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THE RELATION BETWEEN CD SPECTRA OF N-DITHIOETHOXYCARBONYL DERIVATIVES OF β-AMINO ACIDS AND THEIR CONFIGURATIONS

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There have been only few reports on the relationship between the configurations of β-amino acids and their optical behaviors,[1-3] and the relationships are not always satisfactory to be used as empirical rules for determining the configurations of various β-amino acids. A relationship suggested by Sjöberg *et al.*[2] that the dithiocarbamate of a L-β-amino acid shows negative Cotton effect had been considered useful, but we pointed out an exceptional case to it.[4] At the same time, we proposed an empirical rule, similar to that of Balenović,[1] for the assignment of the configuration of a β-amino acid from pH-dependence of its ORD curve.[4] However, two exceptional cases to it have recently been observed.[5,6] We report here the results of our reinvestigations on the relation between CD spectra of β-amino acid derivatives and their configurations. Optically active β-amino acids used for this purpose, summarized in Table 3, were prepared from the corresponding L-α-amino acids, except L-β-Phe[7,8] and L-β-Hpr,[9] by the Arndt-Eistert reaction. These β-amino acids were converted into N-dithioethoxycarbonyl (DTEC) derivatives, and their Cotton effects, especially influences of solvents on them,[10] were examined in detail.

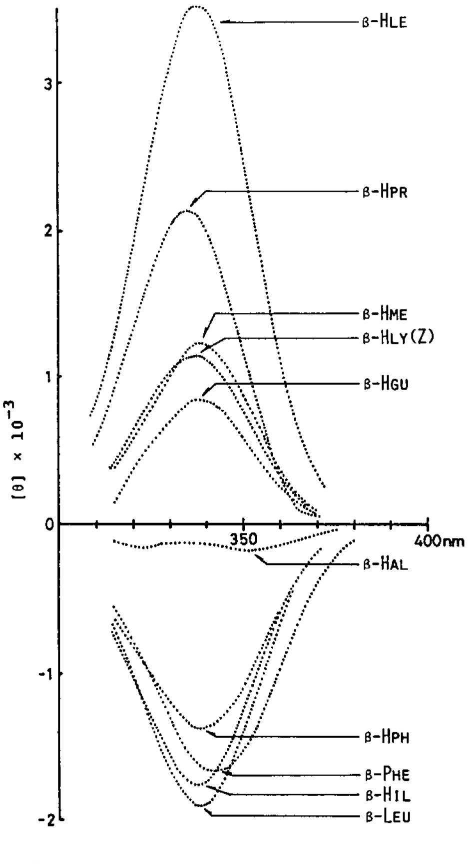

FIG.1. CD SPECTRA OF DTEC-L-β-AA-OH IN MeOH.

Every N-DTEC-L-β-amino acid (DTEC-L-β-AA-OH) showed a CD maximum in the region of 330-350 nm. Unexpectedly, no definite relationship between the sign of the Cotton effect in methanol and the configuration of the parent β-amino acid could be recognized, as is seen in Fig. 1. Moreover, in chloroform or benzene most of the compounds showed positive Cotton effects, just contrary to the Sjöberg's suggestion, though a fairly definite relationship was recognized (Table 1). So, solvent effects upon the Cotton effect

TABLE 1. COTTON EFFECTS OF DTEC-L-β-AA-OH

DTEC-β-AA-OH	MeOH	$CHCl_3$	C_6H_6
β-Hal	−	+	+
β-Leu	−	+	+
β-Hil	−	+	+
β-Hle	+	+	+
β-Hme	+	+	+
β-Hly(Z)	+	+	+
β-Hgu	+	+	+
β-Phe	−	−	−
β-Hph	−	−	−
β-Hpr	+	+	+

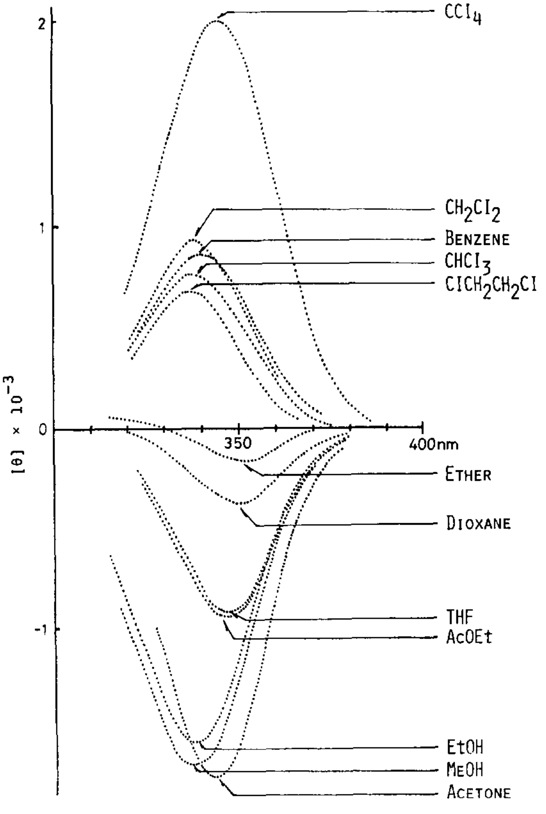

FIG.2. CD SPECTRA OF DTEC-L-β-HIL-OH IN VARIOUS SOLVENTS.

