13. MO-Calculation of the Optical Activity of Oligopeptides. II. Open-Chain Conformations. Comparison with Some Cyclic Systems.

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In Memory of Professor *Heinrich Labhart*

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Summary

Using the Frozen Core (FC) MO procedure described in a previous communication, we have computed the long-wavelength chiroptic properties of oligopeptides in the parallel-chain (PC) pleated sheet conformation, in the poly(L-proline) I and poly(L-proline) II conformations. The main features of the computed results are: a) In the PC pleated sheet conformation the $\pi-\pi^*$ transition with the highest positive rotatory strength appears at shorter wavelength than the $\pi-\pi^*$ transition with highest negative rotatory strength and is polarized mainly perpendicularly to the chain axis. There is an analogy between the computed PC pleated sheet spectrum and that calculated for a cyclohexapeptide of low symmetry, in a conformation which is probably stabilized by intra-annular hydrogen bonds. b) In the polyproline I conformation the computed $\pi-\pi^*$ transition with highest positive rotatory strength is also the longest-wavelength $\pi-\pi^*$ transition and is polarized mainly along the helix axis. There is an analogy between this spectrum and that calculated for cyclo(tri-L-proline) of symmetry C_3. c) The poly-proline II CD. spectrum may be qualitatively reproduced only by invoking very strong $n-\pi$ interaction. The local $n-\pi$ mixing parameter Λ must take on values $\geqslant 3$ eV, which is of the order of a nearest-neighbor core resonance integral between atomic 2p orbitals of same spatial orientation. The question concerning the structural reasons for this situation is raised. As far as comparisons with experimental data are possible, qualitative agreement is obtained.

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1. Introduction. We are exploring the possibility of describing the long-wavelength chiroptic properties of oligopeptides by a simplified molecular orbital procedure, taking explicitly into account only the pseudo π electrons of the amide moieties (and of eventual unsaturated side-groups) and the nonbonding amide-oxygen electrons. As shown in a previous report [1], this Frozen Core (FC) procedure is suggested by the results of semiempirical all-valence SCF-CI calculations of the

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CNDO-type. The CNDO calculations themselves, however, become exceedingly cumbersome as the number of valence electrons exceeds 100–150. The FC procedure, on the other hand, strongly resembles the PPP method, a variant of which has also been successfully applied to the interpretation of the long-wavelength spectral properties of pigments bound to proteins [2] [3]. The basic idea is that local σ-π separation is to some degree preserved, and that very high-lying, localized σ (or n) electrons interact more directly with the (pseudo) π electrons than with the lower-lying σ electrons.

The practical aim of this general investigation is to find semiquantitative criteria relating the long-wavelength spectral properties of oligopeptides to their structure and their conformation in solution. Important progress has already been made using the exciton model [4–9]. The exciton model starts from experimentally determined transition wavelength and transition moments of the amide (or other monomeric chromophore) units. According to the nature of these transitions, the interactions between the monomers i,j are of the electric dipole-electric dipole $(\mu_i - \mu_j$ or $(\pi_i - \pi_i^*) - (\pi_j - \pi_j^*))$ type or the electric dipole-electric quadrupole $(\mu_i - m_j$ or $(\pi_i - \pi_i^*) - (n_j - \pi_j^*))$ type, *etc.* On the other hand, in the MO approach, the input consists of the atomic coordinates of the atoms belonging to the amide groups (and of eventual unsaturated side chains), of a core interaction matrix and of an electron repulsion matrix. As described in [1], the parameters are calibrated on transition and ionization energies of the isolated amide and carbonyl group, as well as on other molecular fragments [10]. The electron repulsion matrix, which enters both the SCF and CI calculations, contains essentially monopole interactions between individual atoms. Thereby the multipole interaction between transition moments, which the exciton model considers step by step, is taken into account in a more comprehensive way. If we designate the amide orbitals by π^+, π°, n and π^* (π^-) and if we take into account all single excitations $\pi_i^+ - \pi_j^*$, $\pi_i^\circ - \pi_j^*$, $n_i - \pi_j^*$, where i and j independently run over all amide groups, then for a given N-mer there will be $3N^2$ singly excited configurations. In oligomers where $N > 7$ we neglect the high-energy $\pi_i^+ - \pi_j^*$ configurations, which anyhow contribute negligibly to the long-wavelength spectrum.

A question of central importance is the mechanism of the $n - \pi$ interaction. For a given amide group i this interaction will be dependent on a) The nature of substituents on adjacent carbon atoms C_i^α and C_{i+1}^α; b) The nature of the interaction of these substituents with the amide electrons (predominantly electrostatic; orbital 'through space'; orbital 'through bond'); c) The absolute configuration at C_i^α and C_{i+1}^α, and the value of the dihedral angles ψ_i and φ_{i+1} (for definitions see [11]); d) The nature of the interaction with adjacent amide groups; e) Eventual longer-range effects.

