The Enantiomers of *N*-Aryl-2-thioxo-4-oxazolidinones and *N*-Arylrhodanines. Investigation by Liquid Chromatography, Circular Dichroism and Thermal Racemization

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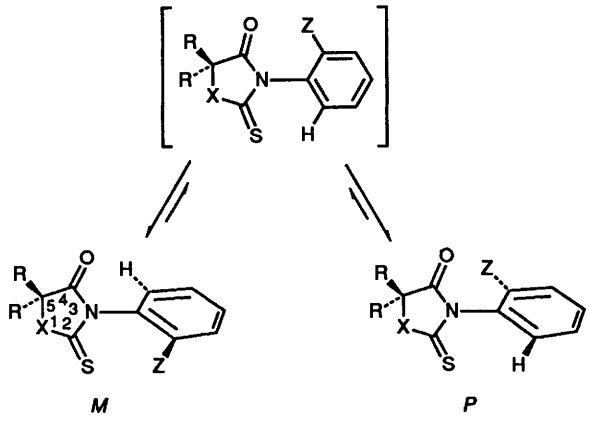
The enantiomers of the sterically hindered title heterobiaryls **1** and **2** have been investigated for the first time analytically and enriched semi-preparatively by liquid chromatography on triacetyl- and tribenzoylcellulose. The circular dichroism spectra of the enriched enantiomers provide relative configurations which are discussed with respect to the order of chromatographic elution. Barriers to rotation about the C–N bond have been determined (104–121 kJ mol^{-1}) and are rationalized qualitatively by repulsive interactions in a planar transition state traversed upon partial rotation.

Sterically hindered heterobiaryls, like simple biaryls, adopt non-planar ground states. This has been shown for several members of this class of compounds by the ^1H NMR signals of suitable groups in the molecules.[1–3] At higher temperatures, the coalescence of such signals is accomplished by rotation about the single bond connecting the two aryl fragments. In particular, our interest was attracted by some heterobiaryls for which Icli and his coworkers had given[3] barriers to rotation of more than 100 kJ mol^{-1}. They had been dealing with some 2-thioxo-4-oxazolidinones **1** (*cf.* Scheme 1, X = O) and rhodanines **2** (X = S). Consequently, enantiomers[4] *M* and *P* of such compounds



M *P*

	R	X	Z
1a	H	O	Me
1b	H	O	Cl
1c	Me	O	Me
2a	H	S	Me
2b	H	S	Cl
2c	Me	S	Me

Scheme 1

may be separated at room temperature. The barriers[3] estimated by ^1H NMR spectroscopy might then be measured precisely by thermal racemization of separated enantiomers and the factors contributing to their height might be revealed.

The separation of enantiomers has been accomplished by liquid chromatography on triacetylcellulose[5] (TAC) and tribenzoylcellulose[6] (TBC) for several other classes of heterobiaryls.[7–9] Therefore, the above mentioned aims of the present work should be attained best by using TAC and TBC for the necessary semi-preparative enrichment of the enantiomers. It was decided that, on this occasion, the relative configurations (helicities) of the separated enantiomers (Scheme 1) should also be determined in order to help rationalize their order of chromatographic elution.

Table 1 Chromatographic data referring to triacetylcellulose. Eluent: Ethanol–H_2O, 96:4 (v/v). Δp = 2.0–2.5 bar. $k_{(m)}$: capacity factors for compounds having relative helicities *m*. $k_{(p)}$: capacity factors for compounds having relative helicities *p*. Signs refer to polarimetric rotation at 365 nm. α': ratios of capacity factor of the more retained enantiomer and the one of the less retained enantiomer. $[\alpha_0]^{25}_{365}$: specific rotations [deg cm^3 g^{-1} dm^{-1}] of pure enantiomers in ethanol–H_2O, 96:4 (v/v).

