Chromatographic enantiomer separation and circular dichroism spectra of chiral rhodanines

Knut Rang,[a] Roland Isaksson[b] and Jan Sandström *,[a]

[a] *Division of Organic Chemistry 1, Chemical Center, University of Lund, PO Box 124, S-221 00 Lund, Sweden*

[b] *Department of Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, PO Box 574, S-751 23 Uppsala, Sweden*

Rhodanines [2-thioxo-2,3-dihydro-1,3-thiazol-4(5*H*)-ones] with isopropyl, *sec*-butyl and neopentyl substituents in position 3 and methyl and phenyl substituents in position 5 have been resolved into enantiomers by chromatography on microcrystalline, swollen triacetylcellulose. While the 5-methyl compounds showed good optical stability, the 5-phenyl analogues underwent racemization in ethanol solution with half-lives of 1–2 h at ambient temperature and were therefore resolved at −3 °C.

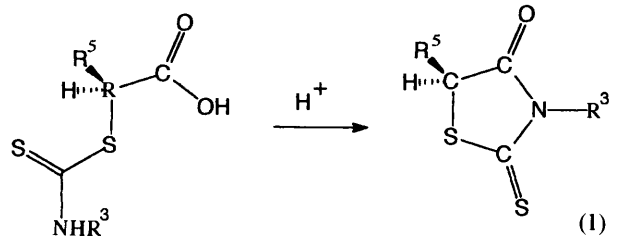
The UV spectra resemble those of *N*-acetyldithiocarbamates but with hypsochromic shifts because of the inclusion of the chromophore in a five-membered ring. Transition energies and absorption intensities were reasonably well reproduced by CNDO/S calculations.

The CD spectra showed bands corresponding to the UV bands but also another band at *ca.* 260 nm, which may be ascribed to an n→π* transition located in the carbonyl group. The absolute configurations of the 5-methyl compounds were assigned on the basis of the signs of the n→π* bands, using Ripperger's quadrant rule for dithiocarbamates. The mechanisms for generation of rotational strengths in the 5-phenyl compounds are more complex and no safe assignments of absolute configurations could be made.

The CD spectrum of 3-neopentyl-5-methylrhodanine in ethanol was found to be insensitive to the temperature from ambient to −97 °C, indicating a 1:1 equilibrium between the *anti* and *syn* forms, whereas the 5-phenyl analogue showed a considerable temperature dependence, indicating a more biased equilibrium.

Introduction

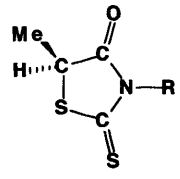
It has been observed[1–3] that cyclization of optically active α-substituted carboxymethyl dithiocarbamates leads to racemic 5-substituted rhodanines [2-thioxo-2,3-dihydro-1,3-thiazol-4(5*H*)-ones] [reaction (1)]. Since the reaction medium in



(1)

general contains an excess of acid, racemization *via* acid-catalysed enolization is a feasible mechanism. In order to study the configurational stability of the chiral centre in position 5 of rhodanine, we have prepared a number of chiral rhodanines and resolved them into enantiomers by column chromatography with swollen microcrystalline triacetylcellulose (TAC)[4] as the stationary phase. We have also recorded the CD spectra of the enantiomers in order to study the electronic transitions in the *N*-acyldithiocarbamate chromophore in the rhodanine ring and to try to determine the absolute configurations of the enantiomers. Chromatographic enantiomer separation and the CD spectra of 3-(*o*-substituted aryl)rhodanines, owing their chirality to hindered rotation of the 3-aryl group, have previously been reported by Dogan *et al.*[5]

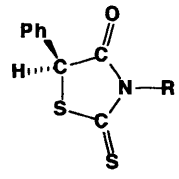
This study deals with 5-methyl- **1** and 5-phenyl-rhodanines **2** with isopropyl, isobutyl or neopentyl substituents in position 3. In previous studies we have determined the crystal structure of



