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95. Electronic Properties and Optical Activity of Oligopeptides. III. Some Cyclohexapeptides with Glycine, L- and D-Alanine

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Dedicated to Professor *André Dreiding* for his 60th anniversary

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Summary

The wavelength range of the CD. spectra of some cyclohexapeptides containing different sequences of glycine, L- and D-alanine is extended down to 170 nm. This allows a relatively complete recording of the $(n-\pi^*)$ and $(\pi^\circ-\pi^*)$ *Cotton* effects. Some striking spectral changes are observed on going from one molecule to another. The relative influence of L- and D-alanyl residues is discussed: Some spectra may be qualitatively related to each other by considering the effect of an L-residue at position q in the ring to cancel partially with the effect of a D-residue at position $q \pm 3$. Assuming these cyclopeptides to occur in a hydrogen-bonded pleated sheet structure, certain dominant changes in the spectra are interpreted as reflecting a transition of the overall backbone conformation from one which is closer to the (optically inactive) symmetry C_i to another which is closer to the (optically active) symmetry C_2. An attempt is made to relate the influence of L- and D-substituents within hairpin bends of the pleated sheet structure to an amide sector rule.

1. Introduction. - The study of the influence of amino acid sequence on peptide conformation is of fundamental biochemical importance. The problem is in general approached from two extremes: a) The study of a great number of larger, mainly natural peptides containing a variety of amino acids; b) The synthesis and study of smaller peptides containing only a restricted number of different amino acids in predetermined sequences. The latter approach is particularly suited for spectroscopic studies and for an investigation of the relation between conformation and electronic properties. For an attempt at an, even crude,

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theoretical interpretation of the optical activity of peptides as a function both of amino acid sequence and conformation, the latter approach is practically the only promising one.

A class of synthetic oligopeptides which has been extensively investigated are cyclohexapeptides containing different numbers of glycine, L- and D-alanine residues. The syntheses were started by *Prelog et al.* [1-3] and pursued by *Ovchinnikov et al.* [4] [5]. The spectroscopic measurements carried out by this group of authors on these compounds include NMR. [7] [8] [10], IR. [9], UV. and CD. down to 185 nm [6]. The general conclusions from NMR. are that most of these cyclohexapeptides in solution occur predominantly in 'pleated sheet' structures [12] [13] with two trans-annular H-bonds. Temperature variations indicate the presence of rapidly interconverting conformers [7] [8] [10] of this type. The structural studies in solution are aided by crystallographic investigations [11]. These confirm the predominance of a pleated-sheet structure in cyclo (D-Ala_2-Gly_4). The CD. spectra [6] show certain general characteristic patterns, but also great variations on going from one compound to the next.

In the present investigation we have measured, or remeasured, the CD. spectra of some characteristic cyclohexapeptides, extending the wavelength range down to 170 nm. Beside the ($n-\pi^*$) band, it has thereby also been possible to study the ($\pi^\circ-\pi^*$) band more completely.

The various methyl sidegroups of the L- and D-alanyl residues influence the *Cotton* effects of the $\pi-\pi^*$ transitions and the $n-\pi^*$ transitions differently. The $\pi-\pi^*$ *Cotton* effects reflect mainly the overall conformation of the polyamide skeleton which, however, is influenced by the sidegroups. On the other hand, it is to be expected that the $n-\pi^*$ *Cotton* effects arise mainly through local interactions and that longer-range coupling is less important. The results of our measurements are therefore discussed and interpreted from two points of view:

i) In previous communications [14] [15] we have attempted by a relatively simple 'frozen core' (FC) molecular orbital model to establish semiquantitative relations between the overall conformation and the CD. spectra of some typical peptide structures. Using the established criteria, we characterize qualitatively the spectra obtained here; ii) The influence of the methyl sidegroups in different relative positions around the peptide ring is discussed, with particular attention to the ($n-\pi^*$) band. The question of the additivity or cancellation of the influence of residues of same or opposite absolute configuration is raised.