In [1] we have assumed that e) may be neglected and that a) – d) may be represented by a local core parameter Λ_i for every amide group i. In regular oligomers Λ_i is taken to have the same value for every amide group, end effects being neglected. This approach is here further pursued, although it is admittedly an oversimplification. In the long run several possibilities must be envisaged: 1) The Λ_i may be computed *ab initio, i.e.*, by local all-valence electron calculations; 2) the Λ_i may be calibrated semiempirically on a number of standard molecules; 3) additional, directly conformation-dependent core matrix elements must be introduced between different amide groups.

2. Results and Discussion. - The coordinates of the atoms entering the MO calculations were computed from the dihedral angles given in [11]. As shown in *Figure 1*, the molecules are placed somewhat arbitrarily in the frame of reference.

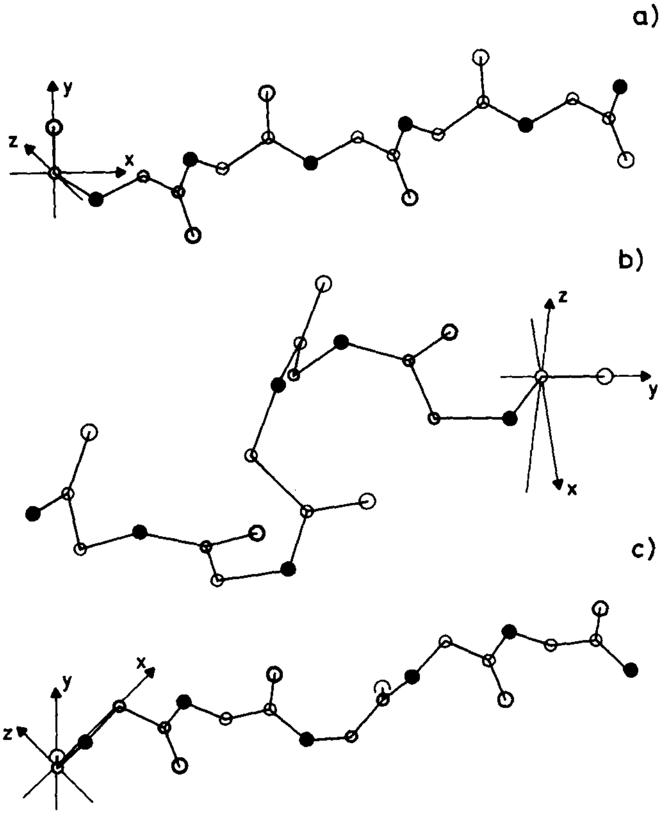

Fig. 1. *Computer drawing of a hexapeptide in different conformations:* a) Single-strand of parallel-chain (PC) pleated sheet; b) Poly(L-proline) I; c) Poly(L-proline) II. Only skeletal C, N, O atoms of the polypeptides are shown

In assessing the computed spectra we look for the dominant features and for characteristic differences between the different conformations. Our method is not aimed at exact predictions of transition wavelengths and of absolute values of rotatory and oscillator strengths. In particular, we notice that with the parametrization adopted in [1] the computed $\pi-\pi^*$ transitions (below 200 nm) in general tend to lie too far to the blue, the $n-\pi^*$ transitions too far to the red. The latter situation may be corrected by varying the valence-state ionization potential of the nonbonding oxygen electrons I_n'. The model consequently cannot make predictions concerning quantities that depend sensitively on small parameter variations. The model is applicable to the study of relative differences between conformations (for a given parametrization) and in predicting symmetry properties. The model should also become useful for selectively investigating the mechanism of $n-\pi$ interaction.

Computed results for the PC pleated sheet conformation are given in *Figures 2* and *8*. The $\pi-\pi^*$ transition with the highest positive rotatory strength (of the $\pi^\circ-\pi^*$ band system) appears at relatively short wavelength and its electric dipole

