Chiroptical and Conformational Studies of Optically Active 2-Aryl-2*H*-1,4-benzothiazin-3(4*H*)-one Derivatives, Related Compounds with a Novel Ca^{2+} Antagonist, Semotiadil (SD-3211)

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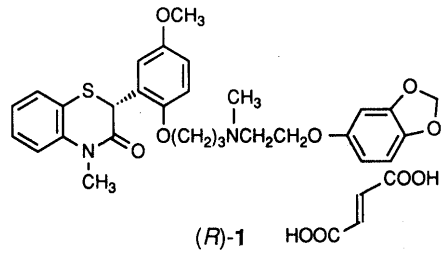
Chiroptical properties of (*R*)-(+)- and (*S*)-(−)-2-(2-hydroxy-5-methoxyphenyl)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one ((*R*)- and (*S*)-2), and (*S*)-(−)-4-methyl-2-phenyl-2*H*-1,4-benzothiazin-3(4*H*)-one ((*S*)-3), related compounds with a novel Ca^{2+} antagonist, Semotiadil ((*R*)-1; SD-3211), were reported. The absorption band of each chromophore was assigned by reference to the ultraviolet (UV) spectra of 2-unsubstituted benzothiazine (4) and thiazine (5); in the circular dichroism (CD) spectra of (*R*)-2, (*S*)-2 and (*S*)-3, their maximum wave lengths corresponded approximately to those of the UV absorptions of each chromophore. The CD spectra suggested that the conformation of (*S*)-3 was similar to that of (*R*)-2 and (*S*)-2, in contrast to the X-ray crystallographic result previously analyzed. The solution conformations of these compounds were discussed by reference to the helicity rule.

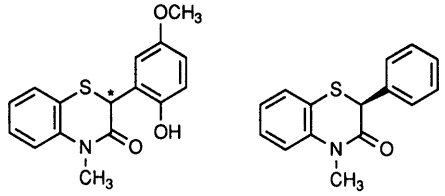
Keywords CD; chiroptical property; conformational analysis; 2-aryl-2*H*-1,4-benzothiazin-3(4*H*)-one; Ca^{2+} antagonist; Semotiadil; SD-3211; helicity rule

In the course of our recent studies on sulfur-containing heterocyclic compounds,[1] we reported the synthetic studies of 2-aryl benzothiazine derivatives.[2] This work led us to develop a novel Ca^{2+} antagonist, Semotiadil[3] fumarate ((*R*)-1; SD-3211).[4] During the progress of this research, the X-ray crystallographic analysis of the optically active phenol compound (*R*)-2, a synthetic intermediate of (*R*)-1, was completed. The X-ray results showed an orientation of 2-phenyl ring in the axial position.[4] More recently, the crystal structure of (*S*)-2-phenylbenzothiazine (*S*)-3 was determined.[5] In contrast to (*R*)-2, the 2-phenyl ring of (*S*)-3 exists in the equatorial position. It is interesting to note that the substituents on the 2-phenyl ring of these benzothiazines affected the molecular conformation.

Ca^{2+} antagonists are useful in the treatment of hypertension, angina pectoris, and certain cardiac arrhythmias, because of their excellent profiles.[6] From structure–activity relationship studies, it has been revealed that the stereochemistry of Ca^{2+} antagonists strongly influence their activity.[7] This prompted us to investigate the stereochemical features of (*R*)-1. Since (*R*)-1 has a flexible aminoalkyl side chain and its X-ray crystallographic structure has not yet been completed, it might provide useful information for the stereochemical study of (*R*)-1 to investigate the conformations of (*R*)-2 and (*S*)-3. Because of their optically active compounds, we studied their conformations in solution by circular dichroism (CD) measurement. Despite many investigations on the correlation between CD spectra and the stereochemistries of aromatic or heterocyclic compounds,[8] as far as we know, no study on the CD spectra of such 2-aryl benzothiazines has been reported.

