Optical Resolution of C3 Cyclotriveratrylenes and D3 Cryptophanes by Liquid Chromatography on Chiral Stationary Phase Chiralpak-OT(+)

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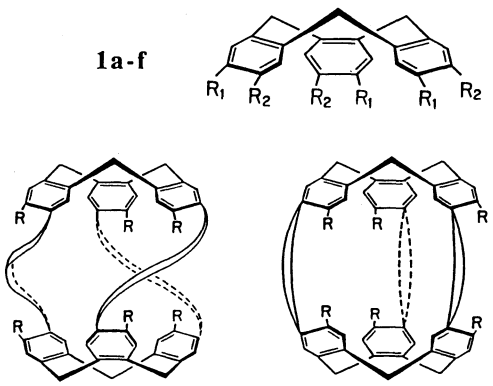
Synopsis. A series of C3 cyclotriveratrylenes and D3 cryptophanes have been resolved by HPLC on Chiralpak-OT (+), allowing the first direct enantiomeric excess assessments for these substances. These results confirm the usefulness of this chiral stationary phase for the resolution of aromatic compounds and extend its scope of application to new classes of highly symmetrical molecules.

Since the first reports on the synthesis of optically active C3 cyclotriveratrylenes (CTV's **1**)[1] in 1978 and D3 cryptophanes (**2**)[2] in 1981, a number of molecules of this kind have been described and have found applications in several fields,[3] including spectroscopy (exciton optical activity),[4-6] liquid crystals,[7] and host-guest chemistry.[8-10] Although a cryptophane was used as a *chiral host shift reagent* for the determination of the enantiomeric composition of a weakly rotating sample of CHFClBr,[11] paradoxically, simple means of establishing the enantiomeric excess (ee) of the resolved CTV's and cryptophanes themselves did not exist so far.



We report herein that the commercially available chiral stationary phase (CSP) Chiralpak-OT(+) is effective for analytical optical resolution of certain C3 CTV's and D3 cryptophanes by HPLC. This CSP can also be used for the structural assignment of D3 (**2**, *dl*) vs. C3h (**3**, *meso*) cryptophane isomers.

Results and Discussion

The use of poly(triphenylmethyl methacrylate), an optically active polymer with a stable helical conformation, was introduced in 1979 by Okamoto et al.[12] This polymer either finely ground or coated on silica gel has since been used for analytical resolution of a wide range of racemates under reversed phase conditions, using a polar eluent such as methanol.[13] Such CSP's and especially Chirapak-OT(+) have proven particularly efficient with regard to two main categories of substances.

Table 1. Optical Resolution of C3 Cyclotriveratrylenes **1a**—**f**[a]

Compd.	First eluted isomer			k'_2[b]	α	T / °C	estd. R_s[c]
	R_1	R_2	confg.				
1a	H	OCH_3	M(+)	25.5	2.29	15	>3
				26.9	2.35	5	
1b	OC_2H_5	OCH_3	P(−)	13.9	1.41	15	≈1
				14.4	1.48	5	
1c	(*O*-allyl	OCH_3)[d]		16.6	1.37	15	≈1.25
				17.2	1.43	5	
1d	$OC_3H_7^i$	OCH_3	P(+)	14.8	1.43	15	≈1.1
				15.4	1.50	5	
1e	$OCOCH_3$	OCH_3	P(+)	12.5	1.38	15	≈1.15
				12.9	1.43	5	
1f	Br	OCH_3	P(−)	16.3	1.48	15	≈1.3
				16.2	1.50	5	

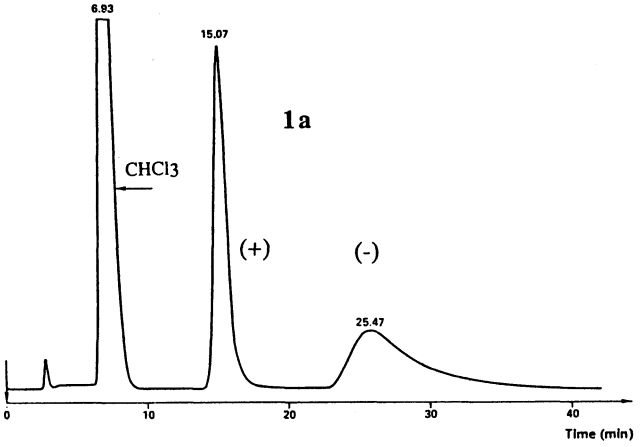
a) Column: Chiralpak-OT(+), 250×4.6 mm i.d.; methanol, 0.5 ml min^{-1}; all solutes were injected in chloroform solution; detection was effected by recording the UV absorption at 230 nm. b) Capacity factor of the slowest eluted enanitiomer; $k'_2=(t_2/t_0)-1$, where t_2 is the retention time of the slowest enantiomer and t_0 that of a nonretained solute. c) The resolution factor R_s is estimated from the depth of valley between the peaks;[14] base line separation corresponds to $R_s>1.3$. d) The enantiomers of this compounds are hitherto unknown.