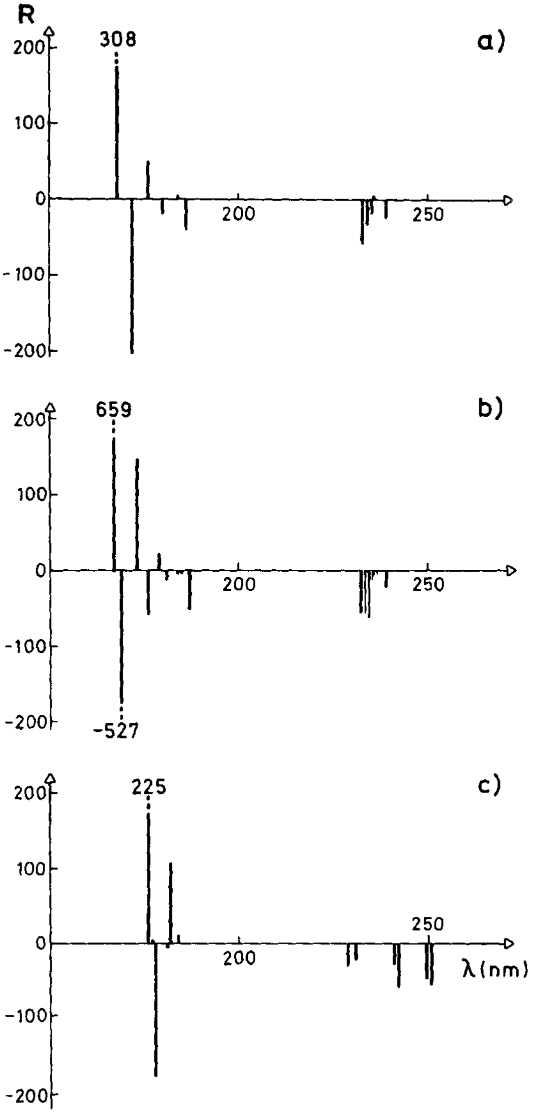

Fig. 2. *R: Computed rotatory strengths* (in cgs units × 10^{40}) *for* a) *a hexamer in the PC pleated sheet conformation,* with $\varphi = -119°$, $\psi = 113°$, $\omega = 180°$; b) *a nonamer in the PC pleated sheet conformation;* c) *a cyclohexamer in the conformation described by Table VII of* [15]. Parameters are $\Delta = 0.5$ eV for all amide groups, $I'_n = 26.80$ eV. The transitions above 200 nm are $n-\pi^*$

transition moment is polarized mainly perpendicularly to the chain axis (see *Table 2* and compare with *Fig. 1a*). It is also the transition with the highest computed f-value. For the PC pleated sheet conformation the maximum of the $(\pi - \pi^*)$ UV. band should thus lie at relatively short wavelength. The longest-wavelength $\pi - \pi^*$ transition is polarized mainly along the chain. Its computed f-value is, however, only about 1/10 that of the above-mentioned shortest wavelength $\pi - \pi^*$ transition. Most of the transitions in between are predicted to be even weaker. A comparison of the simulated CD. spectra of oligomers *(Fig. 8)* with the experimental spectrum of the polymer (see for instance [12]) is at best inconclusive. Of more direct interest is the measured CD. spectrum *(Fig. 5)* of cyclo (Ala-Gly-Gly-Ala-Gly-Gly) [13] which from NMR. [14] and indirect crystallographic evidence [15] may have a con-

Table 1. *Coordinates of the skeletal atoms of the hexamer in the poly* (L-*proline)I conformation,* as used for our computations. They correspond to $\varphi = -83°$, $\psi = 158°$, $\omega = 0°$. The helix extends mainly along the $-$y axis.

	x(Å)	y(Å)	z(Å)
N	1.220	−0.7290	0.
C	0.	0.	0.
O	0.0003	1.2320	0.
C^α	1.1089	−2.1889	0.
N	0.4626	−4.0335	1.4202
C	0.9338	−2.7818	1.3831
O	1.2120	−2.1393	2.3968
C^α	0.1364	−4.7850	0.2117
N	−1.4316	−4.7441	−1.6259
C	−1.2430	−4.4701	−0.3299
O	−2.1217	−3.9932	0.3899
C^α	−0.3822	−5.3094	−2.4690
N	1.7738	−4.7188	−3.3857
C	0.5723	−4.2649	−3.0106
O	0.2470	−3.0795	−3.0933
C^α	2.1477	−6.1263	−3.2829
N	2.5492	−7.8163	−1.6036
C	2.6293	−6.5139	−1.8997
O	3.0632	−5.6721	−1.1118
C^α	2.0330	−8.8048	−2.5459
N	−0.0287	−9.4055	−3.6531
C	0.5206	−8.8928	−2.5460
O	−0.1446	−8.5125	−1.5812

Table 2. *Oligomers in the PC pleated sheet conformation: Vector components of matrix elements between the ground state and the shortest-wavelength π-π^* excited state* (of the π^0-π^* band system; see *Fig. 2*). Dipole velocity transition moments are in au. R designates the total rotatory strength, f the total oscillator strength, undivided by the number of monomers. Notice the relatively large component $\langle\vec{V}\rangle_y$, indicating electric dipole polarization mainly perpendicular to the chain axis (see also Fig. 1).

