Monatshefte für Chemie 115, 1113—1120 (1984)

Monatshefte für Chemie
Chemical Monthly

A Recycling Technique for the Chromatographic Separation of Enantiomers and Diastereomers on Triacetylcellulose

Karl Schlögl*, ** and **Michael Widhalm**

Institut für Organische Chemie, Universität Wien,
A-1090 Wien, Österreich

(Received 12 March 1984. Accepted 28 March 1984)

A simple and inexpensive equipment for the optical resolution of enantiomers (and separation of diastereomers) on triacetylcellulose in ethanol at elevated pressure is described. It involves a closed circuit of solvent (pump—column—detector—pump) allowing a continuous chromatography up to 16 cycles without stopping the flow or handling fractions.

This useful and versatile method permitting also the determination of enantiomeric purities is illustrated by several examples of centro-, axial- and planarchiral arenes and metallocenes.

(Keywords: Enantiomeric purity; Centro-, Axial- and Planarchiral Arenes and Metallocenes)

„Recycling-Chromatographie" zur kontinuierlichen chromatographischen Trennung von Enantiomeren und Diastereomeren an Triacetylcellulose

Es wird eine einfache und preisgünstige Anlage zur Racematspaltung und Trennung von Diastereomeren an Triacetylcellulose in Ethanol unter erhöhtem Druck beschrieben. Sie beinhaltet einen geschlossenen Lösungsmittelkreislauf (Pumpe — Säule — Detektor — Pumpe) und ermöglicht eine kontinuierliche Arbeitsweise bis zu etwa 16 Zyklen, ohne den Fluß unterbrechen oder die Fraktionen handhaben zu müssen.

Diese offensichtlich universelle Methode, welche auch die Ermittlung enantiomerer Reinheiten erlaubt, wird an Hand von einigen zentro-, axial- und planarchiralen Arenen und Metallocenen vorgestellt.

Introduction

Mediumpressure chromatography on microcrystalline triacetyl cellulose has been successfully employed for the optical resolution of various axial and planarchiral arenes and metallocenes[1]. In some cases,

---

** Herrn Prof. Dr. *U. Schmidt*, Stuttgart, zum 60. Geburtstag gewidmet.

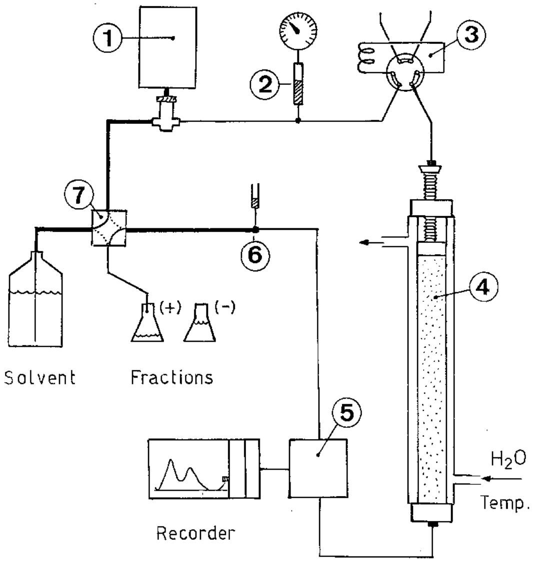


Fig. 1. Equipment for Recycling Chromatography. *1* Pump; *2* pulse dampner; *3* sixway-valve; *4* column with water jacket; *5* UV-detector; *6* compensating tube; *7* fourway-valve. The pipes are made from teflon-tubes: ——— (1/16") and ——— (1/8")

however, only incomplete separations could be achieved and the relatively small capacity of the adsorbent prohibited in many cases the resolution of somewhat larger amounts (as required for subsequent reactions and/or studies of the enantiomers). The nearly exclusive use of ethanol as eluant has additional disadvantages: due to the poor solubilities of several chiral compounds larger sample volumes are required resulting in insufficient separations. According to sometimes unfavourable small k'-values the racemates may pass the column too fast thereby giving an only weak discrimination between the enantiomers.

These problems could in theory be surmounted by using larger columns (both in length and diameter). For these, however, larger quantities of the adsorbent are required and—what is more important—a rather sophisticated packing technique has to be employed.

We present now a rather simple recycling technique* solving most of these problems; it can be employed successfully either for the resolution of enantiomers with small α-values (k'_1/k'_2) and /or for the separation of larger amounts on a preparative scale.

