Chromatographic Enantiomer Separation and Spectroscopic Studies of a Chiral Vinylogous Thiolcarboxylate

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3-Methylthio-5-phenyl-2-cyclohexenone (5) has been resolved into pure enantiomers by chromatography on tris(phenylcarbamoyl)cellulose adsorbed on silica. The electronic transitions in the 3-methylthio-enone chromophore have been studied with the aid of the UV and CD spectra of 5, the UV spectrum of the 5,5-dimethyl analogue 6, and by CNDO/S calculations on enone and 3-methylthio-enone models. One $n \rightarrow \pi^*$ and two $\pi \rightarrow \pi^*$ transitions have been located.

The absolute configuration of (−)-5 has been assigned as S based on a sector rule for cyclohexenones with planar enone systems.

Ultraviolet–visible absorption spectra have been the main source of information on energies of electronic transitions in organic chromophores. However, in many cases this information is incomplete owing to insufficient resolution of close-lying transitions, e.g. when transitions with low probability are hidden under stronger neighbouring bands. In such cases, CD spectra of chiral compounds containing the chromophore of interest can give supplementary information, since close-lying transitions may have rotational strengths with different signs, and transitions, which have low dipole strengths, may have substantial rotational strengths. This is particularly true for $n \rightarrow \pi^*$ transitions in conjugated chromophores, which in UV spectra often give bands that are hidden under near-lying strong $\pi \rightarrow \pi^*$ bands, but which give distinct CD bands of appreciable strength.

An illustration is provided by the simple thiolcarboxylate chromophore and its vinylogue, the 3-alkylthio-enone chromophore. Thiolacetates[1] and γ-thiolactones[2] show only one absorption band at ca. 235 nm (ε ca. 4000) in the UV spectrum, but the CD spectra of chiral thiolacetates show one band at 235 nm ($\pi \rightarrow \pi^*$) and one at ca. 270 nm ($n \rightarrow \pi^*$).[3,4]
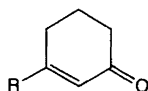
1 a, R = Me

1 b, R = MeS

While 3-methyl-2-cyclohexenone (1a) shows a $\pi \rightarrow \pi^*$ band at 224 nm (ε 13 500) and an $n \rightarrow \pi^*$ band at 310 nm (ε: 62),[5] only one strong band at 287 nm (ε 20 800) is reported for 3-methylthio-2-cyclohexenone (1b)[6] (both spectra in ethanol). (Based on these data, the increment of 85 nm proposed by Scott[7] for a MeS group in the β-position of an α,β-unsaturated carbonyl compound seems to be at least 10 nm too high.) The $n \rightarrow \pi^*$ transition of 1b must be hidden under the strong $\pi \rightarrow \pi^*$ band. In order to locate the $n \rightarrow \pi^*$ transition and also possible higher-energy transitions, we have prepared a chiral analogue of 1b, viz. 5 (Scheme 1), in the hope of obtaining the desired information from its CD spectrum. The UV spectrum down to 190 nm has also been studied for the analogue 6, which contains only the 3-alkylthio-enone chromophore. Compounds 5 and 6, with rigid structures, are well suited to CNDO/S calculations.

Experimental

Preparative part. 5-Phenylcyclohexane-1,3-dione (2) was synthesized by reaction of diethyl malonate with benzalacetone in the presence of sodium ethoxide, essentially as described by Cooks et al.[8] The synthesis of the chloro derivative 3 and the enethiol 4 was performed as described by Dalgaard and Lawesson[9] for the corresponding 5,5-dimethylcyclohexane-1,3-dione ('dimedone') derivatives. The intermediates 3 and 4 are sensitive compounds with an obnoxious smell, and they were used directly in the following steps without purificaiton or detailed characterization. Their identities were ascertained by ^{1}H NMR spectra and MS, and in particular with reference to the identity of the final product 5.

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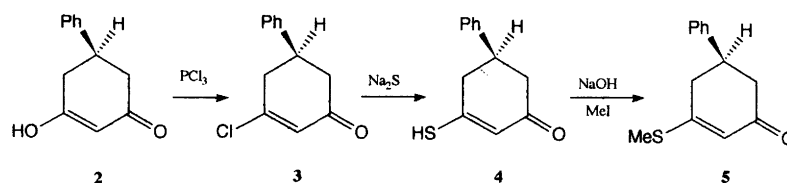
Scheme 1.

