

Circular Dichroism and Absolute Configuration of 2-Thio- and 2-Selenopropionic Acids*

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Circular dichroism (CD) studies of 2-thio- and 2-selenopropionic acids reveal that considerable interaction occurs between the sulfide (or selenide) chromophore and the carboxyl group. The 2-thiopropionic acids show two Cotton effects (CE's) at *ca.* 222 and 250 nm. In the 2-selenopropionic acids these two CE's have shifted to longer wavelengths by *ca.* 15 and 25 nm, respectively, compared to their sulfur analogues. In both series, the sign of the short wavelength CE correlates with the absolute configuration, and is not affected by the nature of an additional chromophore attached to sulfur or selenium.

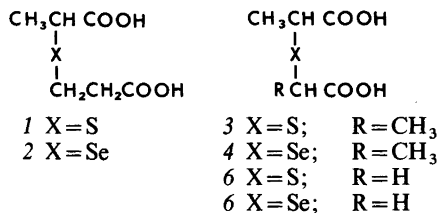
Although the electronic absorption (EA), optical rotatory dispersion (ORD) and circular dichroism (CD) properties of organic sulfides have been extensively investigated and the subject recently reviewed,¹ there are very few studies on open-chain aliphatic thioethers.^{2,3} Moreover, corresponding information on the closely related organic selenides is extremely scarce.⁴

The EA spectra of dialkyl sulfides are complex with at least four transitions present between 190 and 250 nm.^{2,5–7} A moderately strong band (ϵ 1000–2500), often visible only as an inflexion on a more intense high energy band, appears at about 210 nm, with a shoulder of low intensity (ϵ 120–140) in the 225–230 nm region. Another transition giving rise to a very weak band ($\epsilon \sim 20$) at about 240 nm has also been demonstrated.⁷

Rosenfield and Moscovitz⁷ have proposed an assignment for the three lowest lying C–S–C sulfide transitions, which have been shown to be optically active in chiral dialkyl sulfides.^{2,7} The first two transitions ($n \rightarrow \sigma^*$), located at 240 and 220 nm, are from a nonbonding 3p sulfur orbital to antibonding orbitals between sulfur and carbon atoms. The third band (at 200 nm) is assigned to an atomic-like transition which involves electron excitation from a nonbonding orbital to a 3d atomic orbital of sulfur only.⁷ Since Se and S have similar atomic character, dialkyl selenides can be expected to exhibit analogous absorption bands, although shifted to lower energy, the orbitals involved here being the nonbonding 4p and 4d atomic selenium orbitals.

We have previously shown⁸ that in 2,2'-dithio-bisacetic acids and their diselenide analogues considerable interaction occurs between the disulfide (or diselenide) chromophore and the carboxyl group, giving rise to an intense Cotton effect (CE) which dominates the near UV region of the CD spectrum. However, when the disulfide and carboxyl chromophores are separated by two carbon atoms each chromophore gives a separate CE of normal intensity at the expected wavelength.

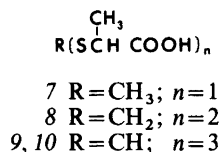
It is known that groups containing π -electrons (*e.g.* carbonyl, carbalkoxy, phenyl) or atoms con-



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taining lone pairs of electrons (*e.g.* sulfur) attached to the C–S–C chromophore have a marked effect on its electronic transitions,^{5,9} causing absorption bands to appear that are not characteristic of either unsubstituted sulfides or of the attached chromophore despite the non-conjugative positions of the groups.⁹ A similar phenomenon, even more pronounced, was observed for selenides.¹⁰ It therefore appears that interactions similar to those observed in disulfides and diselenides can take place between single sulfur and selenium atoms and certain suitably located chromophoric groups. In order to investigate such interactions, we have examined the CD spectra of the 2-thio- and 2-selenopropionic acids 1–6 as well as of some methane-2-thiopropionic acids (8–10). The CD spectrum of S-methyl-2-mercaptopropionic acid (7) has previously been reported.³



RESULTS AND DISCUSSION

The EA and CD maxima of compounds 1–10 are given in Tables 1 and 2. Both the EA and CD spectra exhibit peaks in spectral regions which do not correspond to the absorption maxima of either the isolated sulfide (or selenide) chromophore or the carboxyl chromophore.