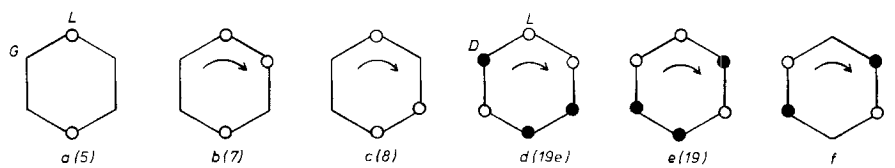

Fig. 1. *Schematic representation of cyclohexapeptides containing various numbers of glycine* (G), L-*alanine* (L) *and* D-*alanine* (D) *units*, the CD. spectra of which are shown in Figures 2 and 3. The arrows denote the sense of progression along the peptide chain, as usually defined (see also *Fig. 7*). In brackets the numbering of the same molecules in [6] [7] [10] is indicated.

2. Recorded CD. spectra. – The CD. spectra of the peptides **a**–**f** *(Fig. 1)* are shown in *Figures 2* and *3*. As we have previously mentioned [15], the spectrum of **a** shows the characteristics computed for an oligomer in a typical 'pleated sheet' conformation. We distinguish three bands: I (217 nm), II (195 nm) and III (179 nm). On going from **a** to **c**, band I is slightly blueshifted and moves towards II. Band II is redshifted to about 200 nm and gains much in absolute value. Band III similarly moves its maximum from 178 to about 184 nm. Beyond doubt, I is to be identified with the $(n-\pi^*)$ band, while II and III conceivably make up the $(\pi^\circ-\pi^*)$ band system. The changes described indicate a gradual modification of the 'pleated sheet' structure, depending on the number and relative position of L-alanyl residues.

Compound **d** contains no glycine, but only L- and D-alanine. Comparing the spectrum of **d** with the spectra of **a**–**c**, one may characterize the difference as an enhancement of band I and the apparent absence of band II in front of III. The particular aspect of the long-wavelength part of the spectrum of **d** is already indicated in ref. [6][2]). A graphical estimate of the integral $\int(\Delta\varepsilon/\lambda)\,d\lambda$ for the

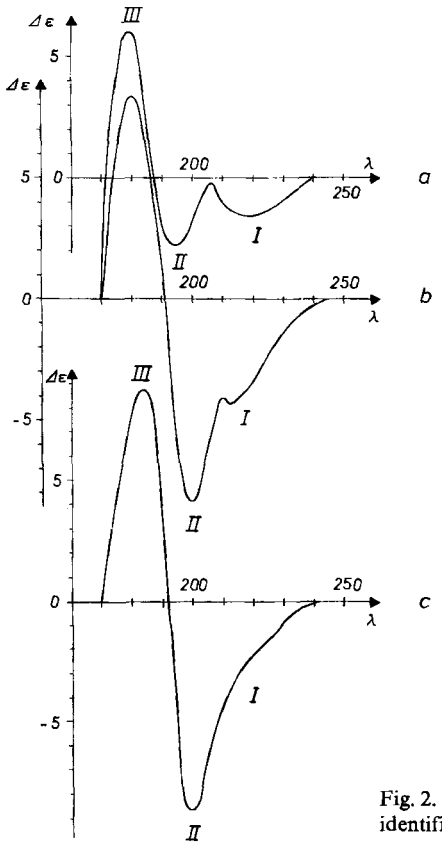

Fig. 2. *CD. spectra of peptides* **a**, **b**, **c** (for identification see *Fig. 1*) in D_2O.

[2]) The compound designated by 19 in refs. [6] [7] does not give the spectrum 19 shown in [6], but rather its enantiomer.

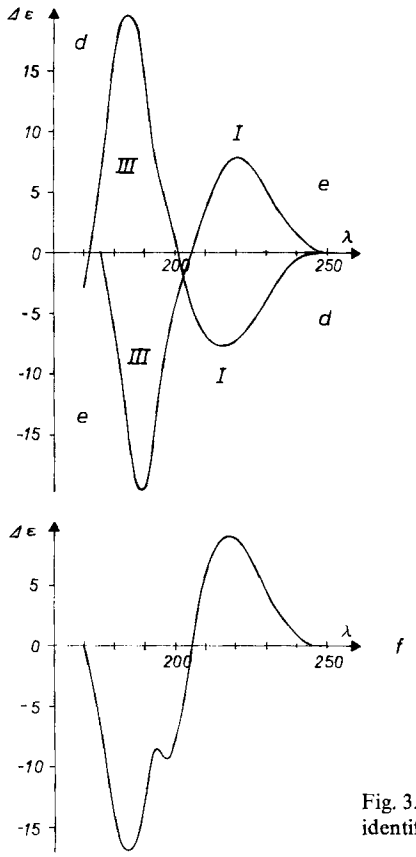

Fig. 3. *CD. spectra of peptides* **d**, **e**, **f** (for identification see *Fig. 1*) in D_2O.

