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Chiral Butadienes, 9[1]

Preparative Enrichment of Enantiomeric 2,3,4,5-Tetrabromo-2,4-hexadienes by Liquid Chromatography

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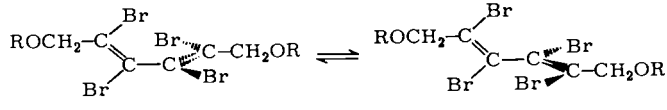
Chirale Butadiene, 9[1]

Präparative Anreicherung enantiomerer 2,3,4,5-Tetrabrom-2,4-hexadiene durch Flüssigkeits-Chromatographie

Die Enantiomeren des Diols **1** wurden durch Flüssigkeits-Chromatographie an Triacetylcellulose teilweise getrennt (Enantiomere Reinheiten P = 29% und 24%), während die Diether (+)- und (−)-**2** mit P = 80% (Tab. 1) erhalten wurden. Ihre Schwellen der Teilrotation um die zentrale Einfachbindung wurden durch thermische Racemisierung gemessen und mit denen entsprechender Tetrachlordiene **3** und **4** verglichen (Tab. 3).

Highly substituted 1,3-dienes adopt nonplanar conformations the chirality of which has been shown[3,4] by NMR spectroscopy at temperatures where enantiomerization is slow on the NMR time scale. Severe non-bonding interactions between substituents may allow a separation of the enantiomers at room temperature which has been demonstrated by *Rösner* and *Köbrich*[5]. They prepared a sample of (−)-**1** via crystallization of diastereomeric salts, the enantiomeric purity of which could not be determined at that time, but was not expected to be high because of possible racemization during crystallization and during removal of the auxiliary[5]. Therefore, we intended to obtain samples with higher specific rotations and, if possible, to measure their enantiomeric purities, i.e. the specific rotations of the pure enantiomers.



(*R*) (*S*)

	R
1	H
2	CH_3

For this purpose, we chose liquid chromatography on microcrystalline triacetylcellulose[1,6,7]. The chromatogram (absorbance *vs.* volume of elution) of **1** showed no sign of splitting, but considerable tailing. On the other hand, the chromatogram of **2** exhibited two overlapping peaks and less tailing. Therefore, the enrichment of enantiomers was more difficult for diene **1** than for its dimethyl ether **2** (Table 1). Also, the order of elution was reversed. Apparently, hydrogen

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bonding of diol **1** to the sorbent has considerable influence upon the relative retentions of the enantiomers[6]. The values $[\alpha]_{589}$ for the pure enantiomers are ± 134 for **2** and ± 100 for **1**, as calculated from the data of Table 1. From the latter number the unknown enantiomeric purity of the earlier preparation[5] of (−)-**1** is calculated to amount to 14% only.

Table 1. Partial separations by liquid chromatography (LC) on triacetylcellulose using EtOH/H_2O (96:4) as an eluent

Predominant enantiomers[a]	R	Amount injected [mg]	Number of column passages	Yields [mg]	$[\alpha]_{589}$ acetone	P[b] [%]	Methods for P
(−)-**1**				80	−29 (20 °C)	29	LC[c]
	H	300	4				
(+)-**1**				120	+24 (20 °C)	24	$[\alpha]_{589}$[d]
(+)-**2**				20	+107 (22 °C)	80 ± 2	^{1}H NMR[c]
	CH_3	100	2				
(−)-**2**				30	−106 (22 °C)	80	$[\alpha]_{589}$[d]

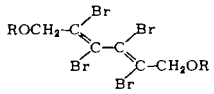
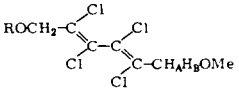
[a] Listed in the order of their elution. – [b] Enantiomeric purity. – [c] See experimental part. – [d] Calculated by means of $[\alpha]_{589}$ and the value for P = 100%, which is known from the *other* enantiomer.

Table 2. Data for partial rotation about the central single bond, obtained by monitoring thermal racemizations in acetone by means of polarimetry

	R	T [°C]	$10^5 k$ [s^{-1}]	$\Delta G^{\neq}$ [kJ/mol]
(−)-**1**	H	39.9	7.12	101.6 ± 0.1[a]
(+)-**2**	CH_3	40.1	2.88	104.0 ± 0.2
(−)-**2**	CH_3	40.1	2.99	103.9 ± 0.2

[a] Calculated from ref.[5] which gives values for the *racemization*, not for the rotational process.

Table 3. Barriers to partial rotation about the central single bond in 1,3-dienes with different substituents

		R	T[a] [°C]	$\Delta G^{\neq}$ (53.5 °C)[b] [kJ/mol]	Origin
	**1**	H	39.9	102.2 ± 0.2	ref.[5]
	2	CH_3	40.1	104.5 ± 0.3	this work
	**3**	H	53	68.8 ± 0.5	ref.[3]
	4	CH_3	54	70.3 ± 0.7	ref.[3]

[a] Temperature of measurement. – [b] Free enthalpy of activation, calculated from the experimental result at temperature T, assuming $\Delta S^{\neq} = -43\ JK^{-1}mol^{-1}$. This value follows from the racemizations[5] of **1**.

The barrier to partial rotation about the central single bond (see formulae) is slightly lower in **1** compared to **2** (Table 2), an effect which had also been found[3] for the corresponding tetrachlorodienes **3** and **4** (Table 3). Their barriers are lower than those in **1** and **2** by 34 kJ/mol (Table 3). The *s-trans*[3] transition states of **1** and **2** suffer from two severe bromine-to-bromine repulsions compared to the chlorine-to-chlorine interactions in **3** and **4**. A more detailed understanding of these barriers necessitates molecular-mechanics calculations for the corresponding ground and transition states of partial rotation.