Two kinds of interactions are generally believed to occur between a divalent sulfur atom and a carbonyl group. The first causes a perturbation of the $n \rightarrow \pi^*$ transition and the second leads to charge-transfer (CT).¹¹ CT transitions have been demonstrated in 1-thiocyclooctan-5-one¹² and in both rigid¹³ and flexible^{14,15} 2-thioketones where an S→CO CT interaction gives rise to a new absorption band normally in the 230–250 nm region. 2-Thioketones also exhibit an absorption band at 300–310 nm due to the $n \rightarrow \pi^*$ transition of the carbonyl group bathochromically shifted through perturbation by the nearby sulfur atom.¹⁶ Although the EA properties of 2-thioketones have been studied rather extensively no systematic study of 2-thiocarboxylic acids has appeared. Some 2-thiocarboxylic acid esters were shown to have an ab-

Table 1. Circular dichroism and electronic absorption maxima of some 2-thiopropionic acids.

Compound	Solvent	EA λ nm (ε)	CD λ nm ([θ])
(S)-(-)-1	<i>a</i>	242(350)	215(-3750)
	<i>b</i>		212(-700) ^h
	<i>c</i>		220(-6010)
(R R)-(+)-3	<i>a</i>	228(620)	256(-2690)
	<i>b</i>		218(+22450)
	<i>c</i>		233(+38730)
(S)-(-)-5	<i>a</i>	233(455)	229(-6790)
	<i>b</i>		217(-4050)
	<i>c</i>		232(-14260)
(R)-(+)-7	<i>d</i>	247(300) ^{g,i}	224(+2700)
	<i>e</i>		221(+1400)
	<i>f</i>		221(+3100)
	<i>c</i>		240(+2900)
(S S)-(-)-8	<i>a</i>	247(670) ⁱ	244(+1130)
	<i>b</i>		240(+2230)
	<i>c</i>		218(-43850)
(R R R)-(+)-9	<i>a</i>	245(1105) ⁱ	250(+5880)
	<i>b</i>		215(-43920)
	<i>c</i>		221(-75350)
(R R S)-(+)-10	<i>a</i>	245(1150) ⁱ	252(+12050)
	<i>b</i>		218(+65680) ^j
	<i>c</i>		249(-28550) ^k
	<i>a</i>		216(+51520)
	<i>b</i>		256(-2580)
	<i>c</i>		220(+80950)
	<i>a</i>		251(-43730)
	<i>b</i>		218(+25770) ^l
	<i>c</i>		250(-11120) ^m
	<i>a</i>		216(+17180)
	<i>b</i>		260(-510)
	<i>c</i>		221(+35950)
	<i>a</i>		252(-18580)

^a H₂O, pH 1. ^b H₂O, pH 7. ^c Cyclohexane-Dioxane (4:1). ^d MeOH. ^e MeOH/NaOH. ^f Hexane. ^g EtOH. ^h Additional CD maximum at 222 nm (+580). ⁱ Shoulder. Rotational strength (R/10³⁹ c.g.s.): ^j +4.95, ^k -2.27, ^l +1.90, ^m -0.77.

Table 2. Circular dichroism and electronic absorption maxima of some 2-selenopropionic acids.