	$k_{(m)}$	$k_{(p)}$	α'	$[\alpha_0]^{25}_{365}$
1a	$\bar{k}$ = 5.3[a]		≈1	448 ± 25
1b	5.3 (+)	6.5 (−)	1.2	63 ± 5
1c	1.3 (+)	1.6 (−)	1.3	470 ± 25
2a	3.9 (−)	4.6 (+)	1.2	440 ± 50
2b	3.6 (−)	4.9 (+)	1.4	267 ± 30
2c	1.2 (−)	1.1 (+)	1.1	1000 ± 270

[a] (−)-**1a** is eluted first.

Results and Discussion

Liquid Chromatography.—The enantioselectivities α' on the sorbents TAC (Table 1) and TBC (Table 2) depend upon the structures of the substrates. Thus, the *o*-chloro substituted derivatives **1b** and **2b** were slightly better resolved than the corresponding *o*-methyl compounds **1a** and **2a**. The sterically more crowded compounds (R = Me) **1c** and **2c** were much less retained than the ones with R = H. Fig. 1 shows this effect by comparison of the capacity factors of **2a** and **2c** on TAC at 40 bar.† These results are consistent with previous explanations[10] of the influence of analyte structure upon retention on TAC. In the case of TBC (Table 2), this behaviour resulted in an almost complete loss of selectivity for **1c** and **2c**.

Except for **1a**, the enantiomers were enriched semi-preparatively on TAC. For **1a**, TBC and ethanol–H_2O, 96:4, had to be chosen as sorbent and eluent. Methanol could not be used because it seemed to partly form the hemiacetal on the carbonyl group of **1a**. This was concluded from an experiment in which (±)-**1a** in methanol was kept at 20 °C for 3 h, the solvent

† 1 bar = 10^5 Pa.

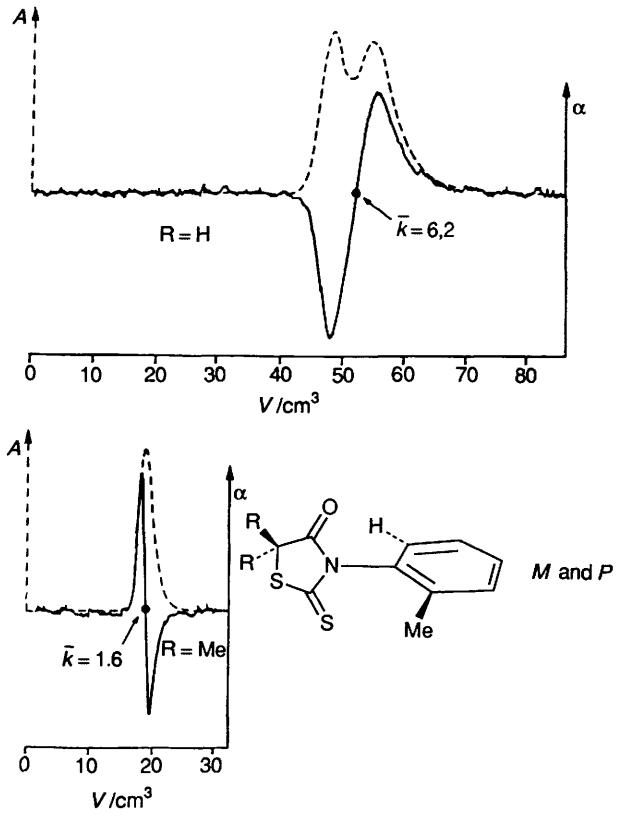


Fig. 1 Influence of substitution of the rhodanine ring upon the mean capacity factor $\bar{k}$ and upon the separation of enantiomers on TAC. A: absorbance at 278 nm. α: rotation angle at 365 nm. V: elution volume (injection at $V = 0$ cm^3). Eluent ethanol–H_2O, 96:4 (v/v). Flow rate 0.5 cm^3 min^{-1}. Pressure 40 bar. Top: 0.45 mg of (±)-**2a**. Bottom: 0.18 mg of (±)-**2c**.