longest-wavelength negative and positive CD. bands of compounds **a**, **c**, **d** is given in *Table 1*. We notice that in the wavelength range considered the spectrum of **a** is approximately conservative, **b** (by inspection) and **c** have a somewhat stronger negative component, while in **d** the positive band is significantly stronger than the negative one. It seems justified to assume (see [15], in particular the Appendix) that in all the molecules considered the sum of the rotatory strengths of the $\pi^\circ - \pi^*$ and $n - \pi^*$ transitions should approximately add to zero. From this assumption one would suspect that in **d** an additional negative band of the type $(\pi^\circ - \pi^*)_-$ exists, but at shorter wavelength than $(\pi^\circ - \pi^*)_+$. In other words, in **d** band II may have moved to the short-wavelength side of III. To judge from spectra previously computed [14] [15] one may, with some reservation, characterize the spectrum of **d** as reflecting a more 'helical' or 'cyclic' conformation. However, it is rather well established that the cyclohexapeptides here considered exist in a 'pleated sheet' structure, stabilized by two intraannular hydrogen bonds [10] [12] [13]. On the other hand, it appears that even such a structure may adopt different geometries. One must also remember that these molecules in solution may coexist in several energetically relatively close-lying conformations, and that the thermally less populated conformations may also influence the spectrum non-negligibly.

Table 1. *Graphical estimate of the integral* $\int(\Delta\varepsilon/\lambda)\,d\lambda$ *for the long-wavelength bands of compounds* **a**, **c** *and* **d**, *shown in* Figures 2 *and* 3 ($\Delta\varepsilon$ in $mol^{-1}\,l\,cm^{-1}$, $\Delta\lambda = 1$ nm)

Compound	Range (nm)	$\sum_i \frac{\Delta\varepsilon_i}{\lambda_i}\Delta\lambda$
a	171–188	+0.34
	188–238	−0.31
c	170–192	+0.63
	192–239	−0.77
d	172–201	+1.65
	201–246	−0.85

Molecules **d** and **e** are cycloenantiomers [1–3]. Although, because of conformational flexibility, a *given* molecule of **d** may not be the exact mirror image of a particular molecule of **e**, on the average the CD. spectra of the two compounds should exactly have equal value and opposite sign at all wavelengths. The fact that in the recorded spectra of **d** and **e** this is not exactly the case *(Fig. 3)*, may be due to some impurities.

The CD. spectrum of **f** shows, apart from the minimum (shoulder) at 197 nm, a general analogy to the spectrum of **e**, or the inverse of the spectrum of **d**. This point will be discussed in the next section. Compound **f** is the only molecule considered here which contains glycine and both L- and D-alanine.

3. Relative influence of L- and D-residues. – In cyclohexapeptides containing different numbers and sequences of residues of glycine and of L-alanine only, the $(n-\pi^*)$ band (I) appears generally to be negative [6]. The effect of the L-alanine residues is not simply additive, however. As already pointed out in [6], the sequence L-Ala-Gly-L-Ala tends to make band I and particularly band II more negative, as compared to the sequence L-Ala-L-Ala.

To discuss the combined effect of both L- and D-alanine, we start out by considering the (hypothetical) molecules **g**, **h**, **i** shown in *Figure 4*. Molecules **g** and **h** are optically active, while **i** is not. On the average, the various possible conformations of **i** must possess a center of inversion, and the effect of the

