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Resolution of Inherently Chiral Resorcarene Derivatives by Enantioselective HPLC

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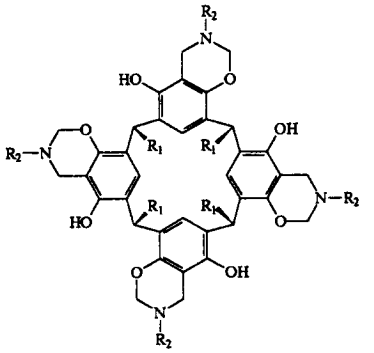
Abstract: The HPLC enantiomeric resolution of five inherently chiral tetrabenzoxazine derivatives of resorcarenes has been achieved by HPLC using Whelk-O1 and in one case Chiralpak AD as stationary phases. Enantiomeric separation was only observed in a very narrow range of mobile phase compositions. On-column enantiomeric interconversion of a racemic compound with a typical plateau-like elution profile was observed using a Chiralpak AD column

Resorcarenes are macrocyclic compounds readily available by acid-catalyzed condensation of resorcinol with various aldehydes.[1] Reaction with primary amines and excess formaldehyde leads to the formation of tetrabenzoxazines.[2-4] Some of them (**1-6**) are reported in the general formula where R_1 stems from the aldehyde that reacts with the resorcinol and R_2 from the amine that reacts with the resorcarene. Four different regioisomers could, in principle, be formed; however, the reaction is regioselective leading only to compounds with C_4-symmetry, due to stabilization by intramolecular O-H...O hydrogen bonding.[2-4] The inherent chirality of these dissymmetric resorcarene derivatives is an intellectually appealing and experimentally stimulating topic.



1	R_1 = methyl	R_2 = benzyl
2	R_1 = pentyl	R_2 = benzyl
3	R_1 = undecyl	R_2 = benzyl
4	R_1 = 2-phenylethyl	R_2 = benzyl
5	R_1 = pentyl	R_2 = *t*-butyl
6	R_1 = pentyl	R_2 = mesityl

In fact, previous attempts to separate the enantiomers of such compounds by chromatography on chiral stationary phases or even to demonstrate this chirality in solution by the formation of diastereomeric complexes have failed[3] and, in spite of the growing attention from several groups in the synthesis and the reactivity of these compounds, no further attempts of enantioseparation have been reported. From our experience in the HPLC resolution of inherently chiral calix[4]arenes[5] and calix[5]arenes,[6] we were interested in the enantioseparation of these resorcinol-derived calixarenes. In the present paper we report our results for compounds **1-6**. In addition, on-column enantiomerization is observed for compound **1** and a rationale for this process is proposed.

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The HPLC enantiomeric resolution was accomplished using mainly a Whelk O-1 Chiral Stationary Phase (CSP).[7a] Table 1 shows the chromatographic results for compounds **1-6** using this CSP. The values of the separation factor (α) range from 1.26 to 1.14 indicating an adequate enantioselectivity. However, the resolution factors (R_s) are always less than 1. The presence of an aromatic group as R_2 is crucial to obtaining enantiomeric separation. When R_2 is aliphatic, as in compound **5** and other unreported compounds, the enantiomers were not separated under the conditions applied.

Enantioselectivity is strongly dependent on mobile phase composition. The mobile phase must be a mixture of *n*-hexane/dichloromethane. In fact, the use of the more common polar modifier 2-propanol, with polarity and proton acceptor parameters (3.9 and 0.55) higher than dichloromethane (3.1 and 0.29) respectively,[8] results in irreversible retention on the column. Furthermore, slight differences in the percentage of dichloromethane in *n*-hexane strongly affect the HPLC behaviour, as shown in Table 1.