Oligomer	$\langle\vec{V}\rangle_x$	$\langle\vec{V}\rangle_y$	$\langle\vec{V}\rangle_z$	$\langle\vec{r}\times\vec{V}\rangle_x$	$\langle\vec{r}\times\vec{V}\rangle_y$	$\langle\vec{r}\times\vec{V}\rangle_z$	R · 10^{40} (cgs)	f	λ (nm)
Tri-	−0.15602	0.41272	−0.05923	1.0344	0.9963	2.2366	103	0.49	170
Hexa-	−0.19468	0.58292	−0.11432	3.8251	3.4560	8.0061	308	0.96	168
Nona-	−0.25447	0.68256	−0.17184	7.0604	7.5037	14.8970	659	1.37	167

formation similar to the pleated sheet, stabilized by intra-molecular, transannular hydrogen bonds. The computed spectrum which with respect to $\Delta\varepsilon$-values agrees best with this measured CD. spectrum is the one of the hexamer shown in *Fig. 8c*, with $\Delta = 0.2$ eV.

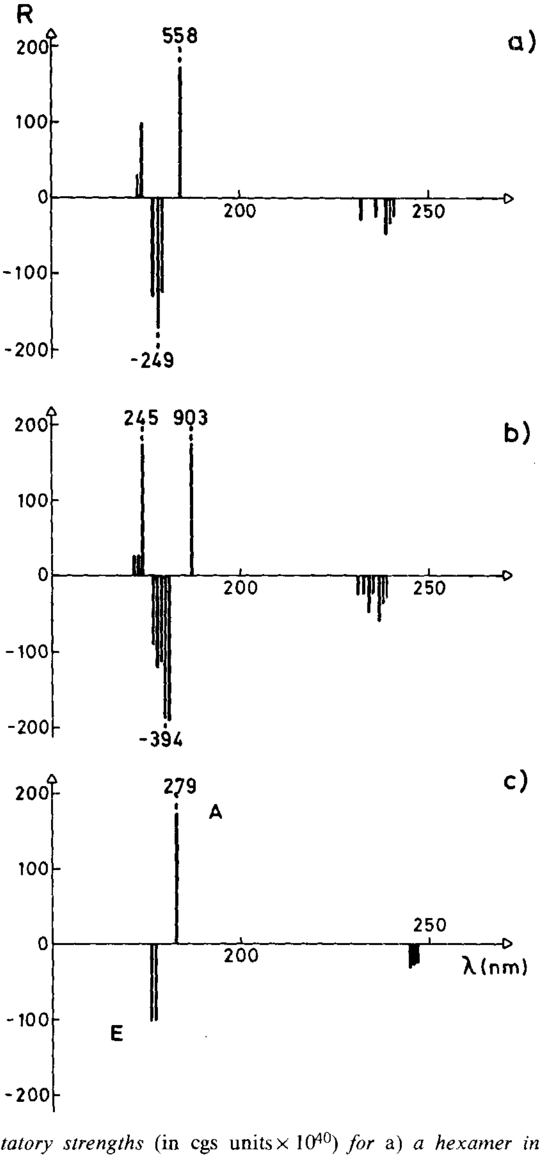

Fig. 3. *R: Computed rotatory strengths* (in cgs units × 10^{40}) *for* a) *a hexamer in the poly(*L*-proline) I conformation*, with $\varphi = -83°$, $\psi = 158°$, $\omega = 0°$; b) *a nonamer in the poly(*L*-proline) I conformation;* c) *cyclo(tri-*L*-proline) in the conformation of symmetry* C_3 *described in* [20]. The coordinates are given in *Table 4a*. Computational parameters are $\Delta = 0.5$ eV for all amide groups, $I'_n = 26.80$ eV. The transitions above 200 nm are n-π^*

From *Figure 1b* one notices that the radius of the poly(L-proline)-I helix is quite large, giving the structure a pronounced cyclic element. The $\pi-\pi^*$ transition with the highest positive rotatory strength (see *Fig. 3*) and highest f-value is predicted also to be the longest-wavelength $\pi-\pi^*$ transition. Its electric dipole transition moment (see *Table 3*) is polarized mainly along the helix axis (approximately the y-axis in *Figure 1b;* see also *Table 1*). There is a definite similarity with the computed spectrum of cyclo(tri-L-proline) of symmetry C_3, in which the longer-wave-

Table 3. *Oligomers in the poly(L-proline) I conformation: Vector components of matrix elements between the ground state and the longest-wavelength π-π* excited state* (see *Fig. 3*). Dipole velocity transition moments are in au. R designates the rotatory strength, f the oscillator strength, undivided by the number of monomers. Notice the relatively large component $\langle\vec{\nabla}\rangle_y$, indicating electric dipole polarization mainly along the helix axis (compare with Table 1 and Figure 1).

