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A SECTOR RULE FOR RELATING OPTICAL ROTATORY DISPERSION WITH THE CONFORMATION AND ABSOLUTE CONFIGURATION OF α-AMINO ACIDS

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All naturally-occurring and most synthetic L-α-amino acids show positive Cotton effect curves with the first extremum at 223 - 227 nm in optical rotatory dispersion (ORD) measurements, and 208 - 211 nm in circular dichroism (CD) measurements in aqueous acid solution (1-7). The aromatic α-amino acids show high molecular rotations at the peak, $(\Phi)_{225}$ = +3300 to +5200, while most aliphatic α-amino acids show moderately high molecular rotations, $(\Phi)_{225}$ = +1600 to +3700, with the notable exceptions of L-proline, $(\Phi)_{225}$ = +410 (1), $(\Phi)_{225}$ = +485 (2), and L-azetidine-2-carboxylic acid, $(\Phi)_{231}$ = -646 (4) among the amino acids with a single asymmetric center.

We wish to report a sector rule for α-amino acids, based on the octant rule for ketones (8), and derived from the sector rule for lactones (9), which relates the sign and amplitude of the Cotton effect with the conformation and absolute configuration of α-amino acids.

Structural analysis of α-amino acids has indicated a preferred conformation in solution in which the N-C^{α}-COO atoms are coplanar (10,11). The C-O bond of the carboxylate ion, or of the unionized carboxyl group, is cis to the C^{α}-N, with the hydrogen atoms on N staggered with respect to C-O. Since an n-π* transition is involved in the absorption of both the ketone and carboxylate groups, for purposes of analysis the two C-O bonds in the carboxylate ion may be considered as two equivalent ketone groups, separated by 120°. The plane bisecting the carboxylate ion is taken as a symmetry plane (Plane A, Fig. 1). By assigning two additional planes, P_1 and P_2, through the carboxylate carbon atom, each perpendicular to a C-O bond, application of the ketone octant rule to each C-O produces cancellation of contributions in some 30° sectors, and reinforcement in others, as seen in Fig. 1. This leads to a positive contribution for substituents in a 30° sector in the center of the upper right rear quadrant, and a negative contribution in a 30° sector in the center of the upper left rear quadrant. Since the carboxylate ion has a true plane of symmetry, the corresponding sectors below the

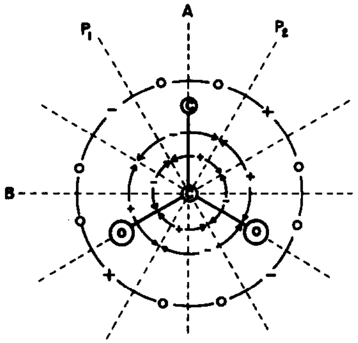
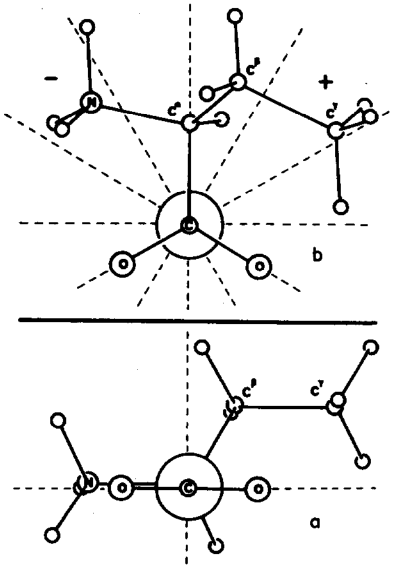


Figure 1. View of the C^{α}-COO plane from the top. A is a symmetry plane bisecting the carboxylate ion. P_1 and P_2 are planes perpendicular to each C-O bond. The inner circles show independent contributions of each C-O by the ketone octant rule. The outer circle shows the resultant 30° sectors where substituents contribute to a positive or negative Cotton effect, or make no contribution.

plane are of opposite sign. Sectors of 60° in which groups make no contributions to rotation have their centers on each of the major perpendicular planes, A and B, Fig. 1.

L-α-amino-n-butyric acid is shown in the favored conformation (10,11) as a typical representative of this series in Fig. 2. A view looking towards the carboxylate group in the OOC-C^{α}-N plane (Fig. 2a) shows that these atoms lie in a nodal or symmetry plane and therefore do not contribute to the optical rotation. The hydrogen atoms on nitrogen are also close to



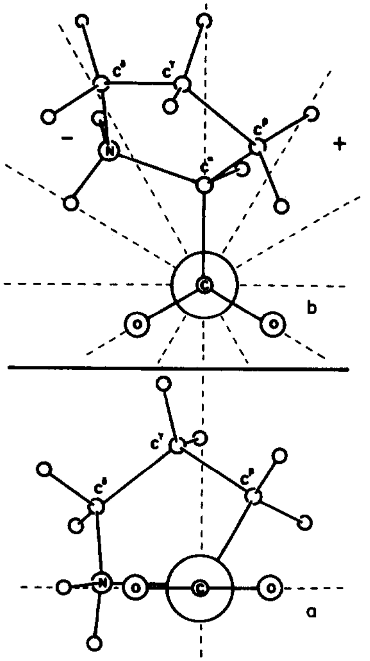


Figure 2. Projection drawing of L-α-amino-n-butyric acid.

