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CONFORMATIONAL ANALYSIS OF N-(1-METHOXYCARBONYLETHYL)-Δ^4-THIAZOLINE-2-THIONES BY TEMPERATURE-DEPENDENT CIRCULAR DICHROISM AND NMR SPECTROSCOPY AND BY MOLECULAR MECHANICS CALCULATIONS

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Abstract

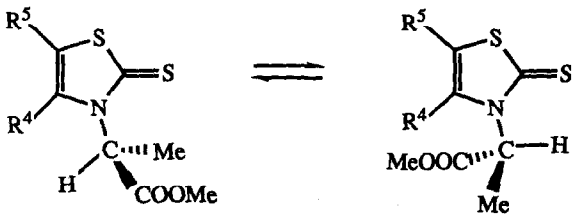
The conformations of seven N-(1-methoxycarbonylethyl)-Δ^4-thiazoline-2-thiones with S configuration of the chiral rotor have been studied by temperature-dependent NMR and CD spectroscopy, and for four compounds by molecular mechanics calculations. The *syn-anti* equilibria previously reported have been confirmed, and other conformational processes, involving low energy barriers, have been shown to be operating, involving rotation of the ester group in the chiral rotor. The dominance of the one-electron mechanism is creating rotational strength of the $n \rightarrow \pi^*$ and first $\pi \rightarrow \pi^*$ transition in the thiazolinethione ring is demonstrated by calculations, and the use of the Moscowitz (WFK) technique for calculating free energy differences from CD spectra recorded over a large temperature interval is discussed.

Introduction

We have initiated a series of studies, exploring the use of temperature-dependent circular dichroism (CD) spectra for conformational analysis of compounds containing a trigonal "chiral rotor", CHR^1R^2 ($R^1 \neq R^2$), attached to a planar chromophore. The rotor should also contain a chromophore to interact with the framework chromophore and create rotational strengths for the transitions in both chirally disposed chromophores. The structure of the rotor is such that it gives rise to two main conformers (syn and anti) in its interaction with the planar framework. Previous studies in this series have treated 1- and 3-(1-phenylethyl)-indoles[1,2] and N-(1-phenylethyl)-Δ^4-thiazoline-2-thiones.[3] The indoles showed the expected syn-anti equilibria, which were observed by CD spectroscopy even when the barriers were too low to permit the observation of individual rotamers by low-temperature NMR spectroscopy, and in some cases finer details in the conformational behaviour could be observed. The thiazolinethiones were found to exist mainly in the anti form but still showed strongly temperature-dependent CD spectra, which was rationalized by an exchange between two conformers within the anti form.[3]

In the work presented here we will discuss the conformational behaviour of N-(1-methoxycarbonylethyl)-Δ^4-thiazoline-2-thiones 1-7 (Scheme 1), in which the chromophore (the ester group) in the chiral rotor is less symmetrical than the phenyl group. Therefore, its orientation may be expected to have a greater influence on the CD spectra.

Compounds 2-6 have earlier been studied by ^{1}H NMR spectroscopy[4] and found to display syn-anti equilibria similar to those observed for the N-isopropyl analogues,[5,6] with syn→anti barriers in the range 13.1 to 14.8 kcal/mol.



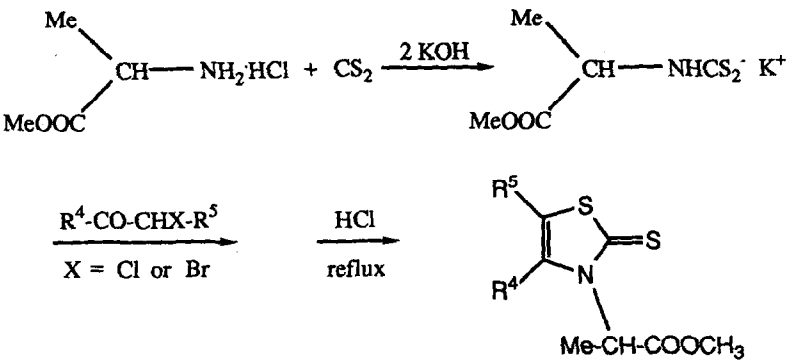
Syn Anti

	R^4					
R^5	H	Me	Et	*i*-Pr	*t*-Bu	Ph
H	1	2		3	4	
Me			5	6		7

Scheme 1

Experimental part

Preparations: Compounds **2** and **4** were prepared as described in Ref. 4, and the other by a modified method, starting from (S)-alanine methyl ester hydrochloride (Scheme 2).



Scheme 2

General procedure: (S)-Ala-OMe·HCl (0.036 mol) was suspended in MeOH (10 ml) and CS_2 (0.036 mol) was added followed by dropwise addition of KOH (0.072 mol) in MeOH (15 ml) under

cooling (+2 °C) and stirring, keeping pH < 9.0. The resulting slurry was used without further purification. The appropriate α-halocarbonyl compound (0.036 mol) was added dropwise with continued stirring and cooling, whereupon the reaction mixture was left for 2 h at room temperature. The solvent was evaporated and the residue shaken with water and ether. After evaporation of the ether phase, the residue was dissolved in MeOH or DMF, conc. HCl was added to give pH 2-3, and the mixture was refluxed. The formation of the product was monitored by the appearance of the strong UV band at ca. 320 nm. When the reaction was complete, the solvent was evaporated, and the residue was shaken with water and ether. The ether phase was dried with anhydrous $MgSO_4$ and evaporated, and the residue was purified by flash chromatography[7] and recrystallized (1 could not be brought to crystallization). The ^{1}H NMR spectra of these compounds are given in Table I. Esterification of the corresponding carboxylic acids with diazomethane was found to be a less convenient method, since some methylation of the thiocarbonyl sulfur atom occurred with formation of betaines.

(S)-N-(1-Methoxycarbonylethyl)-Δ^4-thiazoline-2-thione (1). Pale yellow oil; MS [IP 70 eV; m/e (% rel. intensity)]: 203 (100, M^+), 117 (86, M^+-$CH_3OCOCHCH_2$).

(S)-N-(1-Methoxycarbonylethyl)-4-phenyl-5-methyl-Δ^4-thiazoline-2-thione (7). Colourless prisms after recrystallization from toluene-MeOH (1:1, v/v), m.p. 142-144 °C. MS: 293 (66, M^+), 207 (70, M^+-$CH_3OCOCHCH_2$), 115 (100).

(S)-Ala-OMe·HCl was prepared according to Ref. 8. The α-halocarbonyl compounds were obtainned as described in Ref. 3. The optical purity of compounds 1-7 was ascertained by using chiral shift reagents in ^{1}H NMR experiments (Eu(hfbc)$_3$[9,10] or Pirkle's alcohol[11]). In some cases lower temperature (-20 to -50 °C) was necessary to obtain splitting of resonances of diastereotopic protons. The optical purity could also be estimated by analytical chromatography on a column of swollen microcrystalline triacetylcellulose.[12] All compounds used in this study were enantiomerically pure.

