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OPTICAL ROTATORY DISPERSION AND ABSOLUTE CONFIGURATION—I

α-AMINO ACIDS[1]

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Abstract—Optical rotatory dispersion measurements of six enantiomeric pairs of α-amino acids, both in neutral and in acidic solution, have shown that the direction and slope of the ORD curve between 200 and 225 mμ will indicate the absolute configuration of the α-asymmetric center.

THE use of anomalous rotatory dispersion measurements[2] has not hitherto been applied to the assignment of absolute configuration of α-amino acids because of their unsuitable spectral properties, only plain dispersion curves being obtained in the range extending to 240 mμ,[3] and the preparation of derivatives which absorb in the visible or near UV portion of the spectrum has been necessary to obtain Cotton effects. Thus, dithiocarbamate derivatives of α-amino acids of the L-series exhibited[4] a positive Cotton effect in the 300 to 400 mμ region, indicating the absolute configuration of the α-asymmetric center, and the reverse was true for members of the D-series.

Instruments have recently become available which permit the measurement of rotatory dispersion well below this region, and Jennings and Klyne[5] reported positive Cotton effects at about 225 mμ for three L-amino acids in acid solution, but no curves were given.* We now wish to record measurements of the anomalous rotatory dispersion of α-amino acids in the 225 to 200 mμ region, which make possible the simple and rapid assignment of absolute configuration *using the free α-amino acids themselves* either in neutral or in acidic solution.

The following representative α-amino acids were examined: alanine, β-phenylalanine, phenylglycine, pipecolic acid, proline, and azetidine-2-carboxylic acid. All spectra were recorded both in neutral and in 0·1N hydrochloric acid solution, each

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* After this paper had been submitted, the publications of Dirkx and Sixma[8] and of Gaffield[9] appeared, in which positive Cotton effects at about 225 mμ are reported for a number of L-amino acids, and in which dispersion curves are given down to between 210 and 220 mμ,[8] and down to 193 mμ,[9] respectively.

[1] Supported by research grant HE-5881 from the National Institutes of Health, U.S. Public Health Service.

[2] C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*. McGraw-Hill, New York (1960).

[3] [a] J. A. Schellman, Ref. 2, Chap. 15;
[b] J. Strem, Y. S. R. Krisha-Prasad, and J. A. Schellman, *Tetrahedron* **13**, 176 (1961).

[4] B. Sjöberg, A. Fredga, and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 5002 (1959).

[5] J. P. Jennings and W. Klyne, *Biochem. J.* **86**, 12P (1963).

95% with respect to ethanol (except in the case of phenylglycine where limited solubility permitted only the acid solution to be used). To ensure complete validity for the conclusions, regardless of rising end-absorption by the solvent or of scattered light

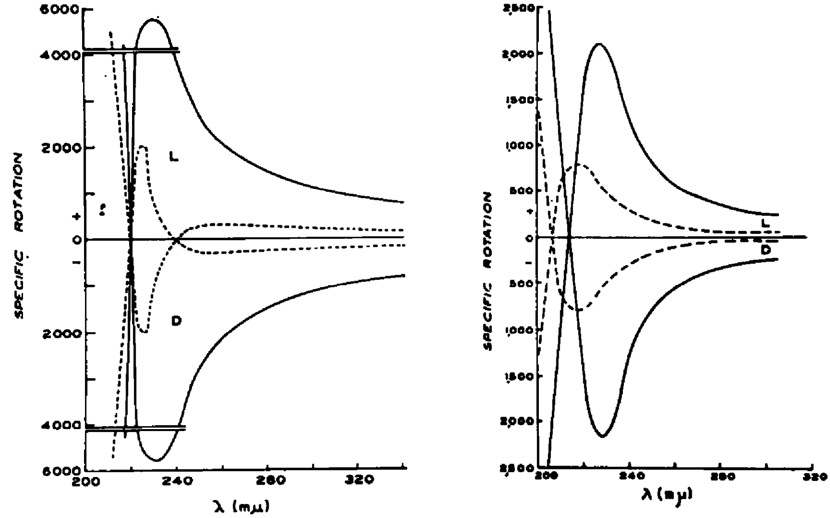

Fig. 1. Rotatory Dispersion Curves. (left) β-Phenylalanine (-----) and hydrochloride (———) (right) Alanine (-----) and hydrochloride (———).