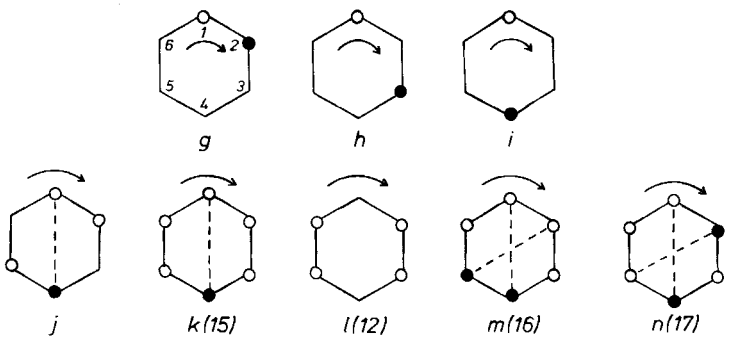

Fig. 4. *Schematic representation of different cyclohexapeptides, to illustrate the effect of 'partial cancellation'.*

L-substituent cancels the effect of the D-substituent on optical activity. Interestingly, it appears that in cyclohexapeptides containing additional alanine residues, an L-alanyl at ring position 1, say, may *partly cancel* the effect of a D-alanyl at position 4. For instance, one might expect the spectrum of **j** *(Fig. 4)* to resemble the spectrum of **a** *(Fig. 1)*. Indeed, in [6] one finds the CD. bands I and II of **k** (15) to resemble those of **l** (12), and, conceivably by double 'partial cancellation', the CD. bands of **m** (16) to resemble those of **n** (17). This effect may then also offer a rough explanation for the qualitative analogy of the spectra of **e** and **f** *(Fig. 3)*. It seems reasonable to assume that an L-substituent at position q may partly cancel the effect of a D-substituent at position $q \pm 3$, to the extent that in their immediate surroundings both substituents are related by a center of inversion. Such a *local inversion* relation does *not* imply that the dominant backbone conformation must have symmetry C_i, however, as we shall presently see.

From the above considerations we conclude that not only in **f**, but also in **e**, the sequences D-Ala-L-Ala at positions 2, 3 and 5, 6 determine both the positive $(n-\pi^*)$ band, as well as the additional characteristics of the spectrum. The two D-L groups must be responsible for the distinct changes in overall backbone conformation, as compared to the other cyclohexapeptides here considered.

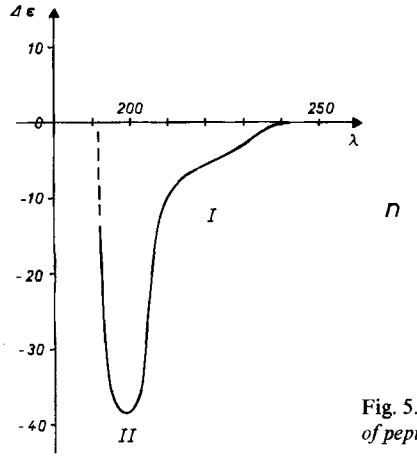

Fig. 5. *Long-wavelength part of the CD. spectrum of peptide n(17)*, redrawn from [6].

4. Overall conformation of the pleated sheet structure. – The pleated sheet structure of cyclohexapeptides is, for instance, depicted in [10] [11] [13]. It is stabilized by two intraannular hydrogen bonds and shows two 'hairpin bends'. Such a bend can occur at the end of any two polypeptide chains hydrogen-bonded in the antiparallel β conformation. It is thus also called 'β-bend'. Inside a hairpin bend there is one amide group, and at the 'corners' of the bend are the C^{α}-atoms adjacent to that amide group. On the basis of conformational energy calculations and of crystallographic data *Chandrasekaran et al.* [16] come to the following conclusions concerning hairpin bends (stated here in somewhat simplified form):

1) In a polypeptide structure with L- and G (Glycyl)-units, a hairpin bend may be expected to contain a glycyl residue quite often;

2) In peptides containing both L- and D-units, a mixed sequence, such as L-D or D-L will be a likely site for a hairpin bend;

3) The amide group inside a hairpin bend may take on essentially two positions with respect to the sense of progression around the ring: Position A: CO-bond 'down'. Position B: CO-bond 'up'. These two conformations are represented both in [16] and [17];

4) Inside a hairpin bend the D-L sequence is energetically compatible with conformation A only, the L-D sequence with conformation B only;

5) The sequences L-L, G-L, L-G and G-G and corresponding enantiomers inside a bend are in that sense less selective and, with smaller variations in relative energy, are essentially compatible both with A and B.