Table 1. HPLC behaviour of inherently chiral resorcarenes on (3*S*, 4*R*) Whelk-O1 CSP.[a]

Compd	R_1	R_2	A (%)[b]	k_1[c]	α[d]	R_s[e]
1	methyl	benzyl	50	0.309	NS[f,g]	-
1			40	0.831	1.14	0.8
1			30	1.738	1.15	0.9
2	pentyl	benzyl	50	0.063	NS[f]	-
2			40	0.252	1.21	0.7
2			30	0.554	1.26	0.8
3	undecyl	benzyl	50	0.000	NS[f]	-
3			40	0.073	NS[f]	-
3			30	0.230	1.26	0.7
4	2-phenylethyl	benzyl	50	0.422	1.16	0.8
5	pentyl	*t*-butyl	70	0.149	NS[f,h]	-
6	pentyl	mesityl	30	0.188	NS[f]	-
6			20	0.651	1.21[h]	0.7
6			10	4.147	NS[f,h]	-

[a] Column 250x4 mm i.d., UV detector at 240 nm, t_0 (column void time) = 6.1 min. at a flow rate of 0.5 mL/min. [b] Percentage of dichloromethane in *n*-hexane. [c] Capacity factor of the first-eluted enantiomer defined as $k' = (t - t_0)/t_0$. [d] Separation factor defined as the ratio k'_2/k'_1. [e] Resolution factor defined as $2(t_2 - t_1)/(w_1 + w_2)$, where w are the peak widths at the base. [f] Not separated. [g] Shoulder in the rising edge of the peak. [h] Large peak tailing.

Figure 1 shows how crucial the composition of the mobile phase is for the enantiomeric resolution of compounds **1-3**. For compounds **4** and **5** a percentage of dichloromethane less than 45% and 60%, respectively, results in the complete retention of the sample on the column. Thus, enantiomeric resolution of compounds **1-4** and **6** can only be obtained under a very strict range of experimental conditions. The oxazine rings of compounds **1-6** are hemiaminal groups and these are sensitive to traces of acid and water. An acid-catalysed interconversion of the enantiomers *via* iminium structures can occur as indicated in Scheme 1 (reaction 1). This was suggested by experiments with a tetrabenzoxazine derived from a chiral amine where this reaction represents an epimerization.[3,9] Cleavage of the oxazine ring to give aminoalkylated resorcarenols *via* a formaldehyde expulsion is indicated in the same Scheme (reaction 2). Indeed, reaction 2 was proved by the easy exchange of $-N-CH_2-O-$ by $-N-CD_2-O-$ upon treatment with CD_2O.[4] Evidence for both reactions was obtained in HPLC experiments, as discussed below.

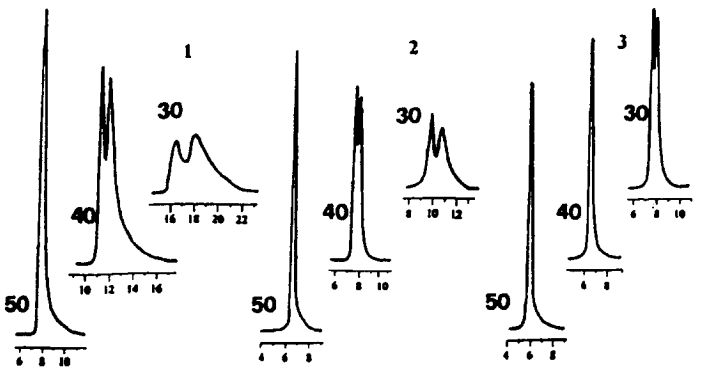
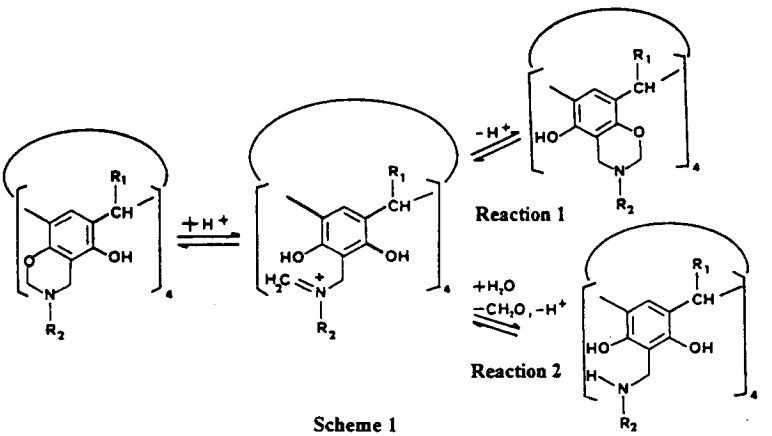


Figure 1. Enantioseparation of compounds 1-3 on Whelk O1 column.
Mobile phase *n*-hexane/dichloromethane (% of the second as indicated), flow 0.5 mL/min.