Oligomer	$\langle\nabla\rangle_x$	$\langle\nabla\rangle_y$	$\langle\nabla\rangle_z$	$\langle r\times\nabla\rangle_x$	$\langle r\times\nabla\rangle_y$	$\langle r\times\nabla\rangle_z$	$R\cdot10^{40}$ (cgs)	f	λ (nm)
Tri-	−0.02142	0.28272	0.23257	−2.1203	0.5069	0.1941	218	0.36	181
Hexa-	−0.07061	0.43903	0.28284	−2.3501	0.4956	0.7171	558	0.75	184
Nona-	−0.12953	0.53213	0.32828	−2.1005	0.8266	0.6821	903	1.12	187

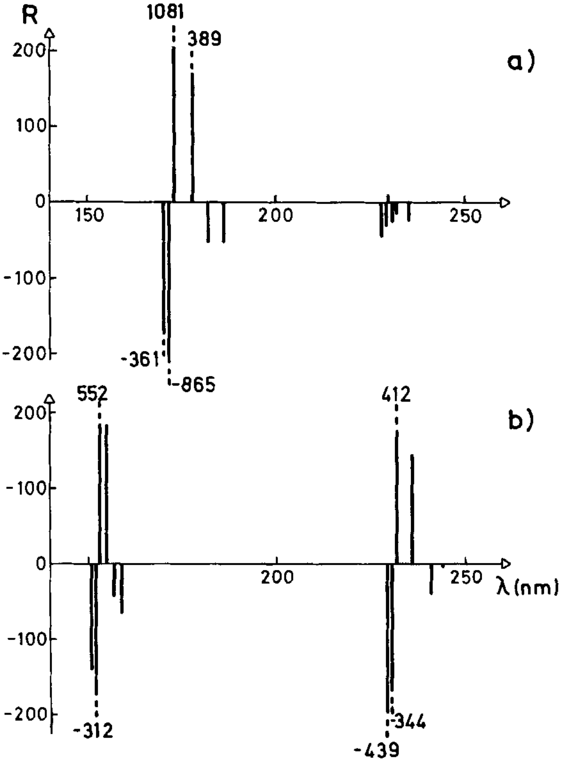

Fig. 4. *R: Computed rotatory strengths* (in cgs units × 10^{40}) *for a hexamer in the poly(L-proline) II conformation,* with $\varphi=-78°$, $\psi=149°$, $\omega=180°$. Parameters are a) $\Lambda=0.5$ eV for all amide groups; b) $\Lambda=2.4$ eV for all amide groups. In both cases $I'_n=26.80$ eV

Table 4. *Cylindrical polar coordinates of atoms belonging to one amide monomer in* a) *cyclo-(tri-*L*-proline)* [20], b) *in cyclo-(tetra-*L*-alanine)* [21]. The coordinates of the atoms belonging to the other amide groups in the given oligomer are obtained through rotation 1) by 120° and 240°, 2) by 90°, 180° and 270° around the z-axis (symmetry axis)

a) Cyclotrimer	r(Å)	Φ(°)	z(Å)
N	1.960	319.20	−0.680
C	1.870	279.70	−0.920
O	2.650	272.70	−1.840
b) Cyclotetramer			
N	2.023	77.45	0.344
C	2.193	102.81	−0.540
O	2.482	96.69	−1.740

length $\pi-\pi^*$ transition, of symmetry A, is polarized along the symmetry axis. A qualitative similarity between polyproline I and cyclo-proline is also borne out by the experimental CD. spectra [16] [17] (*Fig. 6;* compare also with *Fig. 9*). For poly-

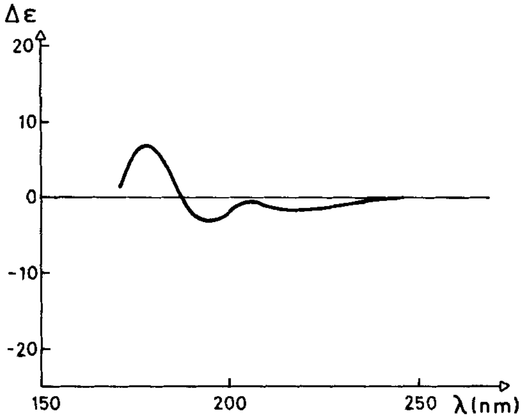

Fig. 5. *Experimental CD. spectrum of cyclo (Ala-Gly-Gly-Ala-Gly-Gly)*[a]) in D_2O (Ala≡L-alanyl). From NMR. [14] and indirect crystallographic evidence [15] the compound may have a 'pleated sheet' structure, stabilized by intramolecular, transannular hydrogen bonds. It must, however, be added that the above spectrum differs quite markedly from that of the polymer in the β-sheet conformation. See, for instance, [12].