Applying these findings to the peptides under investigation here, we notice (see *Fig. 6*) that both **e** (of course also **d**) and **f** are probably constrained to adopt hairpin conformations leading to an overall backbone geometry of symmetry *close to* C_2. In the other molecules **a**, **b**, **c** the possibility exists, and may to varying degrees be preferred, of adopting a backbone conformation *closer to* (optically inactive) C_i symmetry. An example for the latter case in the crystalline state is given by cyclo (D-Ala$_2$-Gly$_4$) [11] (see *Fig. 6*).

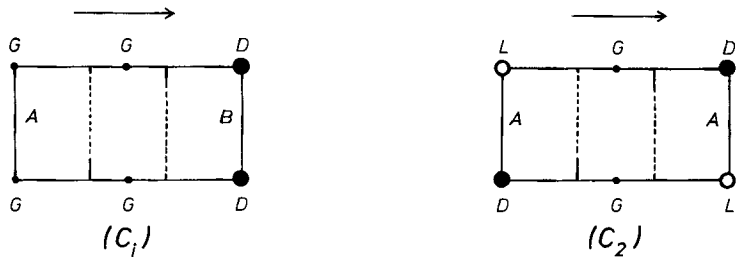

Fig. 6. *Schematic drawing of the pleated-sheet structure* (left) *of cyclo (D-Ala-D-Ala-Gly-Gly-Gly-Gly) and* (right) *of* **f**, *cyclo (D-Ala-L-Ala-Gly-D-Ala-L-Ala-Gly).* The conformation at the hairpin turns is characterized by A or B. Dotted lines symbolize transannular hydrogen bonds. The overall backbone conformation at left has close to C_i symmetry [11], that at right closer to C_2 symmetry [17] [21].

In cyclohexapeptides with backbone conformation close to C_2, the effect of 'partial cancellation' described in section 3 can only be operative between two units D and L *outside* the hairpin bends. On a strictly local basis the inversion relation between such residues is roughly maintained.

5. The perturbed amide model. – The question remains why in **e** and **f** the hairpin sequence D-L should lead to a positive ($n-\pi^*$) band, the sequence L-D in **d** correspondingly to a *negative* one. For this reason we have performed some CNDO/SCF-CI calculations on an amide group perturbed by two methyl groups at adjacent C^α-positions (see *Fig. 7*), with varying dihedral angles η and ξ (see legend to *Table 2*). If the system is considered as part of a polypeptide chain, the relation between η and ψ_1, ξ and Φ_2 depends on the absolute configuration at C_1^α and C_2^α, respectively [18]:

R^1(L): η(L) = $\psi_1 - 60°$, R^1(D): η(D) = $\psi_1 + 60°$
R^2(L): ξ(L) = $\Phi_2 - 120°$, R^2(D): ξ(D) = $\Phi_2 + 120°$

We *estimate* the following angles from *Dreiding* models, without presuming that they correspond to actual energy minima [16], but only to assess relative variations of η- and ξ-values for different C^α-substituents:

Amide *position A:* $\psi_1 = -95°$, $\Phi_2 = -155°$
η(L) = −155°, ξ(L) = +85°
η(D) = −35°, ξ(D) = −35°

Amide *position B:* $\psi_1 = +95°$, $\Phi_2 = +155°$
η(L) = +35°, ξ(L) = +35°
η(D) = +155°, ξ(D) = −85°

Anticipating an approximate sector rule [19] [20] for the $n-\pi^*$ transition of the amide group with respect to η and/or ξ, we attribute the following *relative* signs to the values of these angles[3]):

0–90°: +, 90–180°: −, 180–270°: +, 270–360°: −

We then find from the angles listed above:

Amide *position A:* η(L): +, ξ(L): +
η(D): −, ξ(D): −

Amide *position B:* η(L): +, ξ(L): +
η(D): −, ξ(D): −

In a first approximation one would assume that the methyl substituents R^1 and R^2 *(Fig. 7)* make roughly additive contributions to the $n-\pi^*$ rotatory strengths. It is, however, probable that one substituent, say R^1 (described by η), is dominant, making a larger contribution than R^2 (described by ξ), or *vice versa.* Irrespective of these different possibilities, the above relations suggest that within hairpin turns:

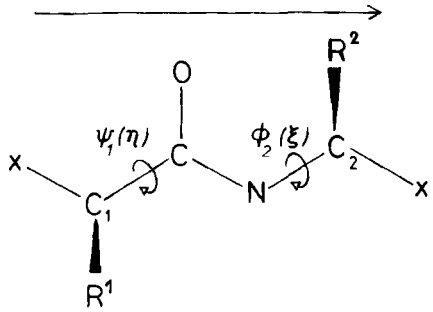

Fig. 7. *Fragment of a polypeptide chain, showing an amide group and two adjacent* C^α*-substituents* R^1 *and* R^2. The arrow denotes the sense of progression, as usually defined. Dihedral angles ψ_i, Φ_{i+1} are defined in [18]. Their relation to η and ξ (see *Table 2*) is given in the text. As here drawn, the conformation at C^α_1 is D, that at C^α_2 is L.

[3]) As defined here and as compared to [19], we actually postulate an octant rule.

1) The sequence L-L leads to the same sign in conjunction with both amide positions A *and* B;

2) The sequence D-D leads to the same sign in conjunction with both amide positions A *and* B. The sign of the contribution of D-D is opposite to that of L-L;

3) The sequence D-L in conjunction with A and the sequence L-D in conjunction with B make contributions of *opposite* sign;

4) For both sequences L-L and D-D, the two substituents R^1 and R^2 lie in quadrants of same sign. For the mixed sequences L-D and D-L, R^1 and R^2 lie in quadrants of opposite sign. The sign of the contribution of the mixed sequences should therefore be sensitive to the relative magnitude of the influence of R^1 and R^2.

It must be remembered that the above discussion is based on angles deduced from a relatively artificial model. Although these angles are in rough agreement with more elaborate data [16], in actual molecules a wide span of possible values will occur, making conclusions of the kind stated above more difficult to arrive at.

We now consider the numerical results shown in *Table 2.* The hairpin sequence L-L may, by the sign of the respective quadrants (+ +), be related to the data for the angles (45/45°) and (– 135/45°). In columns I and II we find negative rotatory strengths, in qualitative agreement with experiment. An analogous situation is encountered for the sequence D-D, where the computed rotatory strengths in columns I and II are positive. Columns III and IV, however (inclusion of a larger number of electron configurations in computing the rotatory strengths),

Table 2. *Computed rotatory strength for the longest-wavelength* $n-\pi^*$ *transition of an amide group pertubed by two axial methyl groups.* The system is shown in *Figure 7*, where R^1, $R^2 = CH_3$ and the end atoms X = H. The dihedral angles are defined as η: $R^1C_1^{\eta}C-C_1^{\eta}CO$ and ξ: $R^2C_2^{\xi}N-C_2^{\xi}NC$. The calculations are of the CNDO/SCFI-CI type [14]. Column I gives the rotatory strength for the one-electron transition from the highest occupied SCF-MO 21(n) to the lowest unoccupied SCF-MO 22(π^*). In column II the three (relatively) low-lying configurations $\pi^+-\pi^*$, $\pi^\circ-\pi^*$ and $n-\pi^*$ are taken into account in computing $R_{n\pi^*}$, in column III the 10 lowest-lying singly excited configurations, in IV the 30 lowest-lying singly excited configurations. Results for the enantiomers to the conformations explicitly considered are obtained by simultaneously changing the signs of η, ξ, and $R_{n\pi^*}$.

η(°)	ξ(°)	$R_{n\pi^*} \cdot 10^{40}$ (cgs)				Relative sign of quadrant	
		I (21-22)	II (3 config.)	III (10 config.)	IV (30 config.)	η	ξ
45	45	– 99	– 24.9	3.2	– 6.9	+	+
45	135	375	– 15.6[a])	6.0	– 3.2	+	–
135	45	– 152	40.8	– 6.8	2.0	–	+
135	135	398	46.7	7.6	6.7	–	–
– 135	45	– 231	– 26.1	14.6	– 11.0	+	+
– 135	135	358	– 23.4	15.7	– 4.7	+	–
– 45	45	– 247	36.5	37.2	– 1.4	–	+
– 45	135	373	8.9[a])	2.7	6.1	–	–