1a R = $CHMe_2$

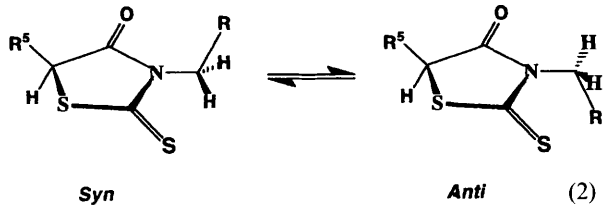
b R = CH_2CHMe_2

c R = CH_2CMe_3



2 a–c as for 1

2a.[6] NMR spectroscopic[7] and empirical force field studies[8] have shown that compounds **1b**, **1c**, **2b** and **2c** exist as mixtures of *syn* and *anti* forms [equilibrium (2)], the first two compounds in a 1:1 equilibrium, the other two in biased equilibria, in which the *syn* form dominates owing to the steric attraction between the 3-alkyl and 5-phenyl groups.



Syn *Anti* (2)

Experimental

Preparation

The preparation of compounds **1a–c** and **2a–c** has been described previously.[6,7]

Chromatography

The chromatographic resolutions of **1a–c** were performed with the equipment described by Isaksson and Roschester.[9] The same equipment was used for **2a–c** with the modification that the glass column was replaced by a steel column (CONBRIO-TAC, 15–25 μm particles, Perstorp Biolytica AB, Lund, Sweden)[10] provided with a jacket, through which ethanol at −3 °C from a thermostat was circulated. In each run 1 ml of a bulk solution (*ca.* 2% of a sample in absolute ethanol) was injected with a Rheodyne 7010 loop-valve injector equipped with a 1 ml loop. The flow rate was 1 ml min^{-1} with absolute ethanol as the mobile phase. 1,3,5-Tri-*tert*-butylbenzene was used to determine the non-retained volume (V_o). Capacity and selectivity factors (k_i and α', Table 1) were calculated by standard methods. The eluted fractions were collected in receivers cooled with dry ice–ethanol. The half-life for racemization of the 5-phenyl compounds **2** in ethanol solution at ambient temperature was found to be 1–2 h, while the 5-methyl analogues **1** were stable for at least 24 h.

Spectroscopy

UV spectra were recorded on Cary Model 219 and 2290 spectrometers and CD spectra on JASCO Model J-41A and J-500A spectropolarimeters. The first eluted fractions from the chromatographic enantiomer separations were used directly for recording of the CD spectra. Their concentrations were monitored by UV spectroscopy. The temperature dependencies of the CD spectra of **1c** and **2c** were studied with the equipment previously described.[11]

Calculations

The CNDO/S calculation on 3-methylrhodanine was performed with a program specifically parametrized for sulfur compounds[12] with the geometry taken from the crystal structure of **2a**.[6] The data presented in Table 2 were obtained from the interactions between 20 singly excited states, without d orbitals and with the two-centre coulomb integrals calculated by the Nishimoto–Mataga method.[13] Inclusion of a larger number of configurations and/or d orbitals gave rather similar transition energies and oscillator strengths, but the analysis of the data in terms of transitions between single MOs became more complicated.

The calculation of rotational strengths was performed by the matrix method developed by Schellman and co-workers.[14,15] The input consisting of the energies, transition moments and transition charge densities for the benzene ^1L_a[16] and the first rhodanine π→π* transition was obtained from experimental UV spectra and CNDO/S calculations as previously described.[17]

Table 1 Capacity and selectivity factors for the chromatographic enantiomer separation of compounds **1a–c** (in 95% ethanol) and **2a–c** (in absolute ethanol) on triacetylcellulose

Compound	k_1	k_2	α'	Sign of $[\alpha]_{365}$ of first eluted enantiomer
1a	2.12	2.44	1.15	(−)
1b	1.94	2.29	1.18	(+)
1c	1.62	1.82	1.14	(−)
2a	1.48	1.70	1.15	(+)
2b	1.55	1.75	1.13	(−)
2c	1.09	1.23	1.13	(+)

Results and discussion

The chromatographic resolutions of the six rhodanines **1a–c** and **2a–c** gave rather similar results (Table 1). Recycling gave higher enantiomeric purity of compounds **1**, whereas compounds **2** showed signs of racemization on repeated chromatography. They were therefore chromatographed only once on a cooled column. Unfortunately no splitting of ^1H NMR signals of the racemic compounds was observed in the presence of chiral shift reagents such as Eu(hfbc)$_3$[18–20] or the 'Pirkle's alcohol', 2,2,2-trifluoro-1-(9-anthryl)ethanol,[21] and therefore no enantiomeric excess (ee) values could be determined. The Δε values given in Table 3 are lower limits, and only the relative values for each compound are reliable.