^{1}H NMR spectra were recorded with a Varian Model XL-300 and a Nicolet Model 360 WB, and UV spectra with Cary Models 118 and 119 spectrometers. Mass spectra are from a Finnigan Model 4021 mass spectrometer and melting points (uncorrected) from a Leitz microscope heating stage Model 350. CD spectra were recorded with a JASCO Model J 41-A spectrometer, and the temperature control was performed with the equipment described in Ref. 3. Correction for thermal contraction of methanol was made according to Passerini and Ross[13] and of EPA according to Korver and Bosma.[14]

Molecular Mechanics Calculations were performed on 1, 2, 4, and 5, using the MM2 force field in the 1985[15,16] version with the interactive computer graphics program MOLBUILD,[17] using a rigid thiazolinethione ring. For compounds 1 and 2, energy maps were calculated by "rigid rotations", implying summation of all energy contributions without energy minimization while varying the dihedral angles C4-N3-C9-C11[18] (the rotor angle, ϕ_1) and N3-C9-C11-O13 (the ester angle, ϕ_2) in steps of 10° (Fig. 1). The geometries of the energy minima of

Table I. Proton Chemical Shifts (δ)

compd	solvent	temp, °C	rotor			R^4	R^5
			CH	CH_3	methoxy		
1	$CDCl_3$	ambient	6.01 (q)	1.68 (d, 7.5 Hz)	3.78 (s)	7.20 (d, 4.9 Hz)	6.64 (d, 4.9 Hz)
2	CD_3OD	+31	5.81 [b] (broad)	1.701 [c] (d, 7.3 Hz)	3.739 [b] (s)	2.267 [a]	6.543 [a] (s)
		-60	5.113 [b] (q),	1.572 [c] (d, 7.4 Hz),	3.655 [b] (s),	2.200 [c] (s),	6.559 [c] (s),
			6.549 [c] (q)	1.719 [b] (d, 6.9 Hz)	3.756 [c] (s)	2.299 [b] (s)	6.586 [b] (s)
		-96	5.141 (q),	1.545 (d),	3.630 (s),	2.187 (s),	6.562 (s),
			6.530 (q)	1.691 (d)	3.747 (s)	2.291 (s)	6.589 (s)
3	CD_3OD	-70	5.247 [b] (q),	1.594 [c] (d, 7.5 Hz),	3.677 [b] (s),	2.866 [b] (m),	6.642 [b] (s),
			6.64 [c,d]	1.748 [b] (d, 6.8 Hz)	3.774 [c] (s)	2.61 [c] (m)	6.754 [c] (s)
						1.246 [e] (d, 6.6 Hz),	
						1.352 [e] (d, 6.6 Hz)	
5	CD_3OD	-70	5.131 [b] (q),	1.573 [c] (d, 7.6 Hz),	3.666 [b] (s),	1.131 [b] [f] (t), 1.184 [c] (t),	2.199 (s)
			6.656 [c] (q)	1.737 [b] (d, 6.8 Hz)	3.759 [c] (s)	2.665 [f]	
6	CD_3OD	-70	5.276 [c] (q),	1.705 [c] (d, 6.4 Hz),	3.657 [c,g] (s),	2.644 [b] (m),	2.289 [b] (s),
			5.206 [c] (q)	1.777 [c] (d, 6.4 Hz)	3.772 [b] (s)	3.05 [c] (m)	2.181 [c] (s)
			6.707 [b] (q)	1.557 [b] (d, 7.1 Hz)		1.354 [e] (d, 7.0 Hz),	
						1.284 [e] (d, 6.9 Hz)	
7	$CDCl_3$	ambient	4.95 (broad)	1.61 (d, 7.0 Hz)	3.71 (s)	7.5 [h]	1.99 (s)
	CD_3OD [3]	ambient	4.94 [b] (broad)	1.58 [c] (d, 7.1 Hz)	3.68 [c] (s)	7.37 [h] (2H), 7.56 (3H)	2.00 [c] (s)
		-70	4.557 [b] (q),	1.268 [c] (d, 7.2 Hz),	3.563 [b] (s),	7.5 [h]	1.992 [c] (s),
			6.042 [c] (q)	1.645 [b] (d, 6.8 Hz)	3.653 [b] (s)		2.038 [b]
	$(CD_3)_2O$	+24	4.95 [b] (broad)	1.559 [c] (d, 7.2 Hz)	3.604 [c] (s)	7.35 (2H), 7.48 (3H)	1.938 [c] (s)
		-95	4.523 [b] (q),	1.233 [c] (d, 7.3 Hz),	3.517 [c] (s),	7.41 (1H), 7.47 (1H),	1.886 [c] (s),
			ca 6.4 [c]	1.670 [b] (d, 6.9 Hz)	3.573 [b] (s)	7.57 (3H)	2.001 [b] (s)
		-128	4.593 [b]	1.238 [c], 1.704 [b]	3.501 [c],	7.46 (1H), 7.53 (1H),	1.896 [c], 2.021 [b]
					3.530 [b]	7.59 (3H)	

[a] Not resolved long-range coupling. [b] Major rotamer. [c] Minor rotamer. [d] Hidden under ring proton signal. [e] Signals of minor conformers are hidden in this area. [f] Center of AB part of an ABX_3 spectrum (4 quartets). [g] The signal of the second minor form is hidden here. [h] Aromatic protons centered around this value.

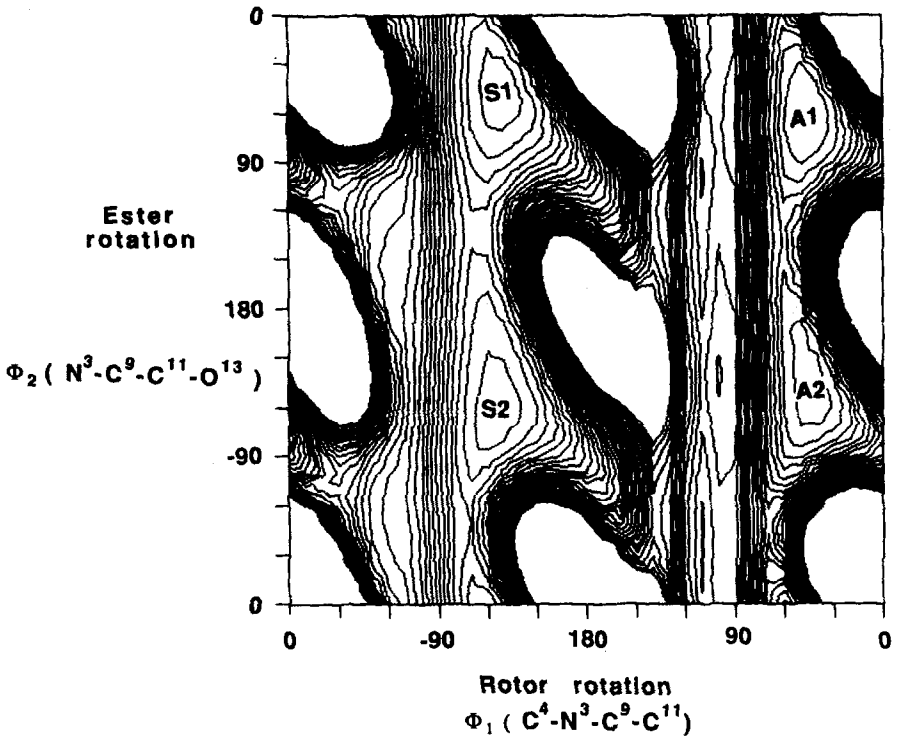


Figure 1. Rigid rotation map for 2. Energy equidistance is 2.0 kcal/mol.