Compound	Solvent	EA λ nm (ϵ)	CD λ nm ($[\theta]$)		
(S)-(-)-2	^a	267(270)		225(-11440)	260(-2490)
	^b			225(-7830)	255(-850) ^d
	^c			231(-8550)	260(-3090) ^d
(R R)-(+)-4	^a	280(240) ^d 243(760) 210(2520) ^d	215(+10060) ^d	243(+32680)	285(-4150)
	^b			231(+25640) ^e	282(-1670)
	^c		215(+6690) ^d	248(+45610)	288(-6810)
(R)-(+)-6	^a	242(590)		220(+5460) ^d	282(-1690)
	^b			225(+7480)	282(-510)
	^c			222(+3670) ^d	249(+13370)

^a H₂O, pH 1. ^b H₂O, pH 7. ^c Cyclohexane-Dioxane (4:1). ^d Shoulder. ^e Broad.

sorption band at 247 nm (ϵ 347–400) assigned to a perturbed carboxyl $n \rightarrow \pi^*$ transition.¹⁴

The acid *1* (Table 1) has an EA band similar in position and intensity to the longest wavelength absorption band of the above-mentioned esters¹⁴ and *S*-methyl-2-mercaptopropionic acid (*7*) indicating that the introduction of a second carboxyl group β to sulfur in a 2-thiopropionic acid has no dramatic effect on the absorption properties. It therefore seems justified to compare the CD spectrum of *1* with that reported³ for *S*-methyl-(2*R*)-mercaptopropionic acid (*R*)-*7* for the purpose of correlation of configurations. The CD spectrum of *1*, like that of (*R*)-*7* (Table 1), contains two CE's of the same sign at *ca.* 220 and 240 nm. As for (*R*)-*7*, the intensity of these CE's is markedly reduced on salt formation. These similarities confirm that the carboxyl group β to sulfur in *1* apparently gives no rotationally significant interactions with the 2-thiopropionic acid moiety. Since (-)-*1* displays CE's opposite in sign to those of (*R*)-*7* the absolute configuration of (-)-*1* may be assigned as *S*. The selenium analogue of *1* *i.e.* *2* (Table 2) shows an EA band at 267 nm which can be looked upon as the 242 nm band of *1* shifted to longer wavelength, and probably corresponds to the 277 nm (ϵ 398) band observed for 3-selenopentanoic acid (in hexane solution)¹⁰ and assigned to a perturbed carboxylic $n \rightarrow \pi^*$ transition.¹⁰ Except for an expected red shift of the CE's, the CD spectrum of *2* is qualitatively similar to that of *1*, and the acid (-)-*2* can therefore also be assigned the *S* configuration. These assignments are in

agreement with previous results. Fredga¹⁷ prepared (-)-*1* from (-)-2,2'-dithiobispropionic acid, whose absolute configuration is *SS*⁸, without affecting the chiral center. The acid (-)-*2* was shown to be configurationally identical with (-)-*1* by the quasaracemate method.¹⁷

Scopes *et al.*³ attributed the 240 nm CE of (*R*)-*7* to an $n \rightarrow \sigma^*$ transition of the sulfur chromophore. However, the corresponding alcohol *S*-methyl-(2*R*)-mercaptopropanol³ shows only a CE of $[\theta] = -370$ at 231 nm, most probably due to an $n \rightarrow \sigma^*$ transition of the C-S-C chromophore, and of opposite sign to that of the 240 nm CE of (*R*)-*7*. Furthermore, the intensity of the relevant absorption band in *1* and *7* is much higher than normally found for simple sulfides in this spectral region (*vide supra*). Finally, the 260 nm CE (and 267 nm absorption band) of *2* can hardly originate from the selenium chromophore alone since dialkyl selenides have their first absorption maximum at 250 nm (ϵ 50) in nonpolar solvents.^{10,18} The marked sensitivity of the 240 and 260 nm CE's of *1*, *2* and *7* to ionization of the carboxyl groups (Table 1 and 2) suggests that the CE's may in fact be due to a carboxyl $n \rightarrow \pi^*$ transition perturbed by the nearby sulfur or selenium atom.

The acids *3*–*6* differ from *1* and *2* in having two carboxyl groups α to the sulfur and selenium chromophores. In the EA spectra this property manifests itself in the appearance of a new absorption band in the 230 nm region for the sulfides *3* and *5* and at 242–243 nm for the selenides *4* and *6*. This may be a CT band analogous to the CT

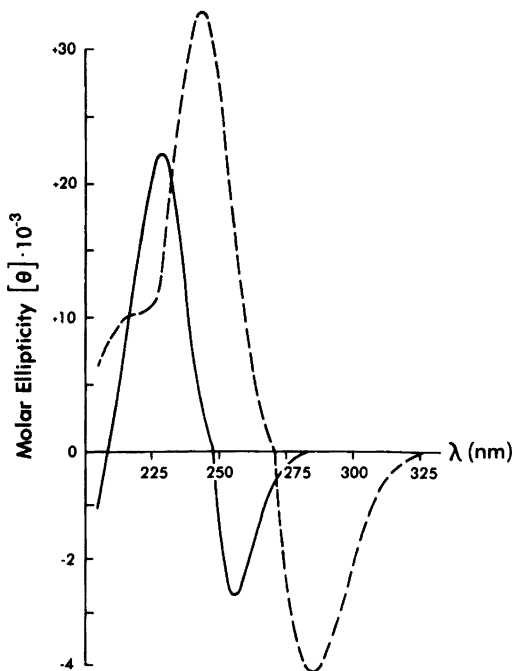


Fig. 1. Circular dichroism of (*R,R*)-(+)-2,2'-thiobispropionic acid 3 (—) and (*R,R*)-(+)-2,2'-selenobispropionic acid 4 (---) in water (pH 1). Note the different scales on the ordinate.

band observed for 2-thioketones^{14,15} but not previously noted in the spectra of 2-thiocarboxylic acids.

It is interesting to compare the CD spectra of 3 and 4 (Fig. 1) with those of the corresponding disulfide and diselenide⁸ which show intense CD bands (positive for the *R,R* configuration) at 225 and 239 nm, respectively. The appearance of analogous CE's in 3 and 4 (at 228 and 243 nm) shows that these CD bands have no connection with the presence of S—S or Se—Se bonds, but rather with the simultaneous occurrence of a carboxyl group and a sulfur or selenium atom. Accordingly, the absolute configuration of (+)-3 and (+)-4 may be designated as *R,R* in agreement with previous assignments.¹⁸ The acids 3 and 4 exhibit additional CE's at 256 and 285 nm, respectively, of opposite sign to the much more intense short wavelength CE's. Both the position and the intensity of these CE's are sensitive to ionization of the carboxyl groups (Tables 1 and 2) and it is suggested that the CE's are of the same origin as the long-wavelength

CE's of 1 and 2. The observed red shift of the CD bands on going from water to cyclohexane is in agreement with that expected for an $n \rightarrow \pi^*$ transition.

As may be anticipated from the similar disposition of the interacting groups, the acids 5 and 6 exhibit CE's which are virtually identical in position to those of 3 and 4, respectively. However, the intensity of the CE's is reduced due to the presence of only a single chiral center. From the sign of the CE's, (–)-5 may be assigned the *S* and (+)-6 the *R* configuration, a result which also follows from the mode of preparation of the acids.^{8,17}

As mentioned above, the introduction of a second carboxyl group β to sulfur in a 2-thiopropionic acid has no profound effect on its CD spectrum [*1 vs. (R)-7*]. On the other hand, if the second carboxyl group is separated from sulfur (or selenium) by only one carbon atom then, for the same absolute configuration, the sign of the long-wavelength CE is reversed while the sign of the short-wavelength CE is unaltered [*1 vs. 3 and 5; 2 vs. 4 and 6*]. It therefore appears that the sign of the short-wavelength CE correlates with the absolute configuration of substituted 2-thio- and 2-selenopropionic acids. A negative CE is always associated with the *S* configuration. If one of the carboxyl groups in 5 is replaced by a phenyl group to give *S*-benzyl-(2*S*)-mercaptopropionic acid, the CD spectrum still contains a negative CE, albeit of higher intensity, at ca. 230 nm³, indicating that the sign of the 215–230 nm CE in substituted 2-thiopropionic acids of a given absolute configuration is apparently independent of the nature of the chromophoric group attached to sulfur. The effect of such a group is primarily to affect the magnitude and position of the CE.

The acid 8 may be regarded as two molecules of 2-mercaptopropionic acid connected *via* their sulfur atoms by a methylene group. The EA spectrum of 8 indeed shows a shoulder at the same wavelength as the spectrum of *S*-methyl-2-mercaptopropionic acid³ but of about double the intensity. Assuming that interactions between the sulfur atoms do not affect the sign of the second CE associated with the 2-thiopropionic acid moieties (*vide supra*) the absolute configuration of (–)-8 may be assigned as *S,S* on the basis of the negative CE observed at ca. 220 nm. Similarly 9 and 10, which are diastereomers, may be looked upon as three molecules of 2-mercaptopropionic acid attached to the same carbon atom. The acid 9 has the same configuration at all

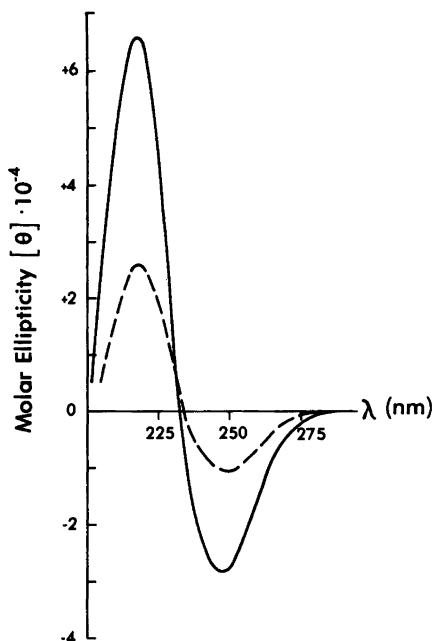


Fig. 2. Circular dichroism of (R,R,R) - $(+)$ -methanetri-2-thiopropionic acid **9** (—) and (R,R,S) - $(+)$ -methanetri-2-thiopropionic acid **10** (---) in water (pH 1).

three chiral centers²⁰ and on the basis of the positive CE observed in the 220 nm region $(+)$ -**9** may be assigned the R,R,R configuration. The high intensity of the CE's associated with **9** is probably due in part to interactions between the sulfur atoms of the three 2-thiopropionic acid moieties. A similar phenomenon has been observed²¹ in djenkolic acid, which also contains the $-S-C-S-$ grouping.

The acid **10** must have the R,R,S or the S,S,R configuration. If the rotatory contributions from the three chiral centers are independent of each other, then with the former configuration $(+)$ -**10** would be expected to give CE's of the same sign but of about one third of the intensity of those observed for **9**. This is indeed the case (Table 1 and Fig. 2).

Comparison of intensities of CE's are best made by using the rotational strengths of the corresponding transitions. The rotational strength may be calculated from the experimental values of the CD.²² The ratio of the rotational strengths obtained from the 250 nm CD bands of **9** and **10** in water at pH 1 (Table 1) is 2.95. For the 218 nm band this ratio is 2.60 in the same solvent. Thus the deviation from

strict additivity of the contributions from the separate chiral centers to the CE's is fairly small (2–13 %).

EXPERIMENTAL

The acids **1–6** and **8–10** were obtained as described by Fredga.^{17,20,23}

CD spectra were recorded with a Jasco J-500A spectropolarimeter at 20 °C. A water solution of the acid was brought to pH 1 by the addition of conc. HCl and the CD spectrum recorded. After the addition of 10 % NaOH to pH 7 the spectrum was again recorded. To verify that no racemization or decomposition had occurred at pH 7 the neutral solution was brought to pH 1 and the spectrum rerun. In every case the two spectra measured at pH 1 were identical. Due to the limited solubility of the acids in hydrocarbon solvents a mixture of cyclohexane and dioxane (4:1) was used.

EA spectra were recorded down to ca. 210 nm, where strong end absorption prevented further measurements, with a Cary Model 118 spectrophotometer.

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