The UV spectra of all six compounds (Table 2) are rather similar with an n→π* band at *ca.* 390 nm and strong π→π* bands at *ca.* 295 and 260 nm. The n→π* band is *ca.* 20 times more intense for compounds **2** than for compounds **1** and occurs at 13 nm longer wavelength. This effect can be ascribed to the overlap between the lone pair orbital on the thiocarbonyl sulfur atom and the π orbitals in the phenyl ring, which, at least in the crystal,[6,8] is nearly perpendicular to the rhodanine ring. This raises the energy of the lone pair orbital and gives the resulting transition a non-negligible transition moment. Similar effects have been observed for β,γ-unsaturated carbonyl compounds, although there the effects are more pronounced for the π→π* transitions than for the n→π* transitions, since the double bond planes in the compounds studied[22] are far from perpendicular. All compounds show a shoulder at *ca.* 230 nm and compounds **1** also show a band at 205 nm. For compounds **2** the band at 205 nm is replaced by a stronger continuously

Table 2 Comparison of experimental UV spectra with transition energies and oscillator strengths (f) calculated by the CNDO/S method

Compound (solvent)	Experimental			Calculated		Assignment
	λ_{max}/nm	ε/dm^3 mol^{-1} cm^{-1}	f	λ_{max}/nm	f	
1b (A[a])	386	55				
(B[b])	394	54	0.002	513	0.000	n→π* (C=S)
				293	0.000	n→π* (C=O)
(A)	295	17 300				
(B)	295	16 800	0.200	276	0.264	π→π*
(A)	262	15 000				
(B)	260	14 000	0.167	213	0.086	π→π*
(A)	230	5 000(S[c])				
(A)	205	10 900	0.155	195	0.055	π→π*
2c (A)	399	1 090				
(A)	297	16 600				
(A)	264	11 800				
(A)	230	5 500(S)				
3[17] (C[d])	410	49				
	308	10 200				
	266	10 500				

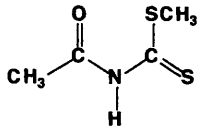
[a] Ethanol (95%). [b] Cyclohexane–dichloromethane (98:2). [c] Shoulder. [d] Heptane.

Table 3 CD spectra of the first eluted enantiomers of compounds **1a–c** and **2a–c**

Compound	Solvent	λ_{max}/nm ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1})
1a	95% ethanol	388 (−0.71), 291 (+2.02), 257 (−1.55), 232 (+1.83)
1b	95% ethanol	387 (−0.23), 296 (+0.67), 271 (+0.74), 253 (−0.69), 230 (+0.34)
1c	95% ethanol	397 (−0.28), 294 (+0.92), 271 (+1.01), 253 (−0.77), 231 (+0.70)
2a	Abs. ethanol	393 (+0.49), 297 (−1.04), 273 (+2.94), 253 (−2.18), 227(S) (−1.71), 210 (+1.5)
2b	Abs. ethanol	389 (−1.11), 298 (+2.46), 270 (−4.68), 246 (+3.57), 213 (−3.57)
2c	Abs. ethanol	390 (+1.40), 296 (−4.43), 270 (+5.42), 242 (−7.16), 210 (+3.45)

increasing absorption without a discernible maximum down to 195 nm. This effect is probably due to the overlap of the ^1L_a and ^1B_b bands of the benzene ring.