[a]) No contribution from $\pi^+ - \pi^*$.

may possibly exemplify one of the pitfalls of all-valence-electron calculations of rotatory strengths, in particular of CNDO, as already pointed out in [20]. The inclusion of higher $\sigma-\sigma^*$ electron configurations tends to blurr clear-cut distinctions and may also lead to artefacts. For the mixed hairpin sequences L-D (angles 45/135° and −135/135°) and D-L (angles 135/45° and −45/45°) an additional uncertainty appears: Interestingly, there is a change of sign already between column I and column II. In conclusion, the results of the CNDO calculations indeed show a certain sector rule behavior, but their usefulness for the prediction of absolute signs of rotatory strengths in the cases under investigation is limited. This, however, does not exclude that similar all-valence calculations of particular segments of oligopeptides could be refined and further extended.

6. Experimental Part. – The CD. spectra of the peptides **a**–**f** were first measured in aqueous solution on the spectrograph *Jouan* CD.-185. Only the longest-wavelength band I (above 205 nm) of **a**, **d**, **e** and **f** as well as the minima of band II (above 198 nm) of **b** and **c** could be recorded.

The spectra shown in *Figures 2* and *3* were then measured using the vacuum ultraviolet CD. apparatus constructed in the *Institut de Recherche en Biologie Moléculaire* (Paris) and partially described elsewhere [21]. The conditions of polypeptide concentration and pathlength were chosen in order to ensure reliable measurements down to 169 nm. The thickness of the probe was of 10 μ and the use of D_2O instead of H_2O allows us to extend the measurement down to 165 nm. The quantitative evaluation of the spectra was calibrated on the $\Delta\varepsilon_{max}$-values of band I for **a**, **d**, **e** and **f** as well as on bands II for **b** and **c** which had been recorded on the CD.-185 apparatus The short-wavelength spectra were then scaled accordingly.

7. General Conclusions. – The extension of the wavelength range of the CD. spectra of the molecules under consideration to 170 nm allows a relatively complete recording of the $(n-\pi^*)$ and $(\pi^\circ-\pi^*)$ *Cotton* effects. Different numbers and sequences of glycine, L- and D-alanine units lead to characteristic spectral changes. Molecules with a high glycine content tend to show typical 'pleated sheet' spectra, as defined in [15]. Cases with several L- and D-units become more involved: Some spectra may be qualitatively related to each other by considering the effect of an L-unit at ring-position q to cancel partly with the effect of a D-unit at position $q\pm3$. Assuming all cyclohexapeptides to occur in a hydrogen-bonded pleated sheet structure, certain dominant changes in the spectra are interpreted as reflecting a transition of the overall backbone conformation from one which is closer to the (optically inactive) symmetry C_i [11] to another which is closer to the (optically active) symmetry C_2 [22].

It is of general interest to also point out some analogies with the spectra of other cyclopeptides and of linear polypeptides:

The CD. spectrum shown in *Figure 2a* is of the type of gramicidine S [23] and resembles that of an α-helix fortuitously. The spectrum for gramicidine S β-turns was also calculated by *Woody* [24].

The spectrum of *Figure 3* is very closely related to the typical β-pleated sheet conformation encoutered in polypeptides poly-L-lysine, poly (Leu-Lys), poly (Val-Lys), *but* with a contribution of β-turns. The contribution of the β-turn to this spectrum can be detected:

a) by the longer wavelength tail of negative CD., normally not observed in a typical β-pleated sheet structure;

b) by the presence of a shoulder at about 200 nm of positive CD.

The combination of these two spectra, *i.e.* of β-sheet and of β-turn may yield a spectrum similar to that of *Figure 3d*. One observes a slight blue shift of the band III, which maximum is at 187–190 nm, probably due to some structural differences. As reference spectrum of β-turn one may consider that of poly Ala_2-Gly_2 which is in agreement with the calculated spectrum by *Woody* [24].

In the present investigation an attempt is made to relate the influence of L- and D-substituents within hairpin bends of the pleated sheet structure to an amide sector rule. There is some indication that the relative signs of sequences L-L, D-D, L-D, D-L may be interpreted on this basis. However, from calculations of the CNDO-CI-type, absolute signs are difficult to predict reliably.

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