The first one gathers weakly polar compounds such as oxiranes, halogenated hydrocarbons, some phosphorus insecticides, metal complexes ($M(acac)_3$), as well as more polar compounds such as alcohols and esters. The second category encompasses a variety of molecules (mostly aromatic) that belong to the C2 symmetry point group, such as binaphthol and related atropisomers, spiro (bis) indanones, etc.[13]

In our hands, Chiralpak-OT(+) proved suitable for the resolution of the C3 CTV's **1a—f**. Cyclotriveratrylenes **1b—f**, bearing two different substituents of comparable size on each benzene ring, showed separation factors α ca. 1.4—1.5 (Table 1); **1a** which bears a single substituents on each ring (OCH_3), and hence is "more chiral," was even better separated ($\alpha \approx 2.3$). A slight selectivity increase was obtained by lowering the temperature to 5 °C, as is generally observed. The resolution factor R_s was low (1 to 1.3) for **1b—f**, and good for **1a** (>3). Baseline separations were obtained for **1a** and **1f**, and were almost obtained for the other compounds (see Fig. 1).

Optically active samples of **1a**, **b**, **d—f**, which in earlier works[4] had been considered, on the basis of indirect arguments, to have>90% ee, were analyzed by this method. In all cases none or trace amounts of the others enantiomer was detected, thus confirming that the reported maximum rotation data are correct.[4] These experiments also allowed us to establish the order of elution of the two enantiomers in all cases but **1c** (not available in optically active form). For the "disubstituted" series **1b**, **d—f**, the P isomer, in which R_1 is bulkier than R_2 (see the stereoformula) was eluted first; the "monosubstituted compound **1a** (R_1=H) showed an inverse behavior. Further comments or interpretation of these results would be premature, as the helicity of C3 CTV's is not easy to define and to compare with that of the C2 binaphthyles and analogous compounds discussed by Okamoto.[13]

D3 Cryptophanes **2a—d** were also resolved on this CSP with good selectivities (Table 2). As expected, the achiral C3h isomers **3b—d** each showed a single peak, and this method can therefore be useful to distinguish between *racemic* and *meso* cryptophanes. The elution orders were determined by using the previously described optically active samples of **2a,b,d**.[6] The helicity



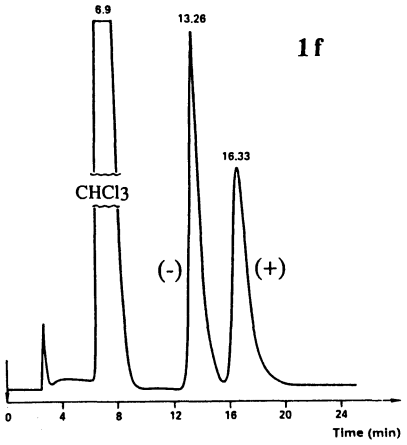


Fig. 1. Chromatographic resolution of (±)-**1a** and (±)-**1f** at 15 °C (conditions indicated in Table 1).

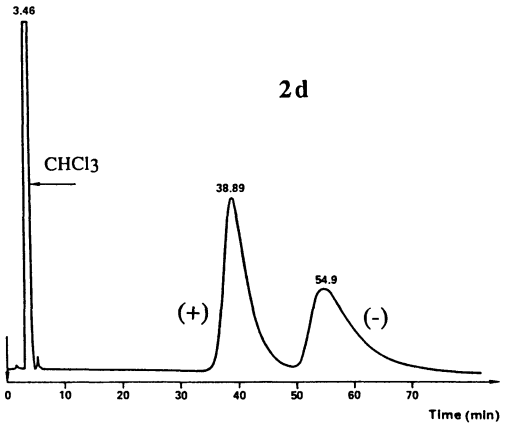


Fig. 2. Chromatographic resolution of(±)-**2d** (conditions indicated in Table 2).

Table 2. Analysis of D3 and C3h Cryptophanes on Chiralpak-OT(+)[a]

Compd.	Symmetry	Bridges	Retn. times/min	k'_2	α
2a	D3	$O(CH_2)_2O$	22.1(+) 30.0(−)	7.58	1.43
2b	D3	$O(CH_2)_3O$	27.4(+) 37.6(−)	9.75	1.42
3b	C3h	$O(CH_2)_3O$	36.0	9.52	
2c	D3	$O(CH_2)_4O$	30.3(?)[b] 75.3(?)	21.1	2.67
3c	C3h	$O(CH_2)_4O$	27.5	6.86	
2d	D3	$OCH_2 \setminus\setminus CH_2O$	38.9(+) 54.9(−)	14.7	1.45
3d	C3h	$OCH_2 \setminus\setminus CH_2O$	31.5	8.0	

a) Same conditions as indicated in Table 1 except flow rate: 1.0 ml min^{-1}; temperature 15 °C.
b) Enantiomers not available.

of the more retained (−) isomers is that of a right-handed screw, when the molecule is viewed along its C3 axis. Typical chromatograms are shown in Fig. 2.

These results raise interesting questions on the mechanisms of the chiral discrimination between a helical polymer and molecules of high symmetry,[15] and suggest that preparative optical resolution of these substances could be carried out on suitable chiral stationary phases.

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