The chromophore of the rhodanine ring is an *N*-acyldithiocarbamate moiety modified by the constraints of the five-membered ring. Absorption bands corresponding to those mentioned above, but at slightly longer wavelengths, are found for the acyclic analogue methyl *N*-acetyldithiocarbamate **3**



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(Table 2).[23] The hypsochromic effect of inclusion of similar chromophores in five-membered rings has earlier been observed in a comparison of the UV spectra of mono- and di-thioglutarimides and -thiosuccinimides[24] and has also been reproduced by CNDO/S calculations.[25] Similar calculations have been performed for 3-methylrhodanine (Table 2). An n→π* transition is predicted at 513 nm corresponding to the experimental band at 390 nm. This transition is mainly located in the thiocarbonyl group. A second n→π* transition predicted at 293 nm is located in the carbonyl group, and its experimental counterpart is hidden under a strong π→π* band in this region. Three stronger π→π* bands with decreasing intensities are predicted at 276, 213 and 195 nm, corresponding to the experimental bands at 295, 260 and 230 or 205 nm, also with the intensities decreasing in this sequence. For further discussion, the bands at 390, 295, 260, 230 and 205 nm are labelled 1, 2, 3, 4 and 5, respectively.

The first two bands in the CD spectra of compounds **1** (Table 3) coincide with the UV bands 1 and 2. Instead of band 3, two CD bands with opposite signs appear at 271–273 and 253 nm, respectively, for compounds **1b** and **1c**, whereas **1a** shows only one band close to the position of UV band 3 in this region. A CD band corresponding to the UV shoulder 4 is found for all compounds **1**, but no band corresponding to 5 is seen above 200 nm.

The rhodanine chromophore is in itself achiral and the appearance of CD bands is ascribed to the chiral centre at position 5. The 3-substituents do not contribute significantly to the chirality. The isopropyl group in **1a** is symmetric to the plane of the rhodanine ring,[6] and the 3-isobutyl and 3-neopentyl groups in **1b** and **1c**, although perpendicular to the ring plane, appear with very similar populations in the *syn* and *anti* forms,[7,8] and their contributions must largely cancel. Besides, these groups have components on both sides of the rhodanine plane, and it is not clear which of them is the most efficient perturber. A solvent effect on the equilibria of **1b** and **1c** cannot be excluded, but does not seem to affect the CD spectra, since these are similar in sign and intensity in ethanol and hexane solution. Furthermore, the spectrum of **1c** has been shown to be temperature-independent (*vide infra*).

The appearance of two bands in the region 275–250 nm may be due to the presence of one allowed π→π* transition and a close-lying forbidden n→π* transition in this region, possibly the one predicted by the CNDO/S calculation to lie at 293 nm and be located in the carbonyl group (Table 2). Owing to their near-degeneracy, two such transitions should give rise to significant CD bands of opposite signs in the one-electron mechanism.[26,27] The positions of the unperturbed transitions are probably both close to 260 nm.

Ripperger[28] has suggested a quadrant rule for the sign of the n→π* band of dithiocarbamate anions and alkyl dithiocarbamates based on the nodal properties of the sulfur lone pair and lowest π* orbitals. Since the CNDO/S calculation predicts the n→π* transition in the rhodanines to be largely located in the S–C(=S)–N moiety, Ripperger's arguments can be shown to be valid for compounds **1** as well. According to his rule, the (*R*)-5-methylrhodanines **1** should have positive n→π* bands, *i.e.* the *S* enantiomers should be eluted first.

The CD spectra of the 5-phenyl analogues **2** are rather similar to those of compounds **1** with the exception of the appearance of a distinct band at *ca.* 210 nm, which is assigned to the ^1L_a transition in the phenyl ring. The band at 242 nm is quite broad and probably contains the bands corresponding to those observed at 253 and 230 nm in the spectra of compounds **1**. Note that the CD spectra of the 3-(*o*-substituted aryl)rhodanines are rather similar to those of compounds **2** with respect to the positions and intensities of the bands.[5]

Compounds **2**, containing two chirally disposed planar chromophores, have access to the coupled oscillator mechanism for creating rotational strength. In favourable cases, interaction between two strong chirally disposed transitions may give rise to a strong couplet, the sign of which allows the determination of the absolute configuration, provided the directions of the transition moments are known.[29,30] In the present case, the benzene ^1L_a transition and the first π→π* transition are candidates for such an interaction. However, a calculation of the CD spectrum of (*S*)-**2** predicts a positive couplet, with $\Delta\varepsilon \approx \pm 1$ dm^3 mol^{-1} cm^{-1}, so weak that the observed bands must owe a significant part of their intensity to other mechanisms. This is borne out by the temperature-dependent CD spectrum of **2c** (*vide infra*), in which $\Delta\varepsilon$ for band 2 changes from −3.7 to −6.1 dm^3 mol^{-1} cm^{-1} in the temperature range −4 to −98 °C. This large change must be due to a shift in the *syn–anti* equilibrium, indicating that the one-electron mechanism must be important.

