has 12 sets of extraction vessels. The cup-cylinders in which the liquid phase is placed are set on the base plate (L_A and L_B), and the piston-cylinders in which the solid phase is set are hooked on the top plate (S_A and S_B), which can be moved up and down by a screw motor. Both the base and the top plates can be rotated. The stepwise rotation of the top plate with the piston-cylinders (solid phase, clockwise), and the base plate with the cup-cylinders (liquid phase, counterclockwise) produces a counter-current motion in the two phases. The equilibration is achieved by the up and down strokes of the pistons. The stroke speed is about 0.25 cm/s. The number of strokes for equilibration, the range of strokes, and the rate of strokes are all variable, and are electronically controlled. A robot is set in-between the two extractors. After equilibrium has been attained by the up-and-down motion of the top and the bottom plates, it replaces the cup- or the piston-cylinders of the pair of extractors at the same time to maintain the counter-current motion. All the integrated circuit-controlled mechanical equipment, namely, the robot and extractor units including the cup- and piston-cylinders, was manufactured by Suction Gas Kikan Co. (Tokyo).

2. Experimental

2.1. Chemicals

Crystalline cellulose (Avicel) and (±)-Troger's base were purchased from Aldrich (Milwaukee, WI, USA). (±)-Troger's base was re-crystallized from ethanol–diethyl ether (9:1) before use. 4-Methylbenzoyl chloride was obtained from Tokyo Kasei Kogyo (Tokyo, Japan). Ethanol and other solvents were purchased from Wako (Osaka, Japan).

2.2. HPLC conditions

For measuring the distribution ratio of the sample and for analysis of the separation results, an HPLC system 980 (Jasco, Tokyo) was used equipped with a Chiralcel OP(+) column (25 cm × 4.6 mm, Daicel, Tokyo) and a Rheodyne sampling valve (20 μl). The eluting solvent was methanol, and monitoring was done at 254 nm.

2.3. Preparation of chiral separator: polystyrene beads coated with tris(4-methylbenzoyl) cellulose

Polystyrene beads (25 μm, supplied by Showa Denko, Tokyo) were coated with cellulose

tris(4-methylbenzoyl) according to a previously reported method [2,3]. Okamoto et al. used diphenylsilanized silica gel as the core beads. However, we chose polystyrene beads because they have numerous phenyl groups and should become well coated with the 4-methylbenzoyl derivatives of cellulose. Thus, 8.8 g of tris(4-methylbenzoyl)cellulose was dissolved in a 10:1 mixture of dichloromethane and nitrobenzene (160 g). To the solution, 20.0 g of polystyrene beads were suspended and stirred for 20 min. The suspension was then poured into 1500 ml of methanol with stirring. The stirring was continued for 1 h. The precipitates were collected on a glass filter, and washed with methanol thoroughly. The collected beads were dried under a vacuum (∼40 °C). Four repetitions of the above coating process (about 26–27 g of the solid phase was obtained each time) provided 100 g of the solid phase.

2.4. Liquid phase

Commercial ethanol (99.8%) was used without further purification.

2.5. Solid phase (chiral separator)

In each piston, 3.25 g of the chiral separator was set and pushed down to soak the gel into the liquid phase (50 ml ethanol) set in the cup-cylinder. After retracting the piston, the liquid in the cup-cylinder was discarded. The weight of the solid phase increased by about 11.9 g with the soaked liquid phase on average.

2.6. Sample solution

Racemic Troger's base (9.6 g) was dissolved in 600 ml of the liquid phase (ethanol). At the start, 50 ml of this solution was introduced into the 10th cup-cylinder, and thereafter 10 ml of this sample solution was added to the cup-cylinder at the 10th position of the extraction stage at every cycle of the operation.