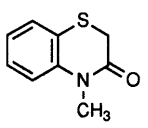


(*R*)-1



(*R*)-2
(*S*)-2

(*S*)-3



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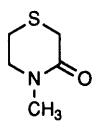

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Chart 1

In this study, first, each ultraviolet (UV) absorption band which originated from the chromophores of (*R*)-2 and (*S*)-3, was assigned by comparing its UV spectra with those of 2-unsubstituted benzothiazine (4) and thiazine (5). Then, based on the UV data, each CD band in (*R*)-2, (*S*)-2 and (*S*)-3 was assigned. This paper deals with the chiroptical properties of (*R*)-2, (*S*)-2 and (*S*)-3. Further, the conformations of these compounds in solution were also discussed.

UV Spectra of 2-Arylbenzothiazines ((*R*)-2, (*S*)-3) and Related Compounds (4) and (5) (*R*)-2 and (*S*)-3 exhibited two common absorption maxima at around 240 nm (band B) and 210 nm (band C) with a shoulder at around 255 nm in their UV spectra. In the 330—270 nm region (band A), (*R*)-2 showed an absorption maximum at 303 nm, while (*S*)-3 showed a weak, broad absorption as a shoulder (See Fig. 1). To assign each UV absorption band of (*R*)-2 and (*S*)-3, 4 and 5 were synthesized and their UV spectra were compared with those of (*R*)-2 and (*S*)-3. In the structure of 4, the 2-phenyl ring in (*R*)-2 and (*S*)-3 was removed. In the structure of 5, the benzene chromophore of the benzothiazine ring was removed from 4. The UV spectra of 4 and 5 are also shown in Fig. 1.

In comparing the UV spectra of (*R*)-2 and (*S*)-3 with that of 4, the absorptions of the shorter wavelength part of band C (210—202 nm; band c_1) which appeared in (*R*)-

2 and (*S*)-3 were diminished and changed into a shoulder in 4. Therefore, band c_1 could be assigned to a ^1L_a[9] transition of the 2-phenyl ring chromophore. Additionally, a ^1L_b[9] transition of the 2-phenyl ring chromophore of (*R*)-2 was assigned to the longer wavelength part of band A (335—290 nm; band a_2), since this band was also diminished in the spectrum of 4. This ^1L_b transition could not be assigned for (*S*)-3; however, it was definitely assigned in the CD spectrum, as will be mentioned later. When the UV spectra of 4 and 5 were compared, the absorption bands of 4 around 240 nm and 300—270 nm were diminished in 5. Each corresponded to band B and to the shorter wavelength part of band A (310—270 nm; band a_1), respectively, in (*R*)-2 and (*S*)-3. Hence, the ^1L_a and ^1L_b transitions of benzene chromophores in a benzothiazine ring could be assigned to band B and band a_1, respectively. The absorption band at around 215 nm in the spectrum of 4, which corresponded to the longer wavelength part of band C (225—210 nm; band c_2) in the spectra of (*R*)-2 and (*S*)-3, could also be determined as an n–π^* transition of an amide chromophore by comparing the spectra of 4 and 5. In the spectrum of 5, this band was shifted to around 210 nm, accompanied by a decrease in its intensity. Such a hypsochromic shift might be caused by the loss of the electronic effect of the aromatic ring of the benzothiazine nucleus on amide chromophore. Assignment of the shoulder at around 255 nm remained unclear. However, because of the appearance of this shoulder in the spectrum of 5, it might originate from the chromophore which makes up the thiazine ring. As will be described in the CD spectra, in the case of (*S*)-3, the ^1L_b transition of the 2-phenyl ring chromophore is also involved in this shoulder. UV data is summarized in Table I. Thus, in the UV spectra of (*R*)-2 and (*S*)-3, the absorption bands which originated from each chromophore could be assigned unambiguously, except for the ^1L_b transition of (*S*)-3.