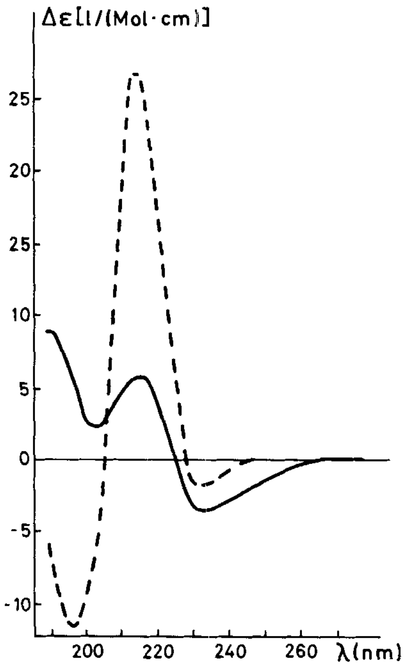

Fig. 6. *Experimental CD. spectrum of cyclo(tri-*L*-proline)* (——) *and of poly(*L*-proline) I* (------), *redrawn from* [16]. In the polymer Δε is related to one mol of the monomer.

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[a]) The compound was synthesized by *Gerlach, Owtschinnikow & Prelog* [13] and the measurement was performed in the laboratory of *J. Brahms*, Institut de Biologie Moléculaire, CNRS, Paris.

(L-proline)-I the maximum of the ($\pi-\pi^*$) UV. band should lie at relatively long wavelength, in agreement with experiment [18].

A particular situation is encountered in poly(L-proline)-II. The long-wavelength CD. spectrum is non-conservative (see *Fig. 7*), and from vacuum-UV. measurements it even appears that there are no positive *Cotton* effects above 130 nm [19], except for the long-wavelength tail at 230 nm. *Figure 4* gives computed rotatory strengths, and *Figure 10* represents the CD. spectra simulated therefrom. For Λ-values of the order of 0.2-0.5 eV, as adopted for the other conformations including the α-helix (see [1]), the computed spectrum is conservative in the long-wavelength region and disagrees with experiment. As the $n-\pi$ interaction is enhanced by increasing Λ, the strong positive band gradually moves into the vacuum-UV. region and the weak positive long-wavelength tail appears. A semiquantitative agreement with the measured spectrum is achieved for a value of $\Lambda \approx 3$ eV. This corresponds to a situation where $n-\pi$ mixing is so strong that the distinction between $n(\sigma)$ and π is practically totally blurred. *Pysh* [19] and *Ronish & Krimm* [18] using the exciton model, including polarizability contributions, are able to reproduce the polyproline II

Table 5. *Rotatory strengths and symmetry of transitions in cyclic peptides, the geometry of which is indicated in* Table 4. Notice approximate partial sum rules (see also Appendix), at least in relation to relative signs and orders of magnitude. Parameters are $I_n' = 26.80$ eV, $\Lambda = 0.5$ eV.

Cyclotrimer				Cyclotetramer			
	Symmetry	λ (nm)	$R \cdot 10^{40}$ (cgs)		Symmetry	λ (nm)	$R \cdot 10^{40}$ (cgs)
	E	246	− 24.2		E	266	− 4.8
n-π^*	E	246	− 24.2	n-π^*	E	266	− 4.8
	A	245	− 30.7		A	264	− 54.6
	A	183	279.3		E	178	131.2
π^0-π^*	E	177	− 100.5	π^0-π^*	E	178	131.2
	E	177	− 100.5		A	159	− 230.6
	A	121	− 97.0		A	120	178.4
π^+-π^*	E	120	59.8	π^+-π^*	E	119	− 52.8
	E	120	59.8		E	119	− 52.8

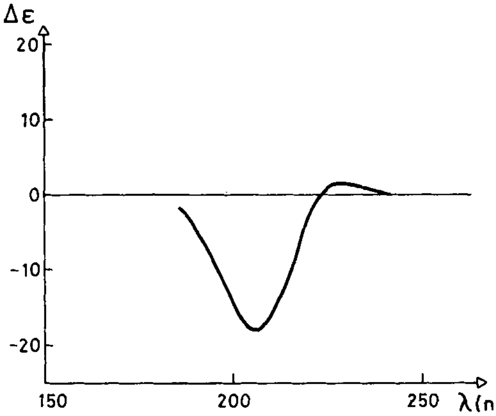

Fig. 7. *Experimental CD. spectrum of poly(L-proline) II, redrawn from* [23]

spectrum only by invoking the presence of far-UV. transitions. The possible existence of enhanced far-UV. transitions in polyproline II is complementary to our conclusion of increased n(σ)-π interaction.