2.7. Measurement of the distribution ratios

Using a test tube with a stopper, the distribution ratios of the sample were measured in an approximately 1/10 scale of the extraction experiment as follows. After introducing the solid phase (0.36 g of dry weight), the ethanol solution of the sample (5.2 g) was added and shaken vigorously. The concentration of the sample in the liquid phase (C_L) was measured by HPLC. The amount of sample absorbed to the dry solid phase (C_S) was then calculated from the initial amount of sample (W_0, mg) and C_L. The distribution ratio (D) is expressed as:

$$D = \frac{C_S}{C_L} = \frac{[(W_0 - C_L W_L)/W_S]}{C_L}$$

where W_L is the mass of the liquid phase in the cup-cylinder and W_S the weight of the dry solid phase. The obtained values are shown in Table 1. The total amounts of (±)-1 listed in Table 1 correspond to the quantities found in a stage in the extraction apparatus and are 10-fold greater than those used to measure the coefficients in the one-tenth scale procedure.

2.8. Operation procedure

The solid phase (chiral separator, 3.25 g each) was introduced in all the piston-cylinders, and wetted with the liquid phase (ethanol). The initial sample solution was placed in the 10th outer cylinder, while in the other 19 separation cylinders (1st to 9th and 11th to 20th), the liquid phase (ethanol, 50 ml) was set. In the remaining four cup-cylinders of the recovery stage (21st to 24th), 110 ml of the liquid phase was set.

The operation steps consisted of four steps for extraction, and five steps for the replacement of liquids. That is, the steps were: extraction (1, see below) → exchanging the solid phase between the two unit-extractors, and rotation (2, 3) → extraction (4) → exchanging the solid phase and rotation (5, 6); and taking out the sample (7) → supplying fresh solvent (8) → sample inlet (9).

Table 1
Concentration dependency of the distribution ratio

Total amount of (±)-1 (mg)	Distribution ratio	
	(+)-Isomer	(−)-Isomer
0.50	12.45	20.24
5.0	8.21	15.53
50	6.39	11.57
100	5.49	9.65
200	5.18	8.4
400	4.63	6.9

For conditions, see text.

(1) Perform 15 strokes of extraction (extraction step 1).
(2) One of each of the piston-cylinders on the two extractors is changed by the robot.
(3) Transfer the solid phases to the next stage (clockwise rotation of the top plate).
(4) Perform 15 strokes of extraction (extraction step 2).
(5) One of each of the cup-cylinders of the two extractors is changed by the robot. (The two vacant positions move to the 24th and 20th positions).
(6) Transfer the liquid phases to the next stage (counterclockwise rotation of the bottom plate).
(7) Remove the 1st (raffinate in the liquid) and the 21st liquid phases (solid adsorbed components recovered by the liquid phase) to the collection reservoirs. (Counterclockwise rotation of the base plate).
(8) Supply new liquid phases at the 24th (110 ml) and the 20th (50 ml) positions.
(9) Add sample solution (160 mg in 10 ml ethanol) to the 10th position cup-cylinder. Thus, the total volume of the liquid at the 10th to 1st stages is 60 ml, which is 10 ml larger than that at the 20th to 11th stages. (The above nine steps are one extraction operation unit (OT = 1)).
(10) Repeat steps 1–9 until the total number of operations reaches the desired total number of operation times (OT = 50).

The solid phase is recycled throughout the experiment.

2.9. Simulation program

The computational program was written in N-88 BASIC on MS-DOS, using a PC-9801US (i386, 32bit) microcomputer (NEC, Tokyo) [1].

2.10. Optimal operation conditions and the simulated results

By inputting optimal extraction conditions (the number of extraction vessels, that of recovery vessels, amount of the solid phase for extraction and for recovery, the initial amount of a sample, the additional amount of the sample at each operation time, and the volume of solvent for the back-extraction), the separation results can be estimated by the program using the distribution ratios (cf. Table 3, the column of "calculated"). After several trial calculations, the ratio of the solid phase to the liquid phase was determined as 3.25 g solid and 50 ml liquid in the separation stage, 110 ml in the recovery stage, and 10 ml in the sample inlet according to the calculated results (Table 2). Thus, the experiment was performed under the conditions described above.

3. Results and discussion

3.1. Experimental results

The amounts of samples in the cylinders (positions 1–24) were also determined by HPLC. They are shown in the left column of Table 2, with the calculated amounts of samples in the right column. Under the optimal conditions, continuous counter-current extractive separation of the racemic mixture was performed (Tables 3 and 4).