---

* A chromatographic resolution by continuous application of the eluate was mentioned without any details in Ref.[2].

2

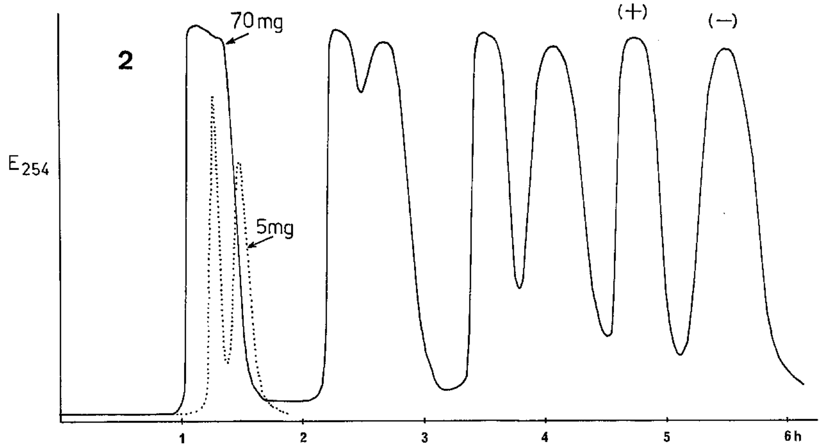


Fig. 2. Chromatographic resolution of the 2,2′-spirobiindane derivative **2** in four cycles. For details see Table 1

Recycling-Technique

The simple equipment is shown in Fig. 1. Its heart is a socalled "rotating-piston" pump (1) working without valves[3]. A model with flowrates variable between 0 and 250 ml/h against 0–7 bar backpressure was satisfactory for our purpose. Its outlet is connected with a simple pulse dampner (2) consisting of a T-tube (with 1/16″ fittings) and a manometer on top of an airfilled teflontube (1/2″) in the flowless sidearm. A saturated (ethanolic) solution of the racemate is introduced via a loop and a sixway-valve (3) in the conventional manner. All resolutions were performed on a glass column (4) (30 by 2.5 cm) thermostated by a water jacket and filled with appr. 80 g of swollen triacetylcellulose[4] (20–40 μm, windsieved, as described previously[1a]). After leaving the column the eluate passes an UV-detector (5) to control the degree of separation. A second T-tube (1/16″) is installed into the pressureless part of the pipe and connected with an open tube of 1 cm diameter (6) in order to compensate the pulses arising from the sucking of the pump. The fourway-valve (7) finally has two positions: either taking fractions and sucking fresh solvent from the reservoir or the recycling mode without consuming fresh solvent.

Results and Discussion

The wide applicability of this recycling technique is illustrated by some typical examples; they include various racemic compounds from our own work (**1**–**9**) and a separation of diastereomers of a natural product (**10**).

Table 1. *Chromatographic separation of enantiomers* (**1**–**9**) *and diastereomers* (**10 a**/**b**) *by the recycling technique. Sample volumes (concentrated solutions in ethanol) 1–5 ml. Flowrate 105–115 ml/h at 1.3 bar*

Compound (no.)	Temp.[a] (°C)	mg	k'[a]	α	R_s	Number of cycles	Sign of rotation[b] at 589 nm	e.e. (%)
4-Methoxycarbonyl-4′-methyl-2,2′-spirobi(5,6,7,8-tetrahydrobenz[f]indan) (**1**)	40	5	0.91 2.04	2.24	2.8	1	+ −	100 100
	40	50			> 1[c]	1	+ −	100 100
4,4′-Diacetyl-2,2′-spirobi … (**2**)	40	5	0.31 0.52	1.68	1.3	1	+ −	100 100
	40	70			1.2	4	+ −	> 90 > 90
4-Acetyl-4′-methoxycarbonyl-2,2′-spirobi … (**3**)	38	5	0.35 0.54	1.54	1.2	3	+ −	100 100
1,2-Diphenylethanol (**4**)	38	10	0.52 0.83	1.60	1.6	1	+ −	100 100