Table II. Nonstandard Force-Field Parameters (Energies in kcal/mol)[a,b]

Torsional Parameters

$$E_t = \tfrac{1}{2}\,[V_1(1 + \cos(w)) + V_2(1-\cos(2w)) + V_3\,(1 + \cos(3w))]$$

angle type	V_1 (kcal mol^{-1})	V_2 (kcal mol^{-1})	V_3 (kcal mol^{-1})
N(sp^2)-C(sp^3)-C(sp^2,carbonyl)-O(methoxy)	0	0	-0.35

Bending Parameters

$$E_b = 0.021914\ k_B\ (\theta - \theta_0)^2[1 + C_f(\theta - \theta_0)^4];\ C_f = 0.007 \cdot 10^{-5}$$

angle type	θ_0 (degree)	k_B (mdyn Å rad^{-2})
C(sp^2,carbonyl)-C(sp^3)-N(sp^2)	109.47	0.42

[a] The motion of the atoms in the thiazoline ring has been restricted in all directions during minimization. [b] For additional nonstandard force-field parameters, see Ref.3.

the map were used as input for calculations with full energy minimization. The nonstandard force-field parameters not reported in Ref. 3 are found in Table II.

Theoretical CD spectra were calculated by using the matrix formalism developed by Schellman et al.[19,20] The computer program uses as input transition energies, magnitudes and directions of electric and magnetic transition moments, electric transition charge densities, transition quadrupoles of $n \rightarrow \pi^*$ transitions, and static charge densities (q). The program calculates contributions to the rotational strengths from three mechanisms: 1) the coupled oscillator mechanism,[21,22] 2) the magnetic-electric coupling (m-μ) mechanism,[23] and 3) the one-electron mechanism,[24] in which perturbation by chirally disposed static charges, q, "mixes" $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions in the same chromophore. The data used for the thiazolinethione chromophore are the same as those used in Ref. 3, but new parameters are needed for the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in the ester chromophore. The $\pi \rightarrow \pi^*$ transition in ethyl acetate has been observed by Nagakura et al.[25] to fall at 164 nm in the gas phase (ϵ = 3600). A similar gas → solution correction as reported for N,N-dimethylacetamide (2400 cm^{-1})[26] leads to λ_{max} = 170 nm for an ester in solution. With an assumed exponential halfwidth of 6 nm, μ = 1.43 D. The direction of the transition moment and the transition charge density (scaled to give μ = 1.43 D) were obtained by a CNDO/S calculation on methyl acetate, using configuration interaction with the 99 lowest singly excited states. The $n \rightarrow \pi^*$ transitions of simple esters fall in the range 208-210 nm in ethanol,[27] and the magnetic transition moment and quadropolar transition charges are calculated as in Ref. 3. The static charges were obtained from a CNDO/2 calculation on 1, and the charges on the methyl protons are mean values for each methyl group. The input data for the calculations are found in Table III. Since the rotational strengths for the ester $n \rightarrow \pi^*$ transitions are not discussed, the static charges used for the thiazolinethione ring are not reported.

The WFK method. If a system containing two components (1 and 2) in thermal equilibrium displays a measurable intensity parameter Q_m, which is the population-weighted sum of the temperature-independent values Q_1 and Q_2 of the two components, it is possible to evaluate Q_1, Q_2, and $|\Delta G^o_{12}| = |G^o_2 - G^o_1|$ from measurements of Q_m over a wide temperature range. The temperature dependence of Q_m reflects only the change in equilibrium constant, and eqn. 3 is obtained from eqns. 1 and 2. The correct $|\Delta G^o_{12}|$ value is the one which makes the

$$K = \frac{[2]}{[1]} = \frac{Q_1 - Q_m}{Q_m - Q_2} \qquad (1)$$

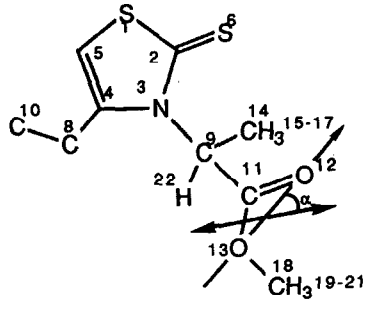
$$K = \exp(-\Delta G^o_{12}/RT) \qquad (2)$$

$$Q_m = (Q_1 - Q_2)[1 + \exp(-\Delta G^o_{12}/RT)]^{-1} + Q_2 \qquad (3)$$

Q_m - $[1 + \exp(-\Delta G^o_{12}/RT)]^{-1}$ relation linear, and then Q_1 and Q_2 are obtained from the slope and intercept of the line.

This technique was first proposed by Wood, Fickett, and Kirkwood,[28] hence its name, for use with temperature-dependent optical rotations. The precision of the method was

Table III. Input data for calculation of rotational strengths

Chromophore	Transition, direction	Energy (kK)	Trans moment E1 (D)	Trans moment Magn (β)[a]	Monopol. charges [b] Trans.	Monopol. charges [b] Static	Quadrupole Charge Y,Z (Å)[c]
	$\pi \rightarrow \pi^*$ $\alpha = 15.6^0$	58.60	1.43		11: -0.1178 12: +0.2018 13: -0.0840		
	$n \rightarrow \pi^*$	48.30		0.805		9: +0.0570 11: +0-5038 12: -0.4675 13: -0.2042 14: -0.0545 15-17: +0.0279 18: +0.0868 19-21: +0.0248 22: +0.0484	11: 0.0443(±0.479) 12: 0.2120(±0.328)

[a] β = Bohr magneton = $9.274 \cdot 10^{-21}$ erg/G = $9.274 \cdot 10^{-24}$ J T^{-1} (Am^2). [b] In units of electronic charge. [c] Local coordinate system, X-axis along C=O, O-C=O in xy plane.

critically studied by Joshua et al.,[29] who also employed optical rotations, and it has been used with NMR parameters[30,31] and CD spectra.[32,33] This latter application has become very popular in view of the often strong conformational dependence of CD spectra. A recent critical study has pointed out other sources of temperature dependence of CD spectra,[34] but these seem to apply mainly to rather weak spectra. In most cases, ΔG^{o}_{12} is assumed to be temperature-independent, which may not always be correct, but with very accurate Q_m and T values it is possible to evaluate also ΔH^{o}_{12} and ΔS^{o}_{12}.[29]

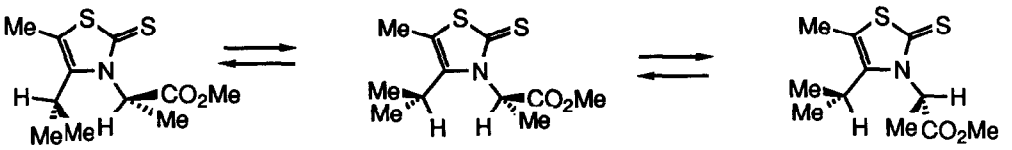
Results and discussion

The ^1H NMR spectra of **2**, **3**, and **5-7** have been recorded in CD_3OD down to -70° (Table I) and separate resonances were observed for the syn and anti forms. The derived ΔG^{o} values are found in Table IV. For **6**, two rotamers were observed within the syn form (Scheme 3), as previously observed for 3,4-diisopropyl-5-methylthiazoline-2-thione.[5] No splittings of the resonances of **1** and **4** have been observed in acetone-d_6 solution above -90 °C. ΔG^{o} (syn → anti) for **2** was found temperature-independent in the range -31 to -92 °C, indicating a nearly zero entropy difference between the syn and anti forms.