3-Methylthio-5-phenyl-2-cyclohexenone (**5**). Methyl iodide (1.0 g) was added with stirring to a solution of **4** (1.33 g) in NaOH (10 ml). After 30 min the organic phase was taken up in dichloromethane, dried, and evaporated to give 1.35 g (95 % yield) of light yellow crystals, m.p. 72–73 °C after recrystallization from toluene–hexane. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.34 (s, 3 H, CH$_3$S), 2.57–2.79 (m, 4 H, 4-CH$_2$ and 6-CH$_2$), 3.37 (m, 1 H, H-5), 5.90 (d, 1 H, *J* 1.5 Hz, H-2), 7.21–7.37 (m, 5 H, C$_6$H$_5$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.41 (CH$_3$S), 38.31 (4-CH$_2$), 40.94 (5-CH), 44.23 (6-CH$_2$), 118.96 (2-CH), 126.67, 127.10, 128.78, 142.52 (C$_6$H$_5$), 165.60 (C-1), 194.96 (C-3). MS [70 eV, *m/z* (% rel. int.)]: 218 (*M*$^+$, 18), 203 (*M*$^+$−CH$_3$, 7), 114 (80), 86 (64), 67 (100), 39 (53). High-resolution MS: Found *M*$^+$: 218.0765, calc. for C$_{13}$H$_{14}$OS: 218.0764. IR (KBr): 1647 (s, C=O), 1560 (s, C=C) cm^{-1}.

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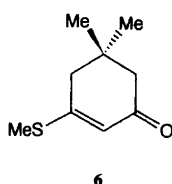
3-Methylthio-5,5-dimethyl-2-cyclohexenone (**6**) was obtained in 88 % yield analogously to **5**, starting from the 5,5-dimethyl analogue of **4** ('thiodimedone').[9] The crude product was purified by flash chromatography[10] on silica (Merck 60) with hexane–ethyl acetate as the mobile phase. The pure product was obtained as an orange oil, which crystallized at −20 °C as orange–brownish prisms, m.p. 27–28 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.00 (s, 6 H), 2.20 (s, 2 H), 2.27 (s, 3 H), 2.28 (s, 2 H), 5.75 (s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.29 (CH$_3$S), 27.88 [(CH$_3$)$_2$C], 34.09 [(CH$_3$)$_2$C], 44.39 (CH$_2$), 51.07 (CH$_2$), 117.96 (CH), 164.43 (C-SCH$_3$), 195.56 (C=O). MS [70 eV, *m/z* (% rel. int.)]: 170 (*M*$^+$, 100), 155 (*M*$^+$−CH$_3$, 42), 114 (57), 94 (16). High resolution MS: Found *M*$^+$: 170.0764, calc. for C$_9$H$_{14}$OS: 170.0765.

Chromatographic enantiomer separation. Attempts to resolve **5** by chromatography on microcrystalline triacetyl-cellulose[11,12] were unsuccessful. However, when tris-(phenylcarbamoyl)cellulose adsorbed on silica[13,14] was used as the chiral stationary phase with hexane–2-propanol (9:1, v/v) as the mobile phase, partial separation occurred. Baseline separation was achieved after three chromatographic cycles. The capacity factors[15] were k_S' 0.48, k_R' 0.67, and

the selectivity factor[15] α 1.37. Tri-*t*-butylbenzene was used as a non-retained reference (void volume marker).

Instruments. NMR spectra were recorded with a Varian Model XL-300 NMR spectrometer, mass spectra with a JEOL Model SX-102 mass spectrometer, the ultraviolet spectra with a Cary Model 2290 spectrometer (0.1 cm cell), and the CD spectrum of **5** with a JASCO Model J-500A spectropolarimeter (0.02 cm cell). The enantiomer resolution of **5** was performed with the equipment described by Isaksson and Roschester (except for the columns).[16] The fractions containing the pure enantiomers were evaporated, carefully dried, and dissolved in acetonitrile (spectroscopic grade). The concentrations were monitored by recording the UV spectra.

Calculations. The CNDO/S calculations were performed with a program specifically parametrized for organic sulfur compounds[17] and with configuration interaction between the 20 lowest singly excited configurations.

The empirical force-field calculations were performed with the MMP2-85 force field[18,19] with a few additional non-standard parameters.