The equilibrium constant for the *syn–anti* equilibrium is close to unity for compounds **1b** and **1c**, but for compounds **2b** and **2c** the *syn* form dominates owing to steric attraction between the phenyl and alkyl groups.[8] In order to study the effect of the conformational equilibrium on the CD spectra, the spectra of the 3-neopentyl compounds **1c** and **2c** were recorded in absolute ethanol solution at temperatures between −3.5 and −98 °C. While the spectrum of **1c** was found to be practically insensitive to the temperature, the spectrum of **2c** showed a considerable sensitivity (Fig. 1). The spectra evidently pass through a number of isosbestic points, which is a clear indication of the existence of only two conformers in equilibrium in significant concentrations. Band 1 clearly consists of one band for each conformer, centred at 380 and 390 nm, respectively. The former increases and the latter decreases in intensity with decreasing temperature. Band 2 increases strongly in (negative) intensity, whereas bands 3 and 4 show little sensitivity.

It has been shown[31–33] that temperature-dependent intensive properties (*e.g.* $\Delta\varepsilon$, [α]) of compounds capable of existing in two conformations can be analysed to give both the

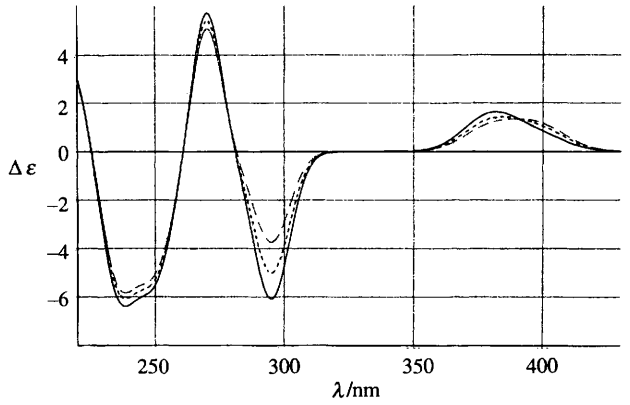

Fig. 1 CD spectra of **2c** in absolute ethanol at −3.5 °C (- - - -), −60 °C (· · · ·) and −98.3 °C (—)

magnitudes of the properties of the individual conformers and their free energy difference $\Delta G°$. The conditions are that the property value for each individual conformer and $\Delta G°$ are temperature-independent. Plotting of the experimental property values against $[1 + \exp(-\Delta G°/RT)]^{-1}$ calculated at each temperature for a selection of $\Delta G°$ values gives a set of curves, the one with the correct value of $\Delta G°$ being a straight line.[17] Application of this technique to the $\Delta\varepsilon$ values of band 2 for **2c** gave $\Delta G° \approx 2.5$ kJ mol^{-1}, in good agreement with the value from NMR spectroscopy[7] and MM2[8] calculations. Unfortunately, the analysis of the CD spectra gives no clue either to the absolute configuration or to the conformation, *syn* or *anti*, of the most stable conformer. The $\Delta\varepsilon$(major) and $\Delta\varepsilon$(minor) values for band 2 were obtained as −24.6 and +14.8 dm^3 mol^{-1} cm^{-1}.

Conclusions

This study shows that 5-alkylrhodanines **1** are optically stable in neutral solvents, whereas the 5-phenyl analogues **2** are more labile and cannot readily be stored in an optically active form in solution. This difference is in the direction expected for the influence of the 5-substituents on the rate of enolization.

The transitions observed in UV and CD spectra agree well with the results of a CNDO/S calculation, and application of a sector rule for the n→π* transition allows assignment of the absolute configuration of the 5-alkylrhodanines. Analysis of the temperature dependence of the CD spectra of **1c** and **2c** gives information about the equilibrium state of the conformational equilibria, but allows no identification of the stable conformer of **2c**.