Table IV. Experimental Free Energy Differences in MeOH (ΔG^{o} in kcal/mol)

compd	CD analysis [a]	DNMR syn → anti		
	ΔG^{o}		ΔG^{o}	minor conf. (%)
1	0.93 [b]		-	-
2	0.0-0.4 [c]		-0.26 (-31 °C)	37
			-0.26 (-92 °C)	34
3	0.51		-1.0 (-70 °C)	7
4	0.69		-	-
5	0.97		-1.1 (-70 °C)	6
6	[d]	syn 1 → anti	+0.59 (-70 °C)	15
		syn 2 → anti	+0.50 (-70 °C)	19
7	0.76		-0.88 (-70 °C)	10

[a] According to Ref. 32. [b] Evaluated for band 1 only. [c] This method gives uncertain results for small ΔG^{o} values. [d] Almost no temperature-dependence.



Syn 1 *Syn 2* *Anti*

Scheme 3

Molecular mechanics (MM) calculations were performed for **1**, **2**, **4**, and **5** (Table V). It should be pointed out that the force field used has no provision for solute-solvent interactions, which can be expected to be considerable with the polar substrates and solvents employed in this study. However, the calculated minimum energy geometries are considered to be realistic, and the differences in solvation energies between the various conformers should be small compared to the total solvation energies. Therefore it is considered meaningful to discuss the calculated conformational energies, although with a certain reserve. Principal syn and anti minima (**S1** and **A1**, Fig. 2) and subsidiary minima with higher energies (**S2** and **A2**) were found for **1** and **2**. In the **A1** and **S1** forms the C=O and C-CH_3 bonds in the chiral rotor are nearly eclipsed, and in the **A2** and **S2** forms the C-OCH_3 and C-CH_3 bonds are similarly related. The energy of **1-A1** is predicted to be 0.6 kcal/mol lower than that of **1-S1**, and 2.6 kcal/mol lower than that of **1-A2**. The energy difference between **1-S1** and **1-S2** is calculated to be 1.4 kcal/mol. The energy of **2-S1** is predicted to be 0.3 kcal/mol lower than that of **2-A1**. **2-S2** is 1.5 and **2-A2** 2.6 kcal/mol higher in energy than **2-S1**. The calculated syn-anti energy difference for **2** agrees well with the NMR results (Table IV), and the value for **1** is at least in qualitative agreement with the expectation for a dominant anti form.

Only one anti form could be found for the 4-t-butyl compound **4**, 6.32 kcal/mol above the lowest syn (**S1**) form, while **S2** was found 1.72 kcal/mol above **S1**. In the syn forms the t-butyl group was gear-meshed[35] with the rotor.

An X-ray crystallographic study of the 4-ethyl-5-methyl analogue **5** has recently been published by Kanagapushpam and Venkatesan.[36] When their geometry (syn, **S1** type) was used as input in a MM2 calculation, an energy minimum with nearly the same geometry was found (**S1b**, Table V). However, it was not predicted to be the global minimum. The ethyl group is as expected perpendicular to the thiazoline ring, and syn to the rotor methyl group in the crystal, but when it was rotated 180° followed by minimization, a new **S1** minimum was found (**S1a**), 0.35 kcal/mol lower in energy (Fig. 3). When ester conformations of **S2** type were used as input, minimization to the **S1** minima occurred. Only one **A2** minimum could be found, 4.04 kcal/mol above the global minimum, but two **A1** minima of very similar energies (1.4 kcal/mol above **S1a**) and differing only with respect to the orientation of the 4-ethyl group.

The UV spectra of **1-7** show a strong band near 320 nm (ϵ = 14000-17600, Table VI), which is assigned to the first $\pi \rightarrow \pi^*$ transition in the thiazolinethione chromophore,[37]

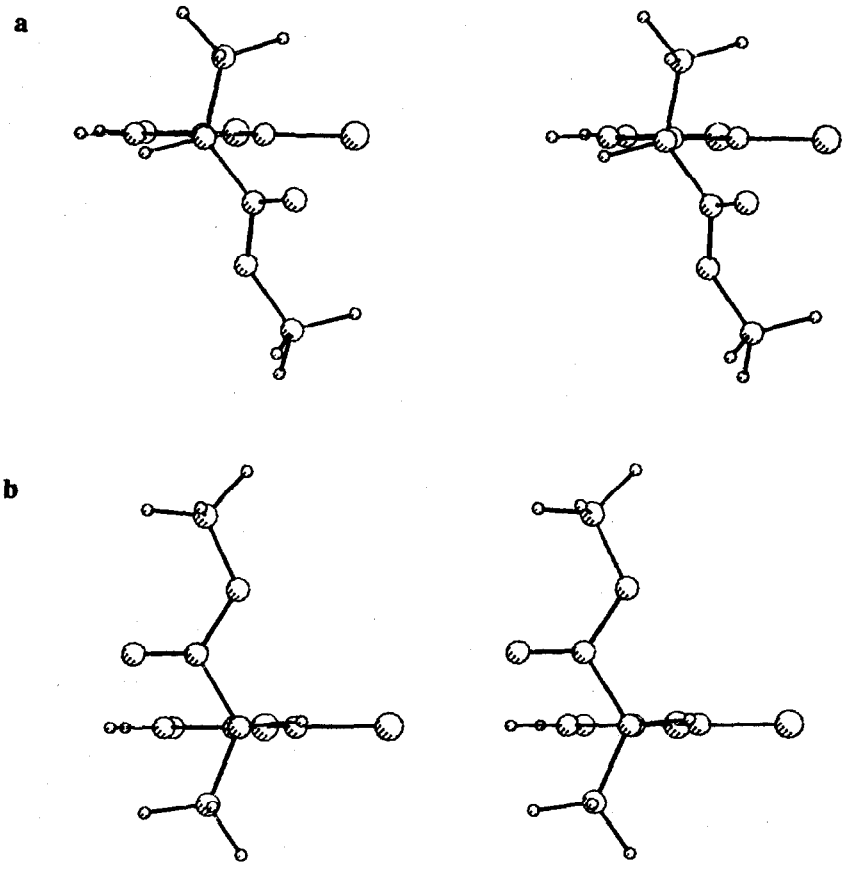


Figure 2. Stereoscopic views of (a) 1-S1 and (b) 1-A1.