The differences between the experimental and calculated values are considered to have arisen from the poor efficiency of the apparatus, namely only 20 plates for the separation stage, and 4 plates for the recovery stage. Also, a slight change in the amount of the soaked liquid with the solid phase was observed (10.77–13.48 g) after OT = 50, which may also cause a reduced efficiency. By recycling the solid phase with adsorbed materials during the operations, the amount of (−)-isomer in the raffinate was increased. Also, there was some deviation in the weights of liquid soaking into the solid phase in the 24 piston-cylinders. The distribution ratios of the samples were found to be temperature-dependent, and although the extraction vessels were not temperature-controlled, the experiments were performed in a room at 24.5–26.5 °C.

3.2. Superior separations

The present apparatus has only 24 vessels, however, much better separations should be obtained with an apparatus which has more extraction vessels connected in series with the robot.

Table 2
Optimal ratio of the solid phase and the liquid phase

Amount of the solid phase (g)	Volume of the liquid phase (ml)			Calculated results	
	Separation stage		Recovery stage	Purity of the enantiomer	
				Raffinate	Back-extract
1st to 24th	1st to 11th	12th to 20th	21st to 34th	(+)-Form (%)	(−)-Form (%)
3.50	60	50	110	95.3	91.5
3.30	60	50	110	95.4	94.2
3.25*	60	50	110	94.3	94.6
3.20	60	50	110	91.9	94.9

These amounts of the solid phase (3.25 g) and the liquid phase (50, 60, and 110 ml) were selected since the purity in both phases became the highest (*).

3.3. The recovery process

In a standard solid–liquid extraction, the strength of the desorption solvent is much stronger than that of the adsorption solvent. In this work, we performed the continuous separation with recycling of the solid phase, using the same solvent for the recovery stage. If re-conditioning of the solid phase with the extraction liquid phase is possible after recovery of the sample, a different solvent can be used in the desorption process.

Table 3
Amount of enantiomers of the Troger's base in each extraction vessel of the extractor (in the raffinate and in the back-extract)

Position	(+)-Isomer in the liquid phase (mg)		(−)-Isomer in the liquid phase (mg)		(+)-Isomer in the back-extract (mg)		(−)-Isomer in the back-extract (mg)	
	Calculated	Experimental	Calculated	Experimental	Calculated	Experimental	Calculated	Expimental
1	31.0	57.2	1.0	26.9				
2	80.3	116.1	1.0	72.7				
3	118.3	141.7	1.0	107.6				
4	149.6	146.6	1.6	126.6				
5	175.5	166.4	3.7	157.5				
6	196.4	167.2	10.0	171.4				
7	212.3	156.6	25.7	165.7				
8	224.0	167.0	52.3	183.1				
9	232.2	164.5	96.5	184.4				
10	238.0	199.7	163.3	228.8				
11	162.0	113.3	165.5	147.4				
12	110.5	58.1	153.3	95.8				
13	77.9	33.4	141.5	68.7				
14	55.0	21.4	130.0	51.7				
15	38.1	13.3	118.6	39.8				
16	25.3	8.8	107.3	30.9				
17	16.5	5.9	95.7	24.2				
18	11.8	3.6	83.1	17.4				
19	8.2	2.2	67.8	12.7				
20	4.7	1.0	44.7	6.8				
21					5.3	0.85	38.0	5.6
22					1.8	0.58	19.9	3.2
23					0.56	0.22	10.3	1.4
24					0.14	0.08	4.3	0.55

The results of calculations and experiments are those after OT = 50 operations.

Table 4
Isolated amount and the composition of Troger's base enantiomers in the raffinate and in the back-extract

	Raffinate (liquid phase)	Back-extract (solid phase)
(+)-Isomer	1.15 g (74.8%)	0.018 g (14.1%)
(−)-Isomer	0.387 g (25.2%)	0.108 g (85.9%)

The extracts (raffinate) came faster than the back-extracts, which should be recovered after the separation stage was over, and the total amount of compounds in the back-extracts was small.

4. Conclusion

An improved apparatus for solid–liquid multi-stage counter-current extraction was developed. Using (±)-Troger's base as a racemic model compound, it was demonstrated that the present technique is a powerful tool for continuous enantioseparation.

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