General Conclusions. The Frozen Core MO procedure proposed in [1] is able to reproduce in a semiquantitative fashion the characteristic differences between the CD. spectra of oligomers in the PC pleated sheet, the poly(L-proline)-I and poly-(L-proline)-II conformation. It is able to establish some instructive connections to the spectra of cyclic oligopeptides, with regards to relative wavelengths, signs of *Cotton* effects and the polarization of transitions. In this connection approximate and partial sum rules (*Table 5* and *Appendix*) are also of interest.

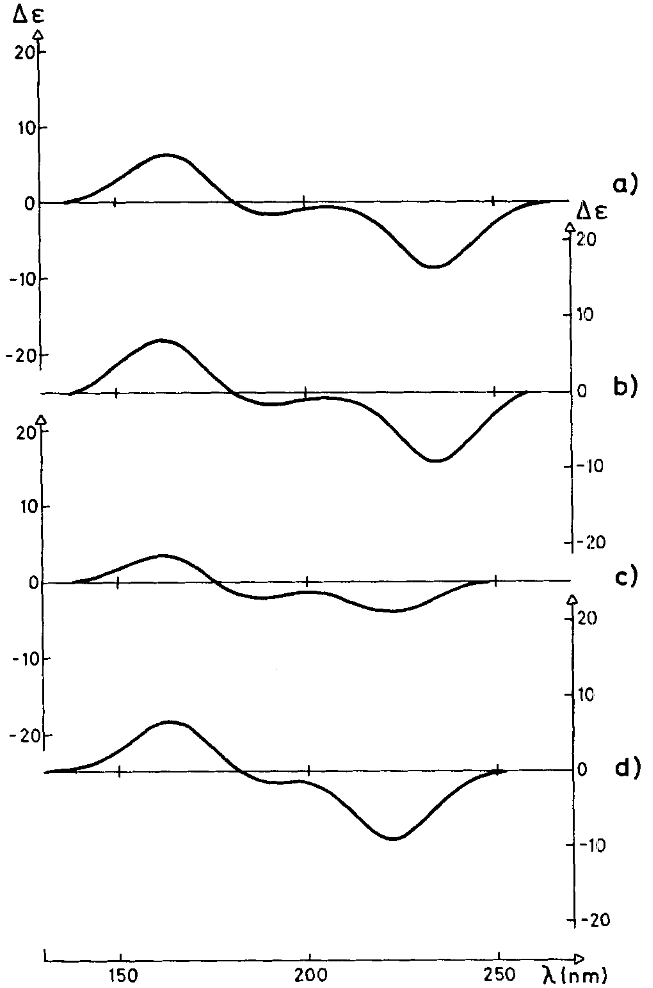

Fig. 8. *Computed CD. spectrum of oligomers in the PC pleated sheet structure:* a) *Hexamer*, $\Lambda = 0.5$ eV, $I'_{n} = 26.80$ eV. b) *Nonamer*, $\Lambda = 0.5$ eV, $I'_{n} = 26.80$ eV. c) *Hexamer*, $\Lambda = 0.2$ eV, $I'_{n} = 27.10$ eV. d) *Hexamer*, $\Lambda = 0.5$ eV, $I'_{n} = 27.10$ eV. Assumed bandwidths: Δ (π-π^*) = 16.0 nm, Δ (n-π^*) = 14.5 nm.