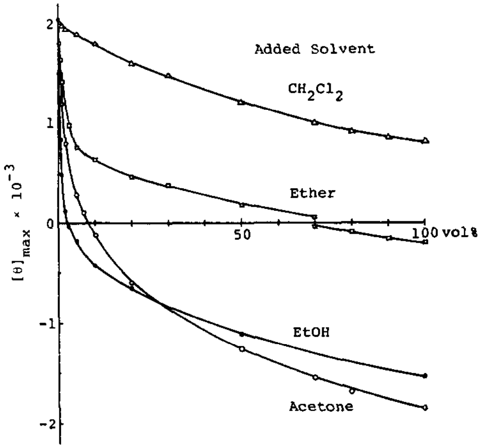

FIG.3. EFFECTS OF ADDED SOLVENTS ON MAXIMA OF CD SPECTRA OF DTEC-L-β-HIL-OH IN CCl_4.

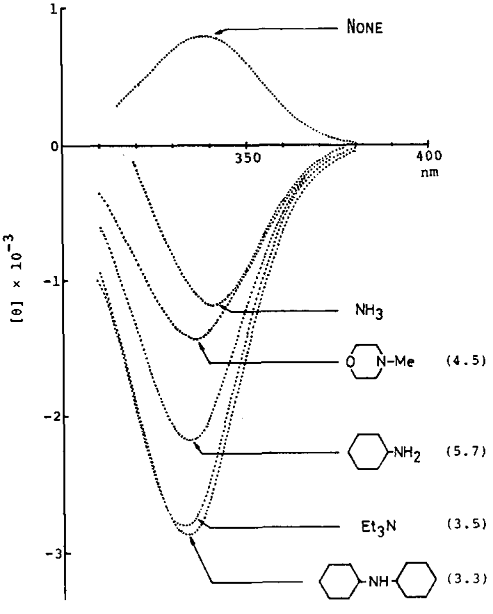

FIG.4. EFFECTS OF ADDED AMINES ON COTTON EFFECT OF DTEC-L-β-HIL-OH IN $CHCl_3$.
(Numbers indicate molar equivalents of amines to DTEC-L-β-Hil-OH)

were further investigated using the β-Hil derivative. Marked results were obtained (Fig. 2). This was also the case for the β-Leu derivative. It should be noted that negative Cotton effects were observed in common in such oxygen-containing solvents as alcohol, ester, ether, or ketone. Figure 3 shows that, in a mixed solvent the strength and even the sign of the Cotton effect change dependent upon the mixing ratio of the solvents. The change was remarkable in the region of the low concentration of an oxygen-containing solvent. These results suggest that the solvent effect is due to the interaction of a carboxyl group of DTEC-β-AA-OH with the oxygen-containing solvent. Therefore, a base can be expected to be a more effective cause of the change of the Cotton effect than these solvents, as Fig. 4 shows. As the dicyclohexylamine (DCHA) was the most effective, the DCHA salts of DTEC-L-β-AA-OH were prepared and their CD spectra were measured. Strikingly, all the DCHA salts, with the only exception of the L-β-Hpr derivative, showed negative Cotton effects in chloroform (Fig. 5) with scarcely any solvent effects (Table 2), in contrast with the case of the free DTEC-L-β-AA-OH. The relationship found here could successfully be applied to the DCHA salts of the N-DTEC derivatives of γ-ethyl D-β-glutamate[11] (positive Cotton effect in methanol, chloroform, or benzene) and (+)-β-(2-thiazolyl)-β-alanine which had been assigned to the L-series[12] (negative Cotton effect in methanol, chloroform, or benzene).