3-Methoxycarbonyl-2,7-methano[10]azaanulen (**5**)	38	5	0.92 1.01	1.09	1.2	10	− +	> 90 > 90
Ferrocenyl-phenyl-carbinol (**6**)	40	2	1.11 1.28	1.16	1.2	3	+ −	> 90 > 90
Bis(α-ketotetramethylen)-ferrocen (**7**)	40	5	0.54 0.59	1.09	~ 0.8	16	− +	~ 60 ~ 60
2,2′-Bis(hydroxymethyl)-biphenyl-bis(tricarbonyl-chromium) (**8**)	40	5	0.99 1.06	1.06	~ 0.8	10	− +	~ 60 ~ 60
2,2′-Bis(methoxycarbonyl)-6,6′-dimethyl-biphenyl-mono(tricarbonylchromium) (**9**)	40	5	0.73 0.78	1.06	~ 0.6	13	+ −	65 61
Farnesiferol A (**10 a**) Koladonin (**10 b**)	40	5	0.29 0.36	1.24	~ 1.0	8		**a**:**b** = 85:15

[a] A pronounced effect of the temperature on k' was observed in all cases (e.g. until 30%, if the temperature was increased from 30 to 40 °C).

[b] In ethanol (if necessary after concentration of the fractions). The enantiomeric relationship was established in all cases by recording the CD-spectra of both fractions (Jobin-Yvon Mark III).

[c] Strong tailing; no exact R_s-value could be determined.

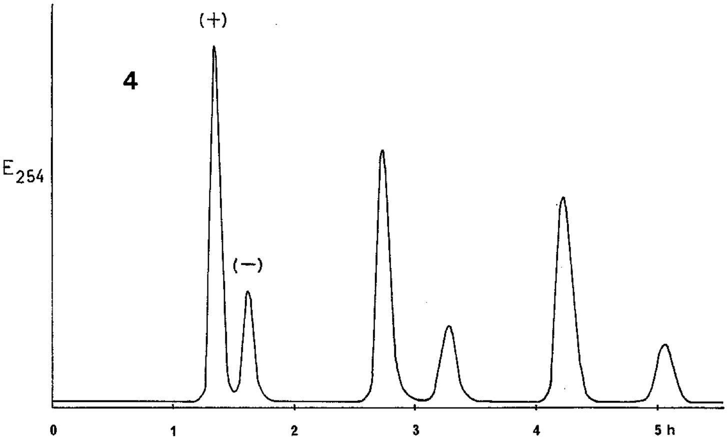
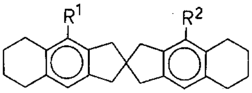
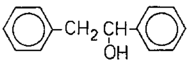


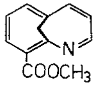
Fig. 3. Chromatographic resolution and enantiomeric purity of 1,2-diphenyl ethanol (**4**). For details see Table 1



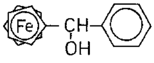
	R^1	R^2
1	CH_3	$COOCH_3$
2	$COCH_3$	$COCH_3$
3	$COCH_3$	$COOCH_3$



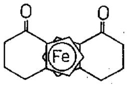
4



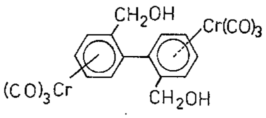
5



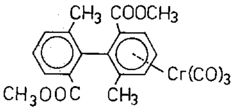
6



7



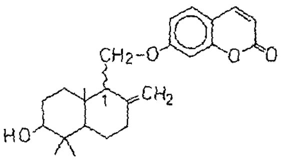
8



9

The results are summarized in Table 1 (see also Figs. 2 and 3).

The spirobiindane derivatives **1** and **2**[5] could be resolved completely on a 5 mg scale in one run; scaling up to 50 mg (**1**) and 70 mg (**2**) required four cycles for the preparative separation of **2** (cf. Fig. 2), whereas one single run was sufficient for **1**. **3** had been resolved by classical means (*via* the salts of the corresponding carboxylic acid)[5]; its enantiomeric purity has now been established by graphical integration of the curves obtained from the chromatographic separation (after 3 runs) thereby proving that crystallization of the α-phenethylamine salts had given optical pure **3**.