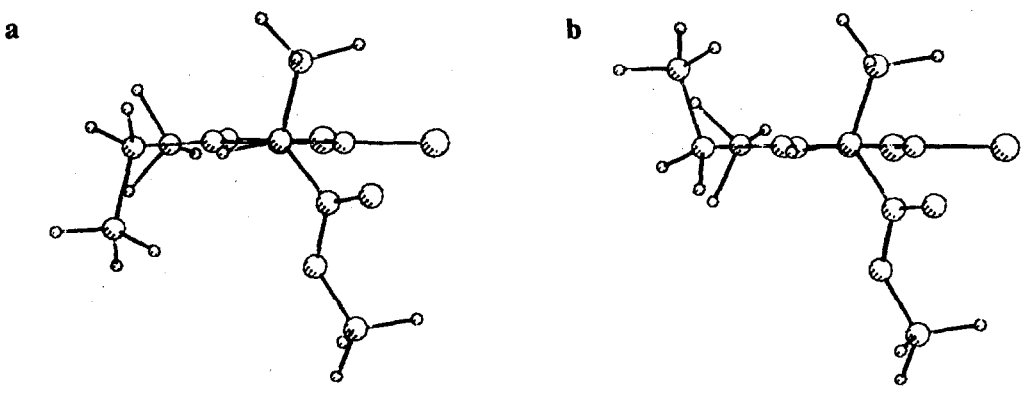


Figure 3. Molecular mechanics energy-minimized conformations of (a) 5-S1a and (b) 5-S1b.

Table V. MM2 Computational Results for Energy-minimized Conformations of 1, 2, 4, and 5 (S Configuration)

compd	conformation	energy, (kcal/mol)	ϕ_1, rotor angle (C4-N3-C9-C11; deg)	ϕ_2, ester angle (N3-C9-C11-O13; deg)	ϕ_3, 4-substituent angle (N3-C4-CB-C1D; deg)
1	anti (A1)	0.00	+58.7	+69.5	
	anti (A2)	2.62	+45.6	-110.6	
	syn (S1)	0.61	-127.8	+39.6	
	syn (S2)	2.03	-121.9	-113.1	
2	anti (A1)	0.26	+47.1	+56.7	
	anti (A2)	2.57	+42.8	-124.8	
	syn (S1)	0.00	-125.6	+40.8	
	syn (S2)	1.48	-121.2	-114.2	
4	anti (A1)	6.32	+50.5	+49.5	-89.0
	syn (S1)	0.00	-125.5	+41.1	-60.2
	syn (S2)	1.72	-121.4	-116.1	-59.8
5	anti (A1)	1.42	+59.3	+58.1	-98.5
	anti (A1b)	1.36	+61.6	+58.3	+94.2
	anti (A2)	4.04	+52.1	-125.5	-104.0
	syn (S1a)	0.00	-129.4	+43.4	+78.9
	syn (S1b)	0.35	-123.8	+36.8	-79.0
	syn (X-ray)	-	-123.6	+38.1	-80.1

$(\pi \rightarrow \pi^*)_1$. A band of similar strength, which appears at 202-206 nm, was not observed in the spectra of the N-(1-phenylethyl) analogues,[3] probably because of overlap with stronger benzene transitions at shorter wavelengths. It must be assigned to a higher $\pi \rightarrow \pi^*$ transition. In the range between the strong bands, two or three weak, more or less distinct shoulders appear. The most prominent falls at 225-230 nm (ϵ = ca. 4000), and a clear maximum is observed at 229 nm in the spectrum of **4** in hexane. A band in the same range was observed both in UV and CD spectra of the N-(1-phenylethyl) analogues and ascribed to a second $\pi \rightarrow \pi^*$ transition,[3] $(\pi \rightarrow \pi^*)_2$. A band at 256 nm ($\epsilon$ = 4300) in the spectrum of **7** in hexane may be related to the ^1L_b transition in the 4-phenyl chromophore.

The positions of the absorption bands are not very sensitive to solvent polarity or

Table VI. Ultraviolet Spectra

compd	solvent	λ_{max} nm ($\epsilon \times 10^{-3}$)	λ_{max}[b] nm ($\epsilon \times 10^{-3}$)	λ_{max} nm ($\epsilon \times 10^{-3}$)	λ_{max} nm ($\epsilon \times 10^{-3}$)
1	MeOH	314.8 (14.8)		223 (sh)	201.2 (13.3)
	hexane	318.4 (16.0)		228 (sh)	202.0 (15.6)
	EPA [a]	317.0 (16.2)		228 (sh)	202.0 (14.9)
2	MeOH	320.4 (15.1)		225 (sh)	202.7 (15.8)
	hexane	321.7 (14.4)		223 (sh)	203.7 (16.2)
	EPA	321.9 (15.4)		227 (sh)	204.0 (16.4)
3	MeOH	320.4 (14.8)		227 (sh)	203.2 (15.1)
4	MeOH	320.0 (14.0)		226 (sh; 4.5)	203.1 (13.4)
	hexane	321.2 (15.2)		229.0 (4.0)	204.8 (15.7)
	EPA	321.4 (14.6)		228 (sh; 4.5)	204.4 (15.2)
5	MeOH	325.1 (15.2)		228 (sh)	203.7 (14.5)
6	MeOH	323.6 (15.9)		228 (sh)	203.7 (16.4)
	hexane	325.6 (17.6)	258 (sh)		205.7 (17.3)
	EPA	324.7 (17.5)	255 (sh)		205.1 (17.4)
7	MeOH	324.7 (16.7)	250 (sh)		204 (sh; 27.0)
	hexane	326.3 (17.5)	256 (4.3)		205 (sh; 27.2)
					190.0 (57.3)
	EPA	325.7 (15.8)	247 (3.9)		204 (sh; 24.9)

[a] Diethyl ether:isopentane:ethanol (5:5:2, v/v). [b] These bands have only been notated when they are especially pronounced.

substituents. Not even the 4-Ph group causes significant bathochromic shifts, probably because the phenyl ring is rotated out of the thiazolinethione plane (by 74.5° in the N-(1-phenylethyl) analogue).[3]

Theoretical rotational strengths, R, were calculated for the $n \rightarrow \pi^*$ and the first two $\pi \rightarrow \pi^*$ transitions in the thiazolinethione chromophore, and for the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions in the ester group. Calculations were made for a grid of ϕ_1 and ϕ_2 values from 0° to 360° in steps of 20° with the 1-A1 geometry for the rest of the molecule. In this way maps of R values were obtained, which could be superimposed over conformational energy maps to obtain the theoretical R values for the various transitions in the calculated minimum energy conformations.