Results and discussion

The UV spectrum of **5** displays a strong band at 284 nm, weak and non-distinct shoulders at 230 and 206 nm, and only rising end absorption at 190 nm (Table 1). The spectrum of **6** is similar, but the shoulder at 206 nm is not observed, and a distinct maximum of medium strength is observed at 190 nm. The difference between the two spectra can be ascribed to the phenyl chromophore in **5**, for which a weak band is expected at 256 nm (^1L_b),[20] one of medium strength at 210 nm (^1L_a), and a much stronger one

Table 1. UV spectra of **5** and **6** and CD spectrum of (−)-**5** in acetonitrile.

| Compound	λ$_{ext}$/nm (ε or Δε)
5 (UV)	284 (19300), 230 sh[a] (2400), 206 sh (7000), 190 (22000)[b]
(−)-**5** (CD)[c]	329 (−1.73), 285 (+2.55), 211 (+5.0), 193 (−19.3)
6 (UV)	282 (18800),[d] 226 sh (770), 190 (7300)

[a]Shoulder. [b]End absorption. [c]First eluted enantiomer. [d]289 (20 100) in ethanol.

Fig. 1. CD spectrum of the first-eluted enantiomer of **5** in acetonitrile.
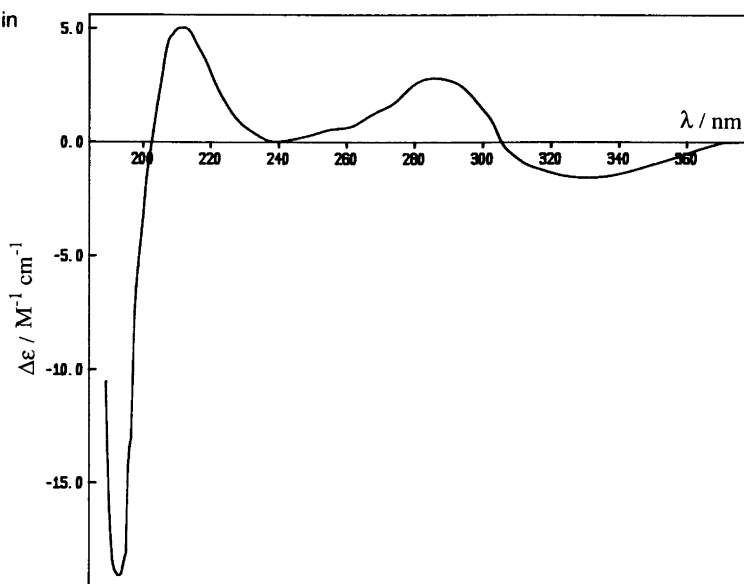
at ca. 186 nm (^{1}B). The ^{1}L$_b$ absorption is completely obscured by the strong band at 284 nm, but the shoulder at 206 nm may be ascribed to the ^{1}L$_a$ and the end absorption to the ^{1}B$_b$ transition.

The CD spectrum of (−)-**5** (Fig. 1) shows a weak, broad, negative band centred at 329 nm, a stronger positive band at 285 nm, corresponding to the strong UV band at the same position, and stronger positive and negative bands at 211 and 193 nm. Two weak positive bands ascribed to the ^{1}L$_b$ transition are seen around 260 nm on the short-wavelength side of the 285 nm band. The 211 nm band may be ascribed to the benzene ^{1}L$_a$ transition, and the 193 nm band to the same transition as the 190 nm band in the UV spectrum of **6**.

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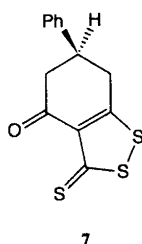
The geometry of **5** was obtained by empirical force-field calculations. A sofa-type conformation with an equatorial phenyl group and nearly planar 3-methylthio-enone part (Fig. 2) was found to be the most stable one, rather similar to the conformation recently found for the somewhat related 6-phenyl-3-thioxo-6,7-dihydro-3H-1,2-benzodi-thiol-4(5H)-one (**7**) by analysis of the ^{1}H NMR spectrum.[21] The energy of the form with axial phenyl group was calculated to be ca. 2.5 kcal mol^{-1} higher. The ^{1}H NMR spectrum of **5** is more complex than that of **7** owing to overlap of the 4-H and 6-H resonances, but analysis of the 5-H resonance gave vicinal coupling constants of ca. 5 and ca.

11 Hz, which is expected for the form with an equatorial but not with an axial phenyl group.

To aid the analysis of the spectra, CNDO/S calculations were performed for simplified models of **1a** and **6** (Table 2). The geometry of the model for **6** was obtained from that calculated for **5** by removing the 5-CHPh fragment to give two 'geared'[22] methyl groups (see Table 2). The model for **1a** was obtained from that for **6** by replacement of MeS by H.