	C-1
10A	axial
10B	equatorial

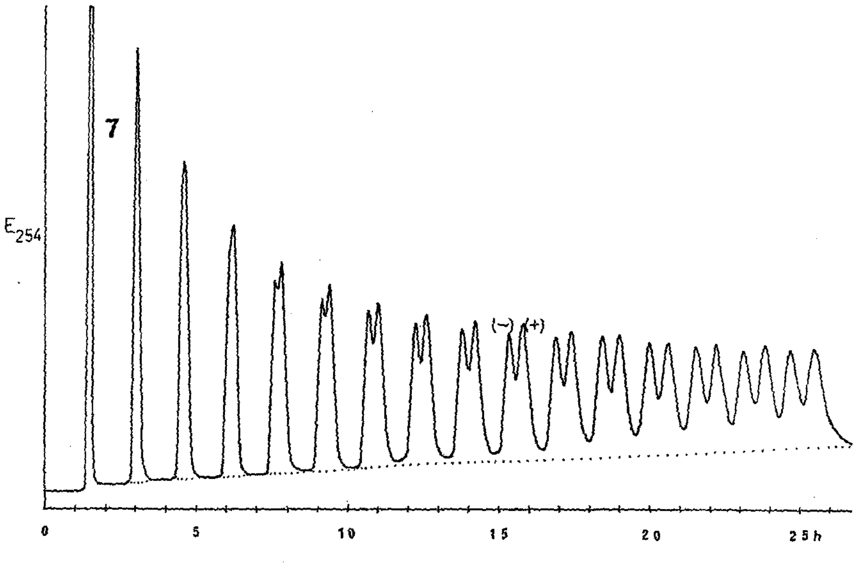


Fig. 4. Chromatographic resolution of bis(α-ketotetramethylene)ferrocene (**7**) in 16 cycles. For details see Table 1

Optical active **4** was of interest for studies of asymmetric reduction of *trans*-stilbene with chiral boranes[6]. The chromatography of the reaction products established their enantiomeric purities and thereby the optical yields of the reduction; these results could be reproduced within ± 2%. (Cf. Fig. 3.)

The optical resolutions of **5**[1d], **6**, **7**[7], **8**[8], and **9**[9] gave poor results (or are impossible) either by classical means or even be asymmetric chromatography[9] after only one run.

10 a (Farnesiferol A)[10] and **10 b** (Koladonin)[11] represent examples for the separation of diastereomeric natural products.

So far, after about 15 runs the capacity of a 30 cm column was usually exhausted, so that no further increase of optical activity (enantiomeric purity) could be achieved (cf. Fig. 4 for the separation of **7**). This is the case when the first fraction of the next run is overlapping the second fraction of the preceding cycle. Also if both peaks exhibit a strong tailing the number of cycles is limited and the results are less satisfactory.

Acknowledgements

This work was supported by the "*Österr. Fonds zur Förderung der wissenschaftlichen Forschung*" (Project P 3574) and by the "*Hochschuljubiläumsstiftung der Stadt Wien*". We are grateful to Dr. *O. Hofer* for a sample of **10 a**/**10 b**.

References

[1] a) *Schlögl K., Widhalm M.,* Chem. Ber. **115**, 3042 (1982) and references cited therein; b) *Schlögl K., Weissensteiner W., Widhalm M.,* J. Org. Chem. **47**, 5052 (1982); c) *Schlögl K., Werner A., Widhalm M.,* J. Chem. Soc. Perkin Transactions I **1983**, 1731; d) *Schlögl K., Widhalm M., Vogel E., Schwamborn M.,* Monatsh. Chem. **114**, 605 (1983).

[2] *Blaschke G., Kraft H. P., Markgraf H.,* Chem. Ber. **116**, 3611 (1983).

[3] FMI-Metering Pump (Fluid Metering Inc., Oyster Bay, NY 11771, U.S.A.).

[4] Cf. *Hagel G., Hesse R.,* Liebigs Ann. Chem. **1976**, 996.

[5] *Neudeck H., Schlögl K., Tscheplak H.,* unpublished results.

[6] Cf. *Brown H. C., Jadhav P. K., Mandal A. K.,* J. Org. Chem. **47**, 5074 (1982).

[7] *Falk H., Schlögl K.,* Monatsh. Chem. **96**, 266 (1965).

[8] *Schlögl K., Schölm R.,* Liebigs Ann. Chem. **1980**, 1877.

[9] *Eyer M., Schlögl K., Widhalm M.,* Monatsh. Chem., in press.

[10] *Caglioti L., Naef H., Arigoni D., Jeger O.,* Helv. Chim. Acta **41**, 2278 (1958).

[11] *Pinar M., Rodriguez B.,* Phytochemistry **16**, 1987 (1977).