For the second thiazolinethione $\pi \rightarrow \pi^*$ transition, $(\pi \rightarrow \pi^*)_2$, positive R values where obtained for the whole map except for a small, conformationally inaccessible region. This is not in agreement with experiments since the corresponding CD band seems to be positive for compounds with predominant anti and negative to those with predominant syn conformation (see Conclusion). This transition gave problems also with the 1-phenylethyl analogues,[3] and the direction of the transition moment had to be changed from the calculated one to obtain agreement with the experimental spectra. The interpretation of the transition as $\pi \rightarrow \pi^*$ may be in error, a $n \rightarrow \sigma^*$ or $\sigma \rightarrow \pi^*$ transition also being feasible. Because of this uncertainty, which also affects the calculated data for the ester $n \rightarrow \pi^*$ transition, and because of a strong band at 205 nm (Table VI) not accounted for, the discussion is confined to the $n \rightarrow \pi^*$ and $(\pi \rightarrow \pi^*)_1$ transitions in the thiazolinethione chromophore. The maps for these transitions appear nearly as mirror images, and according to the calculations the one-electron mechanism is dominant in creating these rotational strengths. This is in agreement with experiments, since the corresponding CD bands in general appear as perfect couplets (Fig. 4). With this mechanism, the R values are given by eqn. 4,[38] where V_{12} is the per-

$$R_{12} = \pm V_{12} [\vec{\mu}_2 \cdot \vec{M}_1]/(\epsilon_1 - \epsilon_2) \qquad (4)$$

turbation energy due to the chirally disposed static charges q, M_1 and μ_2 are the magnetic and electronic transition moments corresponding to the $n \rightarrow \pi^*$ and $(\pi \rightarrow \pi^*)_1$ transitions, and ϵ_1 and ϵ_2 are the corresponding transition energies. The + sign refers to the $n \rightarrow \pi^*$ and the - sign to the $\pi \rightarrow \pi^*$ transition. The high weight of this mechanism in the present case can be ascribed to the low $|\epsilon_1 - \epsilon_2|$ value and the near parallelism of M_1 and μ_2.

All compounds 1-7 with S configuration give a medium strong positive CD band in the range 336-360 nm, but mostly between 336 and 347 nm (Table VII). The band undergoes strong bathochromic shifts from methanol to hexane, which supports the attribution to a $n \rightarrow \pi^*$ transition.[3] A negative band of similar strength appears in the range 309-335, corresponding to the $(\pi \rightarrow \pi^*)_1$ UV band. These bands are referred to as band 1 and band 2, respectively. One band (band 3), which is positive for all compounds except 1 and 6, appears in the range 250-280 nm, and another (band 4, earlier attributed to the $(\pi \rightarrow \pi^*)_2$ transition) in the range 222-238 nm. A sharp band to the short-wavelength side of this interval (band 5), often strongly intensified at low temperatures, falls in the range expected for the ester

Table VII. CD Spectra of 1-7 λ_{max} or λ_{min}, nm ($\Delta\varepsilon$ cm^{-1} M^{-1})

compd	solvent	temp, °C	band 1	band 2	band 3	band 4	band 5	band 6
(S)-1	MeOH	23	337 (3.8)	309 (-5.4)	257 (-1.4)	227 (3.3)	212 (sh)	197 (-2.5)
		-93	336 (5.4)	309 (-5.5)	255 (-1.2)	224 (3.5)	211 (3.3)	199 (-4.4)
	hexane	22	348 (1.5)	316 (-2.4)	280 (-1.0)	225 (4.0)	-	202 (-5.1)
	EPA	22	342 (3.6)	313 (-4.8)	267 (-1.1)	227 (3.7)	215 (sh)	201 (-3.8)
		-168	337 (6.7)	309 (-4.4)	268 (-0.6)	223 (3.6)[a]	209 (6.7)[a]	198 (-4.5)[a]
(S)-2	MeOH	22	344 (3.7)	315 (-4.2)	245 (1.2)	223 (sh)	217 (-3.8)	202 (4.2)
		-92	343 (7.2)	315 (-7.2)	248 (1.3)	223 (sh)	217 (-6.6)	201 (8.1)
	hexane	22	360 (1.1)	328 (-1.5)	[b]	232 (3.4)	214 (-2.6)	197 (-2.9)
	EPA	22	351 (2.2)	320 (-2.9)	-	238 (2.3)	215 (-2.4)	205 (1.5)
		-180	344 (7.1)	314 (-4.9)	264 (-0.4)	[245 (1.9)][c]	218 (-9.9)[d]	204 (8.8)[d]
(S)-3	MeOH	22	344 (1.8)	315 (-2.3)	252 (0.3)	222 (sh)	217 (-1.9)	202 (2.7)
		-93	342 (3.0)	315 (-3.2)	252 (0.6)	226 (-2.3)	217 (sh)	203 (4.1)
(S)-4	MeOH	23	342 (9.2)	315 (-10.1)	255 (0.6)	226 (-6.8)	217 (-7.1)	201 (14.8)
		-92	342 (12.1)	315 (-11.7)	[e]	226 (-9.0)	219 (sh)	201 (17.3)
	hexane	22	352 (10.5)	321 (-12.0)	266 (0.7)	230 (-7.1)	219 (-9.7)	204 (14.0)
	EPA	23	347 (10.5)	319 (-11.6)	260 (0.7)	227 (sh)	219 (-8.9)	204 (15.5)
		-165	344 (15.1)	318 (-13.3)	[f]	220 (-13.9)	-	203 (20.2)
(S)-5	MeOH	23	346 (6.7)	316 (-6.9)	250 (1.4)	225 (sh)	217 (-5.3)	203 (7.9)
		-92	346 (11.0)	316 (-10.0)	250 (1.9)	223 (sh)	215 (-6.9)	201 (9.2)
(S)-6	MeOH	23	346 (2.4)	314 (-2.7)	270 (-0.3)	238 (1.3)[g]	217 (-1.6)	204 (3.6)
		-93	346 (3.0)	317 (-3.0)	271 (-0.6)	233 (1.5)[g]	217 (-1.8)	205 (4.5)
	hexane	22	360 (0.9)	335 (-1.1)	279 (-0.4)	231 (5.6)	214 (-3.2)	
	EPA	23	353 (1.7)	323 (-1.9)	275 (-0.4)	234 (3.6)	216 (-0.5)	203 (2.4)
		-175	350 (1.5) / 342 (-0.5)	331 (-0.6) / 310 (0.1)	270 (-0.9)	228 (5.0)	217 (-0.6)	207 (7.7)
(S)-7	MeOH	23	347 (7.6)	317 (-7.8)	265 (0.6)	[245 (sh)][c]	219 (-5.4)	200 (2.8)
		-92	346 (12.5)	319 (-10.4)	265 (0.6)	[245 (sh)][c]	223 (-6.5)	200 (4.5)
	hexane	22	354 (9.1)	325 (-9.9)	271 (1.7)	[h]	222 (-8.2)	205 (6.2)
	EPA	22	350 (9.0)	322 (-9.3)	269 (1.0)	[248 (sh)][c]	220 (-6.9)	203 (4.8)
		-174	347 (18.5)	321 (-13.0)	263 (1.5)	225 (-9.9)	-	198 (10.3)

[a] -179 °C. [b] Several shoulders in the area 250-290 nm. [c] Probably not band 4. [d] -163 °C. [e] Two bands: 268 (-0.3), 252 (0.5). [f] Two bands: 264 (-0.4), 252 (0.2). [g] Shoulder at 245 nm. [h] Two weak bands in this range: 249 (-0.1), 241 (0.1).

$n \rightarrow \pi^*$ transition. Finally band 6, often quite strong, is observed in the range 197-205 nm, positive for all compounds except 1 in all solvents and 2 in hexane.