Table 2 Chromatographic data referring to tribenzoylcellulose. Eluent: Methanol. $\Delta p \approx 60$ bar. Compounds **1a**, **1b**, **2a** and **2b** react partially with methanol to give hemiketals (identified by ^{1}H NMR spectroscopy) which are eluted at $k \approx 1.3$. $k_{(m)}$: capacity factors for compounds having relative helicities *m*. $k_{(p)}$: capacity factors for compounds having relative helicities *p*. Signs refer to polarimetric rotation at 365 nm. α': ratios of capacity factor of the more retained enantiomer and the one of the less retained enantiomer.

	$k_{(m)}$	$k_{(p)}$	α'
1a	3.3 (+)	3.7 (−)	1.1
1b	2.8 (+)	3.7 (−)	1.3
1c	$\bar{k} = 1.8$[a]		≈1
2a	3.9 (−)	4.6 (+)	1.2
2b	3.4 (−)	4.5 (+)	1.3
2c	$\bar{k} = 2.8$[b]		≈1

[a] (−)-**1c** is eluted first. [b] (+)-**2c** is eluted first.

evaporated, and a ^{1}H NMR spectrum of the residue taken. No such reaction was observed with ethanol under these conditions, after longer times, and at elevated temperatures.

Circular Dichroism and Configuration.—When proceeding from the above relative comparisons of capacity factors to absolute ones, it becomes clear that within Table 1 and within Table 2 only the *k*-values of the enantiomers with the same configuration (helicity) can be compared. This necessity has been stressed also by Roussel and his coworkers for a different class of compounds.[9] Although polarimetric detection of chromatography was useful in the present work, the signs of

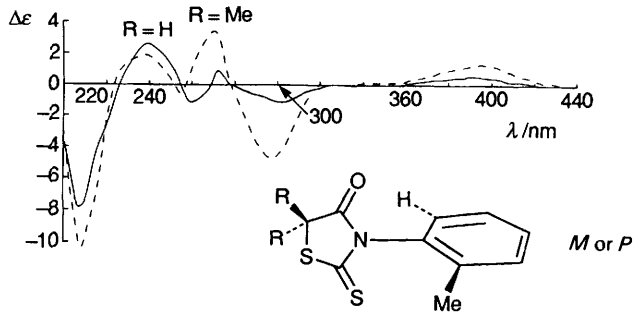


Fig. 2 Circular dichrograms of 0.27 mmol l^{-1} of (−)-**2a** (R = H) and (−)-**2c** (R = Me) in acetonitrile at 22 °C, corrected for enantiomeric purities of 1. (The above signs refer to polarimetric rotation at 365 nm.) Δε in 1 mol^{-1} cm^{-1}. Spectra are smoothed.

rotation in Tables 1 and 2 and the specific rotations (*cf.* Table 1) do not solve the above problem. Therefore, circular dichroism spectra, *e.g.* Fig. 2, of the separated enantiomers were determined and the corresponding maxima are listed in Table 3 for one of the enantiomers. The data of the enantiomers which are not given agree semi-quantitatively with the ones in Fig. 2 and Table 3, although those materials mostly contained traces of TAC.

The maxima in Table 3 are self-consistent, particularly with respect to the signs of the $\Delta\varepsilon_{max}$-values. It is concluded that the (+)-enantiomers, *i.e.* the dextrarotatory ones, of oxazolidinones **1** have the same relative helicity as the (−)-rhodanines **2**. When these stereostructural results are introduced into Tables 1 and 2, it turns out that the order of elution does not correspond to the relative helicity. This finding supports the hypothesis[10,11] that TAC contains unequal 'sites' for the sorption of analyte molecules. Apparently, this is also true for TBC. Two molecules which are compared with respect to their retentions may or may not use the same 'site' of such a multifunctional sorbent.