Figure 3. Projection drawing of L-proline.

Both figures: (a) View in the OOC-C^{α}-N plane.
(b) View from above the OOC-C^{α}-N plane showing sectors contributing to the Cotton effect.

this plane, and the negative contribution to rotation made by those which lie above the plane in the upper left rear sector is cancelled by those which lie in the positive sector below. Thus, *only the side chain group and the hydrogen atom attached to the α-carbon atom, make significant contributions to the rotatory effect*. As seen in Fig. 2b, which shows a projection of the structure of L-α-amino-n-butyric acid from above the plane, atoms or groups attached to the β-carbon (C^{β}) may rotate only through the positive 30° sector, or through the 60° null sectors which adjoin the positive sector. As the bulk of the side chain increases, a greater amount of the positive sector is occupied, and specific rotation increases, as has been observed (1-7).

The unusually low rotation for L-proline is rationalized by the structures shown in Fig. 3. Fig. 3a, looking along the OOC-C^{α}-N plane, shows that only the H^{α} and C^{β}, C^{γ}, and C^{δ} methylene groups are removed from the symmetry and nodal planes and make significant contributions to rotation. Fig. 3b, looking down on the upper sectors, shows that this methylene bridge must coil back through the null sector. The C^{β} methylene group is close to the positive sector, the C^{γ} methylene group is in the center of a null sector, while the C^{δ} methylene group lies close to the negative sector, creating a balanced set of contributions which leads to a small rotation.

The four-membered ring of L-azetidine carboxylic acid has no methylene atoms close to the positive sector, while the C^{γ} methylene group borders the negative sector, accounting for its negative rotation (4).

In order to further test the scope of this α-amino acid sector rule, we have measured the ORD and CD spectra of some additional α-amino acids (12,13). As shown in Table 1, these aliphatic and alicyclic α-amino acids contain a concentration of methylene and methyl groups in the side chain attached to the α-carbon, and as predicted, the L-α-amino acids show a high positive rotation at the first extremum, ORD = 225-226 nm, CD = 209-211 nm, ORD zero crossover at 209-211 nm, with steeply descending curves below 208 nm (4). The one D-enantiomer which was measured showed a mirror image curve to that of the L-α-amino acid. L-α-Cyclohexylglycine, with one more methylene group than L-α-cyclopentylglycine, had the greater molecular rotation. L-α-amino-β-ethylvaleric acid and L-α-cyclopentylglycine have the same number of carbon atoms, however, the steric constraint imposed by the planar cyclopentyl ring reduces its contribution in the positive sector, and the open chain analog shows the higher molecular rotation.

Although the above analysis has been based on the symmetrical carboxylate ion, the unionized carboxyl group may be considered in direct analogy to the lactone group, as having two C-O groups each with some double bond character. Since the carbonyl group has been found to have a preferred conformation cis to the C^{α}-N bond (10,11), this group with greater double bond character should be given a greater weight in assigning sector contributions (9). As a result, the positive sector would be shifted to the left from the center of the upper right rear sector and closer to the C^{β}-atom, thus rationalizing the greater positive amplitude of the α-amino acids in acidic solution.

Table I. Optical Rotatory Dispersion and Circular Dichroism Data on α-Amino Acids,[a,b]: $R\text{-}CH(NH_3^+)COOH$

Compound	R	ORD Peak nm	ORD Mol. Rotn. (Φ)	ORD Zero Cross-over, nm	CD Peak nm	CD Mol. Ellipticity (θ)
L-α-amino-β-ethyl valeric acid	$(CH_3CH_2)_2CH$	226	+3780	211	209	+6500
L-α-cyclohexyl-glycine	$(CH_2)_5CH$	225	+3763	209	211	+6150
L-α-cyclopentyl-glycine	$(CH_2)_4CH$	226	+3019	211	210	+5400
D-α-cyclopentyl-glycine	$(CH_2)_4CH$	226	-2866	211	210	-5400

(a) Concentrations 0.34 to 0.54 g. per 100 ml. in 5 M HCl.
(b) The amino acids were synthesized and resolved as in Reference 13.

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