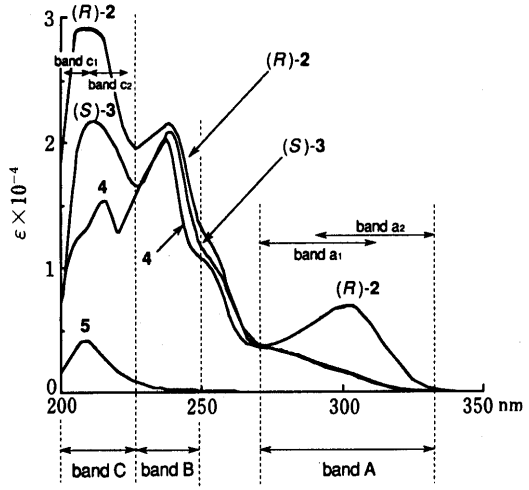

Fig. 1. UV Spectra of (*R*)-2, (*S*)-3, 4 and 5 in Ethanol at 23±2°C

TABLE I. UV Data of (*R*)-2 and (*S*)-3 in Ethanol at 23±2°C

Band	λ_{max} (*R*)-2	λ_{max} (*S*)-3	Chromophore	
Band A	302.5 nm	276 nm (sh)[a]	^1L_b of benzene	(2-phenyl ring)[b,c]
			^1L_b of benzene[d]	(benzothiazine ring)
Shoulder	(254 nm)	(253 nm)	Not assigned	
Band B	239 nm	239 nm	^1L_a of benzene	(benzothiazine ring)
Band C	206.5 nm	212 nm	n–π^* of amide[e]	(benzothiazine ring)
			^1L_a of benzene[f]	(2-phenyl ring)

a) Shoulder. *b*) This chromophore could be assigned only for (*R*)-2. *c*) Band a_2 (335—290 nm). *d*) Band a_1 (310—270 nm). *e*) Band c_2 (225—210 nm). *f*) Band c_1 (210—202 nm).

CD Spectra of 2-Arylbenzothiazines ((*R*)-2, (*S*)-2 and (*S*)-3) CD spectra of (*R*)-2, (*S*)-2 and (*S*)-3 in ethanol are shown in Fig. 2.

In the spectrum of (*R*)-2, which is a mirror image of (*S*)-2, each CD maximum was found at the wavelength approximately corresponding to the UV absorption of each chromophore. Therefore, each CD band could be assigned to each chromophore. In the spectrum of (*S*)-3, a strong negative CD maximum appeared at around 255 nm, while the 340—285 nm bands found in the spectra of (*R*)- and (*S*)-2 were diminished. Because of the appearance of other CD bands at almost the same wavelength as those of (*R*)- and (*S*)-2, these CD bands in the spectrum of (*S*)-3 were assigned according to the cases of these compounds. Since the 340—285 nm bands of (*R*)- and (*S*)-2 were ascribed to the ^1L_b transition of the 2-phenyl ring

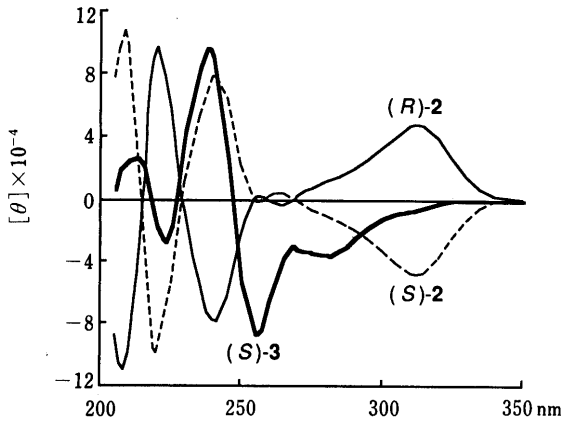

Fig. 2. CD Spectra of (*R*)-2, (*S*)-2 and (*S*)-3 in Ethanol at 25°C

TABLE II. CD Data of (*R*)-2, (*S*)-2 and (*S*)-3 in Ethanol at 25°C

Chromophore		(*R*)-2		(*S*)-2		(*S*)-3	
		Wavelength (nm)	Sign	Wavelength (nm)	Sign	Wavelength (nm)	Sign
^1L_b of benzene	(2-phenyl ring)	340—285	+	340—285	−	270—245	−
^1L_b of benzene	(benzothiazine ring)	285—275[a]	+	285—275[a]	−	310—270	−
^1L_a of benzene	(benzothiazine ring)	250—230	−	250—230	+	245—225	+
n–π^* of amide	(benzothiazine ring)	230—215	+	230—215	−	225—220	−
^1L_a of benzene	(2-phenyl ring)	215—	−	215—	+	220—	+

a) Shoulder.

chromophore, and the band which originated from this ^1L_b transition could not be determined in the UV spectrum of (*S*)-**3**, the CD maximum of (*S*)-**3** at around 255 nm could be assigned to this ^1L_b transition. In the UV spectrum of the benzothiazines reported here, the shoulder which originated from an unassigned transition appeared at this 255 nm region. However, it is assumed that this unassigned transition contributes little to the CD spectra, since only weak CD bands were found at around 255 nm region in the spectra of (*R*)- and (*S*)-**2**. These facts indicate that the negative CD maxima of (*S*)-**3** at around 255 nm originates mainly from the ^1L_b transition of the 2-phenyl ring chromophore. CD data with the assignment of each chromophore is shown in Table II.