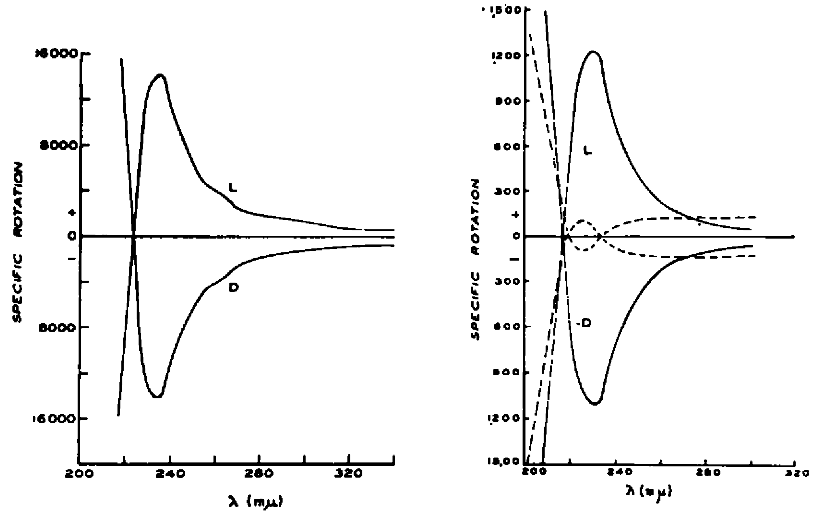

Fig. 2. Rotatory Dispersion Curves. (left) Phenylglycine hydrochloride. (right) Pipecolic acid (-----) and hydrochloride (———).

in the 200 to 225 mμ region, the spectra of both enantiomers were recorded in every case.

The results are shown in Figs 1, 2 and 3. Light absorption in the α-amino acids is due to the carboxyl group which has an absorption band between 210 and 215 mμ,[3] and the curves (with the exception of that of azetidine) show zero rotation in the vicinity of 220 to 225 mμ. The rule of Lutz and Jirgensons[6] is seen to hold for all wavelengths. L-Proline shows a positive dispersion curve, although it was earlier believed[3] to be negative. It would be tempting to conclude that, as in the dithiocarbamate derivatives,[4] all members of the L-series exhibit a positive Cotton effect, but this is seen to be true only in acidic solution. As free rotation is progressively restricted, and ring strain increased, on passing from the open chain compounds to those possessing six-, five- and four-membered rings, the positive Cotton effect diminishes in neutral solution until the rotatory properties approximate to a plain curve.

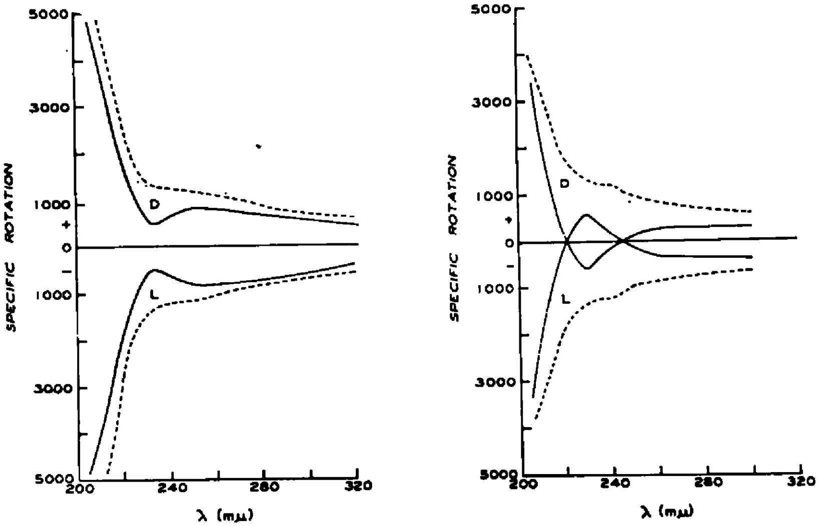

FIG. 3. Rotatory Dispersion Curves. (left) Azetidine-2-carboxylic acid (- - - - -) and hydrochloride (———) (right) Proline (- - - - -) and hydrochloride (———).

However, in both neutral and acidic conditions all members of the L-series exhibit a striking negative "tail" of the ORD curves in the region between 200 and 225 mμ, descending steeply to large and hitherto unreported negatives values (—1500 to —15,000) of the specific rotation after reaching zero rotation at about 220 to 225 mμ. The resulting Cotton effect curves of the free acids themselves can therefore be used for absolute configurational assignments of the α-asymmetric center, *members of the L-series showing a steeply descending negative "tail" of the ORD curve between 200 to 225 mμ, and members of the D-series a steeply ascending positive one.*

Further extensions of this rotatory dispersion approach will be reported in a following paper.