The spectrum of **1a** is reported only for ethanol solution. The position of the n→π* transition is highly sensitive to solvent effects. Polar and, in particular, hydrogen bonding solvents cause blue shifts compared with hydrocarbon solvents. The solvent effect for **1a** should be similar to that for 2-methyl-2-penten-3-one,[23] which has the n→π* band centred at 310 nm in ethanol, at 314 nm in acetonitrile, and at 321 nm in cyclohexane solution. Therefore, 314 nm is a reasonable value for **1a** to be used in comparison with **5** and **6**.
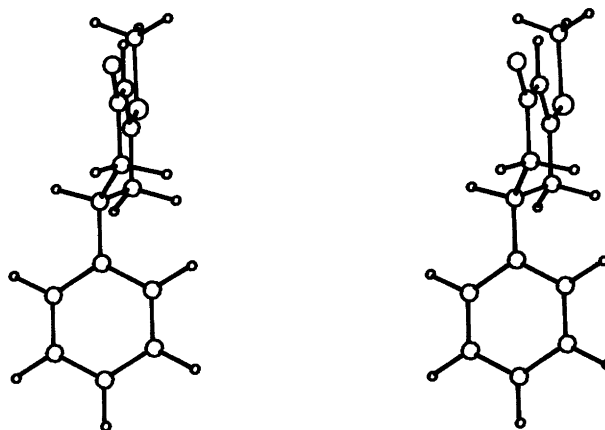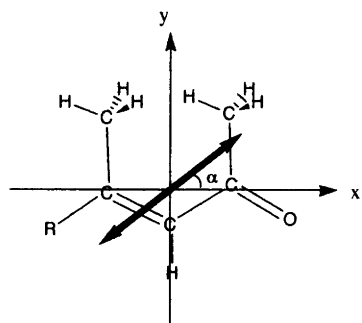

Fig. 2. Stereoview of (S)-**5**.

Table 2. Transition wavelengths, oscillator strengths (f), and transition polarizations calculated by the CNDO/S method.

R	λ/nm	f	α/°	Assignment
H	435.3	0.00	–	$n \rightarrow \pi^*$
	195.1	0.38	-24.1	$(\pi \rightarrow \pi^*)_1$
	160.9	0.0084	-55.6	$(\pi \rightarrow \pi^*)_2$
CH_3S^a	369.9	0.00	–	$n \rightarrow \pi^*$
	212.7	0.34	-13.9	$(\pi \rightarrow \pi^*)_1$
	171.8	0.021	-32.1	$(\pi \rightarrow \pi^*)_2$
CH_3S^b	442.6	0.0	–	$n \rightarrow \pi^*$
	226.5	0.31^c	-13.2	$(\pi \rightarrow \pi^*)_1$
	174.8	0.13^d	-32.5	$(\pi \rightarrow \pi^*)_2$

[a]Without d orbitals. [b]With d orbitals. [c]Exp. value 0.31. [d]Exp. value 0.32.

The CNDO/S method tends to underestimate the energies for $n \rightarrow \pi^*$ transitions and overestimate those for $\pi \rightarrow \pi^*$ transitions for carbonyl compounds. In agreement with this, the calculations for 1a predict the $n \rightarrow \pi^*$ transition at 435 nm and the first $\pi \rightarrow \pi^*$ transition at 195 nm instead of 225 nm. A second $\pi \rightarrow \pi^*$ transition predicted at 161 nm does not correspond to any observed band.

The results of the calculations for the 3-methylthioenone depend on the choice of basis orbitals. Without d orbitals, the $n \rightarrow \pi^*$ transition is predicted at 370 nm, and $\pi \rightarrow \pi^*$ transitions at 213 and 172 nm. When d orbitals are included, the $n \rightarrow \pi^*$ transition falls at 443 nm and the $\pi \rightarrow \pi^*$ transitions at 227 and 175 nm. The polarization directions are not significantly affected by the choice of basis orbitals.

It seems reasonable to assign the band observed at 329 nm in the CD spectrum of 5 to the $n \rightarrow \pi^*$ transition, and the bands at 285 and 193 nm to the two first $\pi \rightarrow \pi^*$ transitions. The red shift of $(\pi \rightarrow \pi^*)_1$ from 1a to 1b, 5 and 6 is better reproduced by the calculations with inclusion of d orbitals. It is probable that $(\pi \rightarrow \pi^*)_2$ is also red-shifted, as predicted by the calculations. The $n \rightarrow \pi^*$ bands of 1a and 5 fall quite close together, with that of 5 at slightly longer wavelength, which is predicted by the calculations with (but not without) d orbitals.

Snatzke[24] has proposed a sector rule to determine the absolute configuration of cyclohexenones of sofa conformation from the sign of the $n \rightarrow \pi^*$ CD band. Application of this rule to 5, which has the prerequisite, nearly planar enone system (Fig. 2), leads to the result that the first eluted enantiomer, (−)-5, has the S configuration.

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