Acknowledgements

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References

1 S. Kallenberg, *Ber. Dtsch. Chem. Ges.*, 1917, **50**, 90.
2 S. Kallenberg, *Rodaninernas och Ditiokarbaminsyrornas stereokemi*, Diss, Lund, 1919.
3 J. Sandström, *Arkiv. Kemi*, 1955, **8**, 487.
4 A. Mannschreck, H. Koller and R. Wernicke, *Merck Kontakte*, 1985, **1**, 40 and refs. cited therein.
5 I. Dogan, N. Pustet and A. Mannschreck, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1557.
6 K. Rang, J. Sandström, L. Thell and Q. Yang, *Acta Chem. Scand., Ser. B*, 1985, **39**, 123.
7 I. Pettersson, K. Rang and J. Sandström, *Acta Chem. Scand., Ser. B*, 1986, **40**, 751.
8 K. Rang, F.-L. Liao, J. Sandström and S.-L. Wang, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1521.
9 R. Isaksson and J. Roschester, *J. Org. Chem.*, 1985, **50**, 2519.
10 R. Isaksson, P. Erlandsson, L. Hansson, A. Holmberg and S. Berner, *J. Chromatogr.*, 1990, **498**, 257.
11 J. Roschester, U. Berg, M. Pierrot and J. Sandström, *J. Am. Chem. Soc.*, 1987, **109**, 492.
12 C. Guimon, D. Gonbeau and G. Pfister-Guillouzo, *Tetrahedron*, 1973, **29**, 3399.
13 K. Nishimoto and N. Mataga, *Z. Phys. Chem.*, 1957, **12**, 335.
14 P. M. Bayley, E. B. Nielsen and J. A. Schellman, *J. Phys. Chem.*, 1969, **73**, 228.
15 V. Rizzo and J. A. Schellman, *Biopolymers*, 1984, **23**, 435.
16 J. R. Platt, *J. Chem. Phys.*, 1949, **17**, 484.
17 J. Sandström, in *Circular Dichroism: Interpretation and Applications*, eds. K. Nakanishi, N. Berova and R. B. Woody, VCH, New York, 1994, p. 443.
18 R. R. Fraser, M. A. Petit and J. K. Saunders, *J. Chem. Soc., Chem. Commun.*, 1971, 1450.
19 H. L. Goering, J. N. Eikenberry and G. S. Koermer, *J. Am. Chem. Soc.*, 1971, **93**, 5913.
20 G. M. Whitesides and D. W. Lewis, *J. Am. Chem. Soc.*, 1971, **93**, 5914.
21 W. H. Pirkle and D. J. Hoover, *Top. Stereochem.*, 1982, **13**, 263.
22 H. Labhart and G. Wagnière, *Helv. Chim. Acta*, 1959, **42**, 2219.
23 J. Sandström, *Acta Chem. Scand.*, 1963, **17**, 678.
24 U. Berg and J. Sandström, *Acta Chem. Scand.*, 1966, **20**, 689.
25 L. Fälth, U. Håkansson and J. Sandström, *J. Mol. Struct. (Theochem)*, 1989, **185**, 239.
26 E. U. Condon, W. Altar and H. Eyring, *J. Chem. Phys.*, 1937, **5**, 753.
27 J. A. Schellman, *Acc. Chem. Res.*, 1968, **1**, 144.
28 H. Ripperger, *Tetrahedron*, 1969, **25**, 725.
29 N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, 1969, **91**, 4555, 4556.
30 N. Harada and K. Nakanishi, *Circular Dichroic Spectroscopy – Exciton Coupling in Organic Stereochemistry*, Oxford University Press, Oxford, 1983.
31 W. W. Wood, W. Fickett and J. G. Kirkwood, *J. Chem. Phys.*, 1952, **20**, 561.
32 K. M. Wellman, W. S. Briggs and C. Djerassi, *J. Am. Chem. Soc.*, 1965, **87**, 73.
33 H. Joshua, R. Gans and K. Mislow, *J. Am. Chem. Soc.*, 1968, **90**, 4884.

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