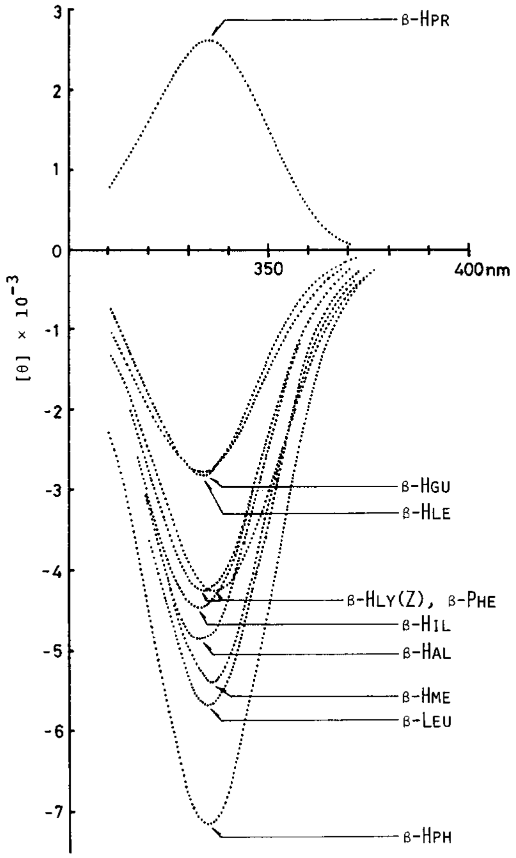

FIG.5. CD SPECTRA OF DTEC-L-β-AA-OH·DCHA IN $CHCl_3$

TABLE 2. COTTON EFFECTS OF DTEC-L-β-AA-OH·DCHA

DTEC-β-AA-OH·DCHA	MeOH	$CHCl_3$	C_6H_6
β-Hal	-	-	-
β-Leu	-	-	-
β-Hil	-	-	-
β-Hle	+ -	-	-
β-Hme	-	-	-
β-Hly(Z)	-	-	-
β-Hgu(2DCHA)	-	-	-
β-Phe	-	-	-
β-Hph	-	-	-
β-Hpr	+	+	+

Consequently, the following rule is thought useful to determine the configurations of β-amino acids, with the exception of such an imino (or a cyclic imino) acid as β-Hpr:

If the Cotton effect of the DCHA salt of a N-DTEC-β-amino acid in chloroform or benzene in the region of 330-350 nm is negative, the configuration of the β-amino acid is assigned to the L-series.

Further investigations on β-imino acids are in progress.

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7) This was prepared by the resolution of the N-phthalyl-DL-compound with ephedrin; *cf.* E. Graf and H. Boeddeker, *Justus Liebigs Ann. Chem.*, 613, 111 (1958).
8) Abbreviations according to the IUPAC-IUB Commission (*J. Biol. Chem.*, 247, 977 (1972)) are used. Hal, homoalanine; Hil, homoisoleucine; Hle, homoleucine; Hme, homomethionine; Hly(Z), ω-N-benzyloxycarbonyl homolysine; Hgu, homoglutamic acid; Hph, homophenylalanine; Hpr, homoproline; Bzl, benzyl.
9) This was presented from Dr. T. Wakabayashi. See T. Wakabayashi, K. Watanabe, and Y. Kato, *Synth. Commun.*, 7, 239 (1977).
10) Drastic solvent effects on the Cotton effects of DTEC-α-AA-OH were found by Yamada, *et al.*; K. Ishikawa, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, 19, 912 (1971).
11) This was derived from Z-L-Asp(OBzl)-OH *via* Z-L-β-Glu(OBzl)-OEt (≡ Z-D-β-Glu(OEt)-OBzl) by the Arndt-Eistert reaction. β-Glu means β-glutamic acid, *i.e.*, β-aminoglutaric acid.
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TABLE 3. L-β-AMINO ACIDS ($\overset{R^1}{HN}\overset{R^2}{CH}CH_2COOH$)

β-AA	R^1	R^2	Mp(dec)(°C)	$[\alpha]_D$ (H_2O)	Ref.
β-Hal	H	CH_3	211 - 212	+34.8° (c 0.48, 19°C)	13
β-Leu	H	$CH(CH_3)_2$	201 - 202.5	+55.2° (c 1.0 , 22°C)	14
β-Hil	H	$CH(CH_3)C_2H_5$	190 - 191	+46.0° (c 1.0 , 22°C)	-
β-Hle	H	$CH_2CH(CH_3)_2$	216 - 217.5	+34.7° (c 1.0 , 22°C)	15
β-Hme	H	$(CH_2)_2SCH_3$	190 - 191.5	-33.8° (c 0.5 , 22°C)	-
β-Hly(Z)	H	$(CH_2)_4NH$-Z	191 - 193	+16.5° (c 1.0 , 20°C)	-
β-Hgu	H	$(CH_2)_2COOH$	187 - 188.5	+70.2° (c 0.5 , 24°C)	-
β-Phe	H	C_6H_5	236 - 237	+ 6.2° (c 0.65, 19°C)	7
β-Hph	H	$CH_2C_6H_5$	224 - 224.5	+ 1.3° (c 7,N-HCl,20°C)	-
β-Hpr	$-CH_2CH_2CH_2-$		182 - 184	+43.7° (c 1, 3N-HCl)	9