Barriers to Rotation.—The free enthalpies of activation (Table 4) for thermal enantiomerization may be compared semi-quantitatively with one another despite unequal temperatures of racemization.

The *o*-chloro derivatives **1b** and **2b** show barriers which are *ca.* 6–7 kJ mol^{-1} higher than the ones of the corresponding *o*-methyl derivatives **1a** and **2a**. The van der Waals radius for chlorine is smaller than the one for the methyl group.[12] Therefore, this difference in barriers is not expected from a consideration of the relative sizes in the planar transition states (Scheme 1, Z = Me, Cl) of partial rotation about the C–N bond. Dipolar repulsion between the oxygen and chlorine atoms apparently increases the free enthalpy of the transition state of **1b** and **2b** relative to the one of the methyl derivatives **1a** and **2a**, thus causing larger barriers. Similar results had been observed for arylhydantoins[2] and arylquinolones.[8]

The barriers of 2-thioxo-4-oxazolidinones **1** (Scheme 1, X = O), are lower by 8–11 kJ mol^{-1} than the ones of rhodanines **2** (X = S). We interpret this difference by means of the standard lengths[13] of the O–C (143 pm) and S–C (182 pm) bonds. Therefore, in the transition states of rotation (Scheme 1) the repulsive interaction between the thiocarbonyl sulfur atom and the *ortho*-proton of the aryl ring will increase upon replacement of the ring oxygen atom by sulfur. Similar observations were made in a DNMR study[14] concerning the effect of the ring element X (X = O, S) on the barriers of arylazolinethiones.

The above discussion has been based on a transition state in which the more bulky hindering groups S and Z are far from each other (Scheme 1). Although calculations of corresponding energies have not been performed, the alternative transition

Table 3 Circular dichroism data in acetonitrile at 22 °C. Signs of polarimetric rotation refer to 365 nm. λ_{max} in nm. $\Delta\varepsilon_{max}$ in 1 mol^{-1} cm^{-1} refers to an enantiomeric purity of 1.

	R	X	Z	λ_{max} ($\Delta\varepsilon_{max}$)					
(+)-**1a**	H	O	Me		234 (+3.0)	260 (−2.3)			330 (+0.4)
(+)-**1b**	H	O	Cl	219 (−4.0)	239 (+3.0)	264 (−1.2)			332 (+0.3)
(+)-**1c**	Me	O	Me		240 (+8.3)	262 (−10.5)			336 (+1.8)
(−)-**2a**	H	S	Me	208 (−7.8)	240 (+2.6)	259 (−1.1)	272 (+0.9)	300 (−1.1)	389 (+0.6)
(−)-**2b**	H	S	Cl	213 (−6.0)	251 (+0.8)	263 (−0.1)	274 (+0.9)	296 (−1.2)	390 (+0.3)
(−)-**2c**	Me	S	Me	209 (−10.2)	238 (+1.9)	254 (−0.5)	270 (+3.4)	298 (−4.7)	394 (+1.3)

Table 4 Results of thermal racemizations in diglyme, monitored by polarimetry at 365 or 436 nm

	R	X	Z	$\Delta G^{\ddagger}$/kJ mol^{-1}	T/°C	$t_{0.5}$/min
1a	H	O	Me	103.8 ± 0.2	55.7	26.0
1b	H	O	Cl	110.3 ± 0.2	67.3	67.1
1c	Me	O	Me	104.3 ± 0.2	57.6	25.0
2a	H	S	Me	114.4 ± 0.2	75.4	110.6
2b	H	S	Cl	121.2 ± 0.3	114.5	15.5
2c	Me	S	Me	112.6 ± 0.2	78.0	45.0

Table 5 Enantiomeric purities P, melting points, and specific rotations [deg cm^3 g^{-1} dm^{-1}] in ethanol–H_2O, 96:4 (v/v), not corrected for P. Semi-preparative separations were accomplished at Δp = 2–3 bar on TBC for (±)-**1a** and on TAC for the other compounds, using ethanol–H_2O, 96:4 (v/v) in all cases.