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Experimental Part

^{1}H NMR spectra: Varian T-60 (CW mode, 60 MHz) and Bruker WH-90 (PFT mode, 8K data points, 90 MHz) spectrometers. – Specific rotations: Perkin-Elmer 141 M polarimeter. – CD spectra: Jasco J-40A, at 20°C. – Mass spectra: Varian-MAT CH-5 spectrometer, 70 eV. – Liquid chromatography: Microcrystalline triacetylcellulose (particle sizes 0.03 to 0.06 mm) as described in ref.[7]. – Racemizations: Perkin-Elmer 141 M polarimeter using 0.02 to 0.04 M solutions in acetone. Rates were measured by plotting the rotation angles at 365 nm *vs.* time during two half-lives. The racemizations turned out to be of the first order. Temperatures ($\Delta T = \pm 0.1$ °C) of the thermostated cell were read at its inlet and outlet and the mean values taken as actual temperatures. The evaluations of kinetic parameters (Table 2) were carried out with the program[8] KIN 3 on the CGK computer TR 440.

(+)- and (−)-(E,E)-2,3,4,5-Tetrabromo-2,4-hexadiene-1,6-diols (**1**): 300 mg of (±)-**1**[5] were conducted (flow rate 2.0 ml/min) through two columns of triacetylcellulose using the recycling technique[7]. Altogether, 4 column passages took place. Two early eluates and the first fraction of the final eluate contained 80 mg of (−)-**1a**, $[\alpha]_{589}^{20} = -29 \pm 4$ (2.48 g/l acetone), m.p. 99–100°C. The last fractions of the final eluate contained 120 mg of (+)-**1**, $[\alpha]_{589}^{20} = +24 \pm 4$ (4.80 g/l acetone), m.p. 98–99°C. The ^{1}H NMR spectra did not show any impurity. They had no suitable signals for the determination of the enantiomeric purity in the presence of an optically active auxiliary. Therefore, 35 mg of (−)-**1a** were injected again into one of the above columns. Chromatograms $A(v)$ and $\alpha(v)$ as well as an $\alpha(A)$ diagram resulted in an enantiomeric purity[9] of 29%.

(±)-(E,E)-2,3,4,5-Tetrabromo-1,6-dimethoxy-2,4-hexadiene (**2**): 3-Methoxypropyne[10] was coupled according to a general procedure[11] forming 1,6-dimethoxy-2,4-hexadiyne, which was brominated[12] with two equivalents of Br_2 in $CHCl_3$ at −10°C. The crude reaction product was chromatographed on silica gel (Merck, Fertigsäule), petroleum ether (40–60°C)/diethyl ether (2:1) serving as an eluent. The sample of **2** still contained a small amount (^{1}H NMR) of the above diyne and was therefore subjected to chromatography on triacetylcellulose, ethanol/H_2O (96:4) being the eluent. Slightly yellow oil. – ^{1}H NMR (CCl_4, 25°C): $\delta = 4.29$ and 4.38 (AB, $^2J = 13.3$ Hz, CH_2); 3.36 (s, CH_3). – MS: Molecular ions at $m/e = 454$, 456, 458, 460, and 462 with the relative intensities expected for the 4 bromine atoms in **2**.

	$C_8H_{10}Br_4O_2$ (457.8)	Calc.	C 20.99 H 2.20 Br 69.82
98% $C_8H_{10}Br_4O_2$ (457.8) + 2% $C_8H_{10}O_2$ (138.2)		Calc.	C 21.96 H 2.30 Br 68.42
		Found	C 21.87 H 2.37 Br 68.49

(+)- and (−)-(E,E)-2,3,4,5-Tetrabromo-1,6-dimethoxy-2,4-hexadienes (**2**): 100 mg of (±)-**2** were conducted (flow rate 2.2 ml/min) through two columns of triacetylcellulose. The early fractions contained the small amount of 1,6-dimethoxy-2,4-hexadiyne (from the (±)-**2** sample)

which was eluted first but could not be completely separated from (+)-**2**. The middle fractions contained 20 mg of (+)-**2**, $[\alpha]_{589}^{22} = +107$ (8.59 g/l CCl_4), the late fractions 30 mg of (−)-**2**, $[\alpha]_{589}^{22} = -106$ (8.25 g/l CCl_4). The ^1H NMR spectra showed no impurities. The sample with predominant (+)-**2** exhibited in the presence of 0.4 equivalents of (+)-tris(3-heptafluorobutyryl-D-camphorato)europium(III) (Regis Chemical Co., Morton Grove, Ill., USA) two methyl ^1H NMR signals: $\delta_{(+)} = 5.23$, linewidth 1.35 Hz, and $\delta_{(-)} = 5.21$, CCl_4, 25 °C, 90 MHz. As the two peaks overlapped partially, spectrum copies were repeatedly divided into the two components, which were cut out and weighed. The result was an enantiomeric purity $P = 80 \pm 2\%$ for the (+)-**2** sample. CD (n-hexane, 25 °C, calc. for $P = 100\%$): $\lambda_{max} = 219$ nm ($\Delta\varepsilon = -32.1$ l cm^{-1} mol^{-1}), 229 (−30.0), 250 (−9.9).

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[12] An ionic bromination mechanism is assumed which results in the (*E,E*)-product. Cf. ref.[5].

[25/81]

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