Scheme 1

The use of a Chiralpak AD column,[7b] whose chiral recognition mechanism is very different from the Whelk-O1 column, was restricted by the very low solubility of the compounds in *n*-hexane/2-propanol. Indeed, this mobile phase is typically used in connection with this CSP and is compatible with its stability. However, injection of a dichloromethane solution overcomes this problem only for compound **1.** When **1** is chromatographed at low temperature, two baseline-resolved, symmetrical peaks are observed with excellent separation (α = 3.77) and resolution (Rs = 2.5) factors at -3 °C, as shown in Figure 2.

In the absence of a chiroptical detector, the area ratios of the peaks were measured (in a number of different experiments) with the UV detector set at a different wavelengths (240, 265 and 280 nm). As expected for an enantiomeric pair these area ratios were equal and equal to one, due to their racemic origin.[10] However, increasing the column temperature resulted in the appearance of an interconversion plateau between the resolved peaks because of an increased enantiomerization rate taking place *via* achiral iminium structures, as indicated in reaction 1 of Scheme 1. The plateau (i.e. the chromatographic profile between the terminal peaks higher than the zero baseline) is particularly evident at 31 °C and 34 °C, and in the inset experiment carried out at a lower polarity of the mobile phase. Although the column efficiency (N) is low, as indicated by the peak broadening, the enantioselectivity α is still very good (α = 2.8 at 31 °C). Deformation of the chromatographic profile with typical

odd-shaped "Batman"[11] elution pattern occurs at 47 °C. Very similar interconversion plateau were reported for allyl *p*-nitrophenylsulfoxide[12] and 1-dimethylamino-8-dimethylcarbamoylnaphthalene.[13]

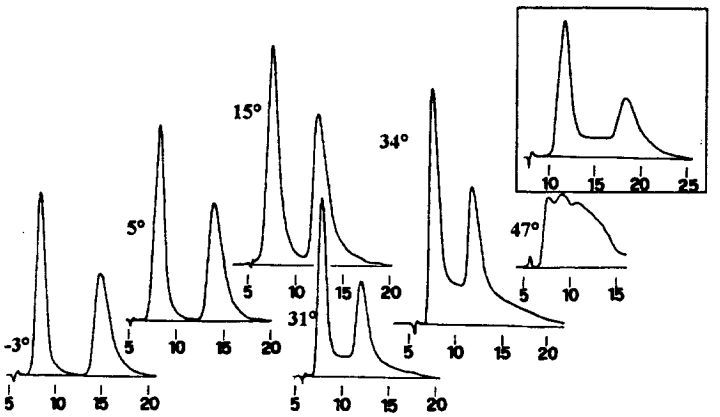


Figure 2. Enantioseparation of compound **1** at various temperatures (-3°C÷ 47°C) on Chiralpak AD column. Mobile phase *n*-hexane/2-propanol 9:1. Flow 0.7 mL/min, t_0= 5.4 min. Inset: same mobile phase 92:8; Flow 0.5 mL/min, t_0= 6.7 min, T= 30°C.

A comparable "Batman shape" was observed for N,N-dimethylthio-2,4,5-trimethylbenzamide.[14] The large tailing of the second peak at 31 °C and 34 °C and the large final shoulder at 47 °C could be due to one or more compounds formed according to reaction 2 in Scheme 1, while eluting at higher temperatures on the CSP. Analogously, this tailing was observed in some chromatograms in Figure 1, as for **1** at 40 and 30 percent of dichloromethane and for **2** at 30 percent of dichloromethane in *n*-hexane.

In conclusion this is the first example of a resolution of inherently chiral tetrabenzoxazine derivatives of resorcarenes and thus the first proof of their chirality in solution. Furthermore, evidence for the stereolability of these derivatives is presented.

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7. (a) (3*S*, 4*R*) Whelk O-1 [4—(3,5-dinitrobenzamido)-tetrahydrophenantrene] covalently bonded to 5 μm 3-propyl silica from Regis Technologies (Morton Grove, IL); (b) Chiralpak AD (amylose tris-3,5-dimethylcarbamate) coated on 10 μm silica gel from Daicel (Tokyo).
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