The CD spectra of the individual compounds will now be discussed, beginning with S-1. Bands 1, 5, and 6 increase notably in intensity with decreasing temperature, whereas the other bands are only slightly temperature-sensitive. The spectra in methanol pass through isosbestic points at wavelengths above 240 nm, but at shorter wavelengths the curves behave less regularly. This indicates that more than two forms participate in the conformational equilibrium. The isosbestic behaviour at long wavelengths may be due to an equilibrium between three forms like A1, S1, and S2, where e.g. S1 and S2 have very similar spectra above 240 nm but more different at shorter wavelengths.

A WFK treatment of band 1 using $\Delta\epsilon_{max}$ gave ΔG^0 = 0.93 kcal/mol. Assuming Gaussian shape for this band, R_{maj} = +0.10 DBM[39] and R_{min} = -0.04 DBM could be obtained. However, the significance of a ΔG^0 value, derived by the WFK method when more than two forms are present, is doubtful. Model calculations by eqn. 5 at five temperatures with n = 3 and

$$\Delta\epsilon_{obs} = [\Delta\epsilon_1 + \Delta\epsilon_2 \exp(-\Delta G^0_{12}/RT) + \cdots \Delta\epsilon_n \exp(-\Delta G^0_{1n}/RT)]/[1 + \exp(-\Delta G^0_{12}/RT) + \\ + \cdots + \exp(-\Delta G^0_{1n}/RT)] \qquad (5)$$

assuming $\Delta\epsilon_1 = \Delta\epsilon_2$ were used in a WFK treatment, and a ΔG^0 value was found which gave a linear $\Delta\epsilon_{obs}$ - $[1 + \exp(-\Delta G^0/RT)]^{-1}$ relation, but the quantitative significance of this ΔG^0 value is uncertain.

Low-temperature NMR spectra of 1 have not shown splittings which could indicate the existence of both syn and anti forms. This has generally been ascribed to strong dominance of the anti form, but a low barrier is also a possible explanation. With support of the MM calculations, the temperature-dependent CD spectra could plausibly be interpreted as showing an equilibrium between 1-A1 and 1-S1 with a third unidentified form involved. The dominant form must be anti, and probably A1. This is supported by the calculated R values for bands 1 and 2. The A1 geometry falls on a nodal line on the R map, which separates regions with low negative and high positive R values, and the same regions with opposite signs for band 2. Integration over areas corresponding to reasonable low-amplitude torsional vibrations of the rotor and ester groups leads to positive band 1 and negative band 2 for A1, in agreement with experiment for the major form.

The spectra of 1 in EPA show no isosbestic behaviour, but the general temperature effects are similar to those in MeOH, bands 1 and 5 showing the strongest temperature-dependence. Band 5 is invisible at room temperature but appears strong ($\Delta\epsilon$ = +6.7) and sharp at -179 °C.

The 4-methyl analogue, 2, is found by NMR to have a slight predominance of the syn form ($\Delta G^0_{syn \rightarrow anti}$ = -0.26 kcal/mol). The CD spectra in MeOH and EPA have positive band 1 and negative band 2 as for 1, but opposite signs for bands 5 and 6 compared to 1. The spectrum in hexane is different, with rather weak bands and with positive band 4 and negative band 6.

The spectra in MeOH show strong temperature dependence and isosbestic points over the whole spectral range (Fig. 4). Unfortunately, the combinations of ΔG^0 and R values for the

bands in MeOH are such that the WFK treatment produces rather uncertain ΔG^0 values. By using a technique similar to that employed by Lei and Vogel,[40] an upper limit of 0.5 kcal/mol was established for $|\Delta G^0|$. ΔG^0 = 0.26 kcal/mol gives R_{maj} = +0.33, R_{min} = -0.32 for band 1 and R_{maj} = -0.55, R_{min} = +0.58 for band 2, all in DBM. The R values for bands 1 and 2 calculated for the S1 and A1 (but not for S2 and A2) rotamers have the correct signs and orders of magnitude, assuming that S1 is the major form, as predicted by the MM calculations.

However, the spectra in EPA show strong temperature dependence, but in particular the curves for band 1 do not pass through isosbestic points. This, together with the considerably divergent spectrum in hexane indicates that other rotamers than A1 and S1 are present in non-negligible quantities in these solvents.

The preference for the syn form is more pronounced for the 4-isopropyl analogue 3 with $\Delta G^0_{syn \rightarrow anti}$ = -1.0 kcal/mol by ^{1}H NMR in MeOH (ΔG^0_{NMR}). The CD spectrum in MeOH is quite similar to that of 2 with reasonable isosbestic behaviour. However, a WFK treatment gives ΔG^0 = 0.51 kcal/mol with an apparent uncertainty of only ± 0.05 kcal/mol. Two syn rotamers with different orientations of the isopropyl group are observed by NMR for the 4-isopropyl-5-methyl analogue 6 (Scheme 3), and it is possible that similar forms exist in 3, although the barrier separating them must be too low to permit their observation by NMR. Considering also the different possible orientations of the ester groups, the potential for conformational variation in 3 is considerable. However, in two syn forms differing with respect to the orientation of the 4-isopropyl group, the orientation of the ester group may be the same, and then it is not unreasonable to assume that they have rather similar CD spectra. The isosbestic points in the spectra could then be explained by an equilibrium between a major anti form and two minor syn forms, syn 1 and syn 2, the latter with similar CD spectra. This could then also explain the difference between ΔG^0_{NMR} and ΔG^0_{CD}. The former should be temperature-dependent even if all forms have the same entropy (eqn. 6), unless

$$\Delta G^0_{NMR} = \Delta G^0_{13} + RT \ln[1 + \exp(-\Delta G^0_{12}/RT)] \qquad (6)$$

ΔG^0_{21} = 0. Forms 1 and 2 are syn 1 and syn 2, form 3 is the anti form. The presence of significant quantities of further rotamers should lead to more complex temperature dependence of the CD spectra.

The 4-t-butyl compound 4 is according to NMR entirely in the syn form, but the CD spectra in methanol and in EPA show temperature dependence with isosbestic behaviour, giving ΔG^0 = 0.7 kcal/mol in a WFK treatment. This must be due to exchange within the syn form. The WFK treatment gives $R_{maj} > 0$, $R_{min} < 0$ for band 1, $R_{maj} < R_{min} < 0$ for band 2. The signs are in agreement with a conformation of S1 type for the major form. According to the MM calculations (Table V), the minor form should be of S2 type. This geometry falls close to nodal lines on the R maps for both bands 1 and 2, and no safe conclusion can be reached from the theoretical R values. It is also clear that the geometries of the S1- and S2-like forms of 4 are different from those of 1 and 2, the chiral rotor being bent ca 5° closer to C=S in 4-S1 than in 1-S1 according to MM calculations. The signs of all bands in the CD spectra of 4 in MeOH, EPA, and hexane are the same as those for 3, in agreement with

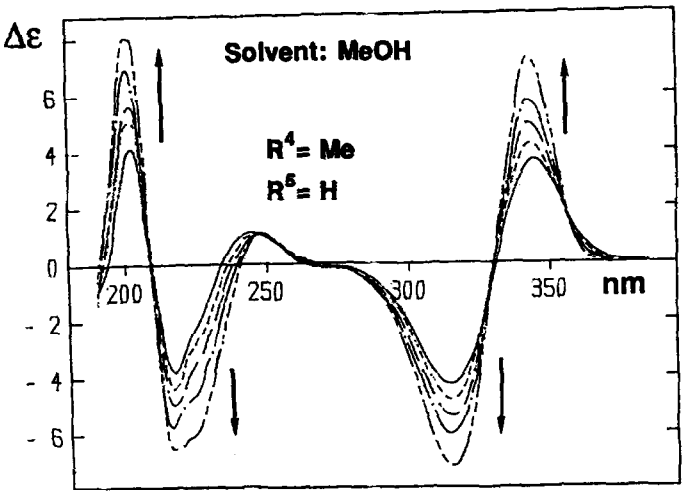


Figure 4. CD spectra of 2 in MeOH at +21, -5, -31, -57 and -92 ^{o}C. The arrows indicate lowered temperature.