	P	$[\alpha]_{365}^{25}$	m.p./°C
(+)-**1a**	0.99[a]	+443 ± 22	
(−)-**1a**	0.47[b]	−211 ± 11	
(+)-**1b**	1.0[c]	+63 ± 5	
(−)-**1b**	> *ca.* 0.75[d]	−45 ± 4	
(+)-**1c**	0.94[e]	+441 ± 24	104
(−)-**1c**	0.86[e]	−420 ± 20	103
(+)-**2a**	0.94[e]	+390 ± 40	
(−)-**2a**	1.0[c]	−440 ± 50	
(+)-**2b**	0.99[c]	+265 ± 30	
(−)-**2b**	1.0[c]	−267 ± 30	112–113
(+)-**2c**	0.98[f]	+980 ± 270	77–81
(−)-**2c**	0.71[f]	−680 ± 130	71–76

[a] Base-line separation by HPLC on TBC. [b] Computer decomposition[17] of the UV peaks obtained by HPLC on TBC. [c] Base-line separation by HPLC on TAC. [d] ^{1}H NMR spectroscopy in the presence of (+)-1-(9-anthryl)-2,2,2-trifluoroethanol showed only one signal for the C-5 methylene protons. Upon warming the solution in order to effect racemization, two signals were obtained, however without a base-line separation. [e] UV peaks obtained by HPLC on TAC; decomposition by hand, followed by cutting and weighing. [f] Computer decomposition[17] of the UV peaks obtained by HPLC on (+)-poly(trityl methacrylate)/SiO_2 using hexane/propan-2-ol as an eluent.

state is thought not to contribute. In this state, the more bulky hindering groups S and Z would be close to each other and would give rise to an additional repulsive interaction.

Experimental

Apparatus.—The liquid chromatography systems have been previously described.[15] ^{1}H NMR spectra were recorded on a Bruker WM 250 spectrometer (PFT mode, 32 K data points, 250 MHz). Circular dichroism spectra were measured on an ISA CD6 instrument using 0.2–1.0 cm quartz cells. The dichrograms were monitored by the software of the instrument and plotted using a HP plotter. A Perkin-Elmer 241 polarimeter served for the measurement of rotation angles. Melting points were determined on a Büchi 510 apparatus.

Racemates.—The preparation and the characterization, including the UV spectra, are described elsewhere.[16]

Chemical Purity of the Enantiomers.—All enantiomers were obtained as solids. Their chemical purity was checked by ^{1}H NMR spectroscopy. Except for **1a**, **1c**, and **2c** (which were eluted relatively rapidly, see Tables 1 and 2), the enantiomers were found to contain trace amounts of the column material TAC.

Enantiomeric Purity.—The determination of enantiomeric purities P by computer decomposition[17] of the UV-detected HPLC peaks was not possible (apart from the enantiomers of **1a** and **2c**) due to weak polarimetric detections. ^{1}H NMR spectroscopy in the presence of (+)-1-(9-anthryl)-2,2,2-trifluoroethanol (Ega-Chemie) could only be used to put a lower limit to P where appropriate because no baseline separations of signals of the enantiomers were obtained.[16] Determination of P was otherwise done by decomposing the partially overlapped UV-detected chromatographic peaks by hand, then cutting and weighing the corresponding pieces of paper. From the P-values and the specific rotations (Table 5), the specific rotations of the pure enantiomers (Table 1) were calculated.

Racemization.—Experiments up to 80 °C were done in a thermostatted cell of the polarimeter. In case of slower kinetics, racemization was carried out in a flask kept in a constant temperature oil bath. Samples were removed at certain time intervals, racemization was quenched in an ice bath, and the rotation angle was measured at 24–26 °C. First-order kinetics were followed for at least two half-lives until the angle was close to zero. The barriers to rotation were obtained by use of a personal computer program.[18]

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