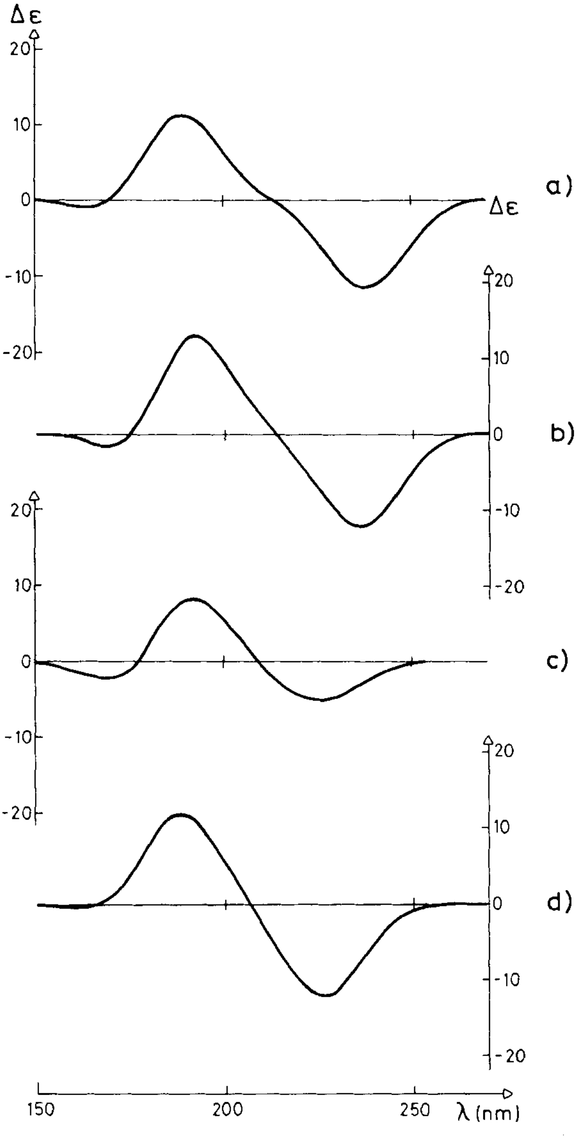

Fig. 9. *Computed CD. spectrum of oligomers in the poly*(L-*proline*) *I structure:* a) *Hexamer,* $\Delta = 0.5$ eV, $I'_n = 26.80$ eV. b) *Nonamer,* $\Delta = 0.5$ eV, $I'_n = 26.80$ eV. c) *Hexamer,* $\Delta = 0.2$ eV, $I'_n = 27.10$ eV. Assumed bandwidths: $\Delta(\pi\text{-}\pi^*) = 16.0$ nm, $\Delta(\text{n-}\pi^*) = 14.5$ nm.

The CD. spectrum of polyproline II may be semiquantitatively reproduced only by assuming very strong n(σ)-π interaction. This conclusion does not disagree with the result based on the exciton model that in this system far-UV. transitions play an important role [18] [19]. In search for a structural explanation for this apparent anomaly, we notice that i) the radius of the polyproline II helix is much smaller than that for the polyproline I helix, making it more like a strand; ii) the arrangement of the amide groups along the skeleton (strand) is quite different from that of the pleated sheet conformation. Further calculations are being carried out in search for structural criteria to assess n(σ)-π interaction.

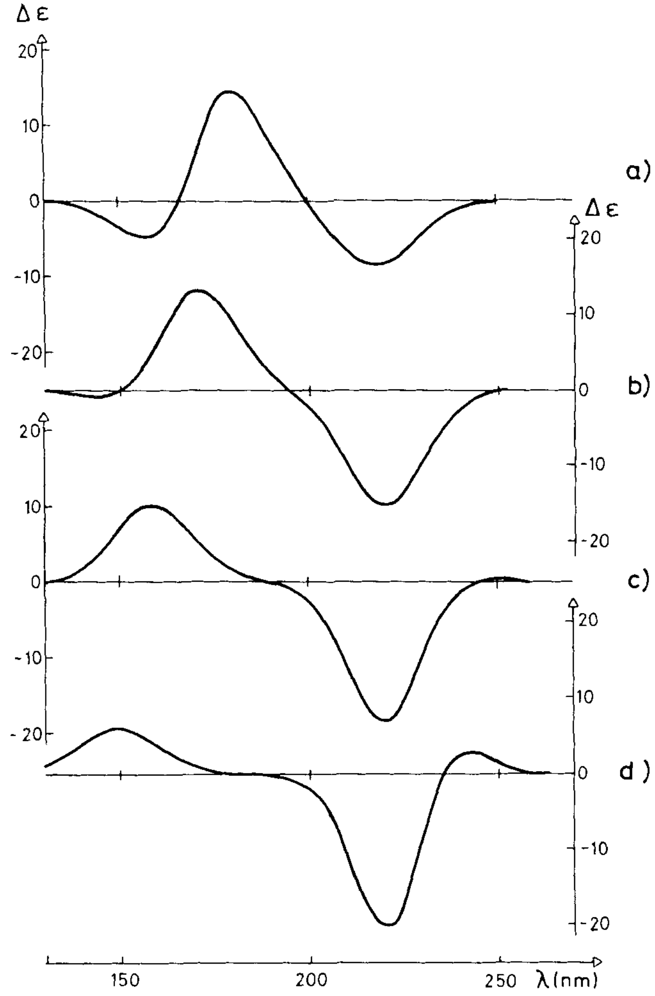

Fig. 10. *Computed CD. spectrum of the hexamer in the poly(L-