Discussion

Each CD band of (*R*)-**2**, (*S*)-**2** and (*S*)-**3** was assigned based on the UV data of these compounds. Comparing the CD spectra of (*S*)-**3** with those of (*R*)-**2** and (*S*)-**2**, all CD bands which originated from the chromophores of (*S*)-**3** gave the same signs as those of the corresponding chromophores of (*S*)-**2**, and the opposite signs to those of the chromophores of (*R*)-**2**. These findings indicate that the conformation of (*S*)-**3** is similar to those of (*R*)-**2** and (*S*)-**2** under certain conditions such as the CD measurements. It is interesting to note that the conformational similarity between these compounds in solution is in contrast to the X-ray crystallographic results previously analyzed. In the crystals of (*R*)-**2** and (*S*)-**3**, a marked conformational difference was observed concerning the orientation of the 2-phenyl ring; the orientation is axial for (*R*)-**2** and equatorial for (*S*)-**3**. In order to assume their solution conformation concerning the 2-phenyl ring, we made an attempt to apply the helicity rule to the relationship between CD spectra and conformation. Recently, Kajtár *et al.*[10] reported on the chiroptical properties and stereochemistry of the optically active 5-aryl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-ones (**6**). They showed that the sign of the CD band which originated from the benzene chromophore of the benzodiazepine nucleus was determined by the helicity of the seven-membered diazepine ring, and the sign of the ^1L_a band of the chromophore could be correlated with the conformation of the benzodiazepin-2-one moiety using the simple helicity rule; positive and negative signs corresponded to *M*- and *P*-helicities,[11] respectively. The researchers also described that this rule was confirmed by theoretical calculations. On the theoretical calculations for the CD band of the benzene chromophore of the benzodiazepine ring, 4-chloro-2,*N*-dimethylformanilide **7** was chosen as a model compound. In the structure of **7**, the smallest moiety comprising all the atoms that can influence the chiroptical properties of **6** is involved.

In the case of our benzothiazines, the sign of the CD band which originated from the benzene chromophore of the benzothiazine ring was assumed to be determined by the helicity of the thiazine ring, as well as the benzodiazepines quoted above or the tetralines reported by Snatzke *et al.*[8d,12] The benzothiazines and the benzodiazepines share a common partial structure which is inherently a chiral chromophoric system consisting of the benzene ring of the benzothiazine or the benzodiazepine nucleus and the amide moiety bound to it non-coplanarly. Additionally, the result of the theoretical calculations made for the benzodiazepines might also be available, though the aromatic ring substituents on the 2- and 4-positions of the model compound for the benzothiazines should be different from those of **7**. Consequently, the conformation of the benzothiazine ring was investigated using the helicity rule for the benzodiazepines. In the CD spectra of (*R*)-**2**, (*S*)-**2** and (*S*)-**3**, the signs of the ^1L_a band of the benzene chromophore of the benzothiazine ring are negative for (*R*)-**2** and positive for (*S*)-**2** and (*S*)-**3**, respectively. Applying the helicity rule, *P*-helicity and *M*-helicity arises for (*R*)-**2** and for (*S*)-**2** and (*S*)-**3**, respectively. As depicted in Fig. 3, it is reasonable to assume that the 2-phenyl ring exists in the equatorial position in these three compounds.