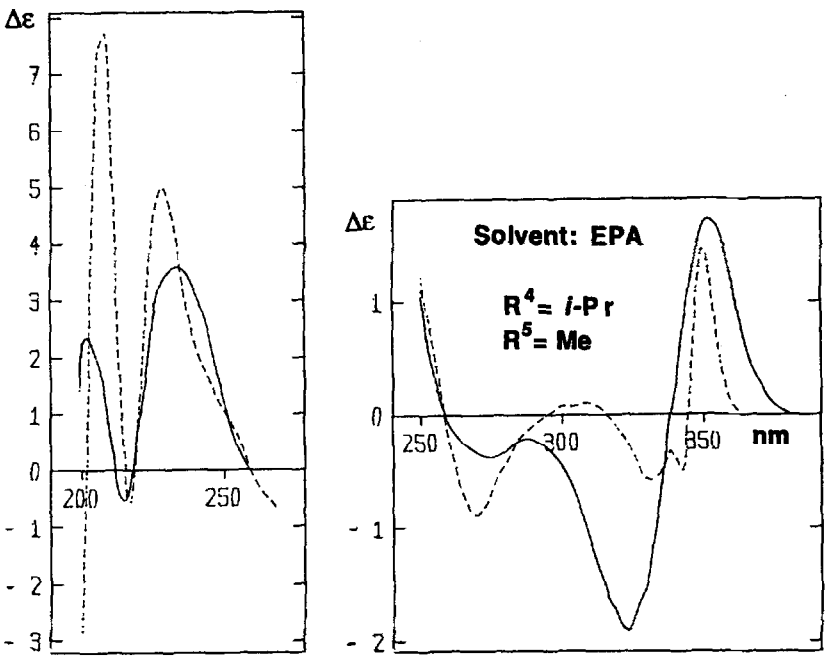


Figure 5. CD spectra for 6 in EPA at +24 and -176 ^{o}C for long wavelength section and +23 and -165 ^{o}C for short wavelength section (line of short dashes corresponds to low temperature).

dominance of the same form (S1). In conclusion, CD, NMR, and MM data for **4** support an equilibrium between a major S1 and a minor S2 form.

In the 4-ethyl-5-methyl compound **5** the syn form dominates in solution ($\Delta G^{o}_{syn \rightarrow anti}$ = -1.1 kcal/mol by NMR), and it is the only form found in the crystal.[36] The CD bands in MeOH show the sign sequence +,-,+,-,-,+, also in agreement with syn dominance, and with reasonable isosbestic behaviour. A WFK treatment gives $|\Delta G^{o}|$ = 0.97 kcal/mol, in good agreement with ΔG^{o}_{NMR}. However, this does not necessarily mean that only two forms are present. According to the MM calculations, **5** has two S1 and two A1 type rotamers. In each pair, energies and $\emptyset_1$ and $\emptyset_2$ are quite similar, the only significant difference being the orientations of the ethyl group ($\emptyset_3$, Table V), which must have only a small effect on the CD spectra. The temperature-dependence of the spectra of such a system may well be similar to that of a two-component equilibrium system. It follows from eqn. 7 that the apparent

$$K_{obs} = \frac{[A1a] + [A1b]}{[S1a] + [S1b]} = \exp[-(G^{A}_{1a} - G^{S}_{1a})/RT] \frac{1 + \exp(-\Delta G^{A}_{ab}/RT)}{1 + \exp(-\Delta G^{S}_{ab}/RT)} \qquad (7)$$

syn → anti equilibrium constant will show a temperature dependence approximately determined by the free energy difference between one anti and one syn form, if the ratio between the two [1 + exp(•••)] terms is only slightly temperature dependent and close to unity. This will be the case if either $\Delta G^{A}_{ab} \approx \Delta G^{S}_{ab}$ or both are large. Thus the temperature-dependence of the CD spectrum of **5** may reflect an equilibrium between two S1 and two A1 forms.

The 4-isopropyl-5-methyl compound **6** is shown by NMR to contain two syn forms in nearly equal proportions, differing in the orientation of the 4-isopropyl group (Scheme 3), and one dominant anti form. The CD bands in methanol show the sign sequence +,-,-,+,-,+ and, surprisingly, no significant temperature dependence. The spectra in EPA show a quite complex behaviour, indicating the presence of at least three forms. A form with negative band 1 and positive band 2 is found to increase in weight with decreasing temperature and should be an anti form (Fig. 5). The ambient temperature spectrum in hexane has the same sign distribution as in methanol, but much weaker bands 1 and 2 and stronger band 4, indicating a larger proportion of the anti form in hexane than in methanol.

The 4-phenyl-5-methyl derivative **7** shows isosbestic behaviour both in methanol and in EPA with deviations only at the lowest temperatures. The band signs, +,-,+,-,-,+, are in agreement with a major syn form, as also observed by NMR ($\Delta G^{o}_{syn \rightarrow anti}$ = -0.88 kcal/mol). The value found by a WFK calculation, $|\Delta G^{o}|$ = 0.76 kcal/mol, agrees well with ΔG^{o}_{NMR} and may indicate an equilibrium between a major syn and a minor anti form with only small contributions from other forms.

Conclusion

Compounds **1-7** present complex conformational problems, since beside the NMR-observable syn-anti equilibrium of the chiral rotor, exchange between different orientations of the ester group and in some cases (**3** and **6** and probably also **5** and **7**) also of the substituent in position 4 influences the temperature dependence of the CD spectra. Of the latter

processes, only the isopropyl rotation in **6** is NMR-observable. Because of the supplementary conformational variation, it has not been possible to find general CD characteristics for the syn and anti forms. While **1**, which is mostly in the anti form, has the sign sequence +,-,- for bands 1, 2, and 3, the same bands have -,+,- for the anti form of **6**. Only band 4 seems to have a diagnostic value for the syn-anti equilibrium since it is positive and increasing in intensity at lower temperatures for **1** and **6** , dominant anti, and negative for all other compounds, dominant syn.

Our study has shown that the temperature dependence of the CD spectra of conformationally mobile system may give information about the presence of two or more conformers. At present it is not possible to obtain quantitative information about energy difference except for two-form equilibria. On the other hand, isosbestic behaviour is not a definite proof for the existence of such an equilibrium.

Finally, the clear symmetric couplet character of bands 1 and 2 shows that the one-electron mechanism is the dominating one for generating rotational strength for the $n \rightarrow \pi^*$ and first $\pi \rightarrow \pi^*$ transitions in all conformers.

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