EXPERIMENTAL

Rotatory dispersion curves were measured with a Bendix Model 460-C or a Cary Model 60 spectropolarimeter using 1 mm or 1 cm cells (c 0·01 to 0·05 in 95% ethanol) at 25°, and were reproducible to within 5%. Specific rotation and wavelength are quoted (1) at the highest and lowest

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[6] O. Lutz and B. Jirgensons, *Chem. Ber.* 63, 448 (1930); 64, 1221 (1931).

[7] We thank Dr. V. Rodwell and Mr. M. Apple for a sample of pipecolic acid.

[8] I. P. Dirkx and F. L. J. Sixma, *Rec. Trav. Chim.* 83, 522 (1964).

[9] W. Gaffield, *Chem. & Ind.* 1460 (1964).

wavelength used, (2) at the troughs and peaks, and (3) at the points where [α] = 0. Since measurements taken for enantiomeric pairs normally agreed within 5%, figures for only one isomer are given in each case.

(*L*)-(+)-*Alanine*. R.D. (*c* 0·030 in 95% ethanol) $[\alpha]_{300}$ 40°, $[\alpha]_{217}$ 800° (peak), $[\alpha]_{207}$ 0°, $[\alpha]_{205}$ −333°. The hydrochloride had $[\alpha]_D$ 14·4° (*c* 2·0 in N-HCl), and R.D. (*c* 0·030 in 95% ethanol) $[\alpha]_{300}$ 250°, $[\alpha]_{227}$ 2117° (peak), $[\alpha]_{214}$ 0°, $[\alpha]_{205}$ −2550°.

(*L*)-(−)-*β-Phenylalanine*. $[\alpha]_D$ −34·5° (*c* 2·0 in H_2O). R.D. (*c* 0·046 in 95% ethanol) $[\alpha]_{238}$ −143°, $[\alpha]_{233}$ 0°, $[\alpha]_{225}$ 2045°, (peak), $[\alpha]_{219}$ 0°, $[\alpha]_{216}$ −5440°. The hydrochloride had R.D. $[\alpha]_{238}$ 816°, $[\alpha]_{230\cdot5}$ 5520° (peak), $[\alpha]_{219}$ 0°, $[\alpha]_{218}$ −4200°.

(*L*)-(−)-*Phenylglycine*. $[\alpha]_D$ −158° (*c* 2·0 in 2N HCl). R.D. (*c* 0·051 in 95% ethanolic 0·1N HCl) $[\alpha]_{232}$ 798°, $[\alpha]_{224}$ 14,080° (peak), $[\alpha]_{223}$ 0°, $[\alpha]_{217}$ −15,810°.

(*L*)-(−)-*Pipecolic Acid*[7]. $[\alpha]_D$ −21° (*c* 6·0 in H_2O). R.D. (*c* 0·053 in 95% ethanol) $[\alpha]_{300}$ −94°, $[\alpha]_{225}$ 94° (peak), $[\alpha]_{205}$ −1133°. The hydrochloride had R.D. $[\alpha]_{300}$ 56°, $[\alpha]_{220}$ 1230° (peak), $[\alpha]_{216}$ 0°, $[\alpha]_{210}$ −1274°.

(*L*)-(−)-*Proline*. $[\alpha]_D$ −85° (*c* 5·0 in H_2O). R.D. (*c* 0·012 in 95% ethanol) $[\alpha]_{300}$ −567°, $[\alpha]_{228}$ −1284° (shoulder), $[\alpha]_{210}$ −3033°. The hydrochloride had R.D. $[\alpha]_{300}$ −352°, $[\alpha]_{243}$ 0°, $[\alpha]_{227}$ 615° (peak), $[\alpha]_{220}$ 0°, $[\alpha]_{202}$ −3934°.

(*L*)-(−)-*Azetidine-2-carboxylic acid*. $[\alpha]_D$ −124° (*c* 3·6 in H_2O). R.D. (*c* 0·17 in 95% ethanol) $[\alpha]_{320}$ −552°, $[\alpha]_{235}$ −1289° (shoulder), $[\alpha]_{210}$ −5450°. The hydrochloride had R.D. $[\alpha]_{252}$ −438°, $[\alpha]_{236}$ −804° (trough), $[\alpha]_{231}$ −640° (peak), $[\alpha]_{205}$ −4840°.