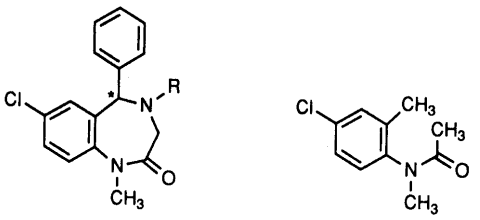

Chart 2

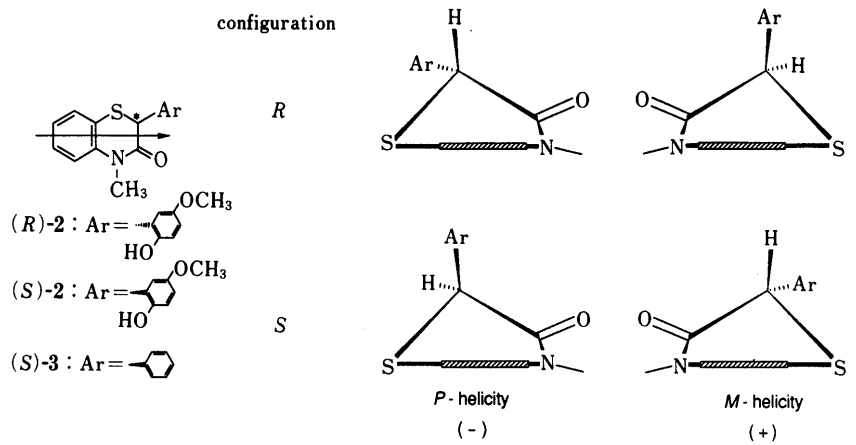

Fig. 3. Schematic Projection for the Structure of 2-Aryl-2*H*-1,4-benzothiazin-3(4*H*)-one Derivatives

The arrow indicates the direction of projection. The signs given are those for contributions to the ^1L_a band CD of the benzene chromophore of the benzothiazine ring according to the helicity rule.

In the crystal structure of (*R*)-**2**, an intermolecular hydrogen bonding exists between the amide carbonyl group of a molecule and the phenolic hydroxyl group of a neighboring molecule. Under the CD measurement conditions of the present study, such an intermolecular hydrogen bonding formation is unlikely to occur, since the sample solution is sufficiently diluted and the solvent is ethanol, a protic solvent. If the axial position of the 2-phenyl ring in the crystal is caused by this intermolecular hydrogen bond, it is not unreasonable to suppose that the 2-phenyl ring exists in the equatorial position in solution.

In summary, the CD spectra of 2-aryl-2*H*-1,4-benzothiazin-3(4*H*)-one derivatives (*R*)-**2**, (*S*)-**2** and (*S*)-**3** were analyzed by comparing their UV spectra with those of **4** and **5**. The CD spectra indicated that the conformation of (*S*)-**3** was similar to those of (*R*)-**2** and (*S*)-**2** in solution. From the helicity rule reported by Kajtár *et al.*, the existence of a 2-phenyl ring in the equatorial position was suggested for these compounds. Since these compounds have one proton on the thiazine ring, it seems difficult to analyze their solution conformations only by ^{1}H-nuclear magnetic resonance (^{1}H-NMR). CD measurements could offer useful information for this purpose. Based on the data reported here, the correlation of the CD spectral pattern for (*R*)-**1** with its solution conformation is now under investigation.

Experimental

UV spectra were recorded at 23±2 °C with a Shimadzu UV-240 spectrometer. CD spectra were measured at 25 °C using a 10 mm cell on a JASCO J-500 spectropolarimeter. All samples were 0.01 mg/ml ethanol solutions. (*R*)-(+)- and (*S*)-(−)-2-(2-Hydroxy-5-methoxyphenyl)-4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one ((*R*)- and (*S*)-**2**),[4] 4-methyl-2*H*-1,4-benzothiazin-3(4*H*)-one (**4**)[13] and 5,6-dihydro-4-methyl-2*H*-1,4-thiazin-3(4*H*)-one (**5**)[14] were synthesized as previously described. (*S*)-(−)-4-Methyl-2-phenyl-2*H*-1,4-benzothiazin-3(4*H*)-one ((*S*)-**3**) was prepared by the direct preparative high performance liquid chromatography (HPLC) resolution of racemate ((*R,S*)-**3**).[2] For the resolution, the commercially available chiral column (Chiralcel OB® (Daicel Chemical Industries, Ltd.), a cellulose benzoate coated silica gel stationary phase[15]) was used with *n*-hexane and 2-propanol mixture (4:1) as the eluent. Detailed procedures will be described in another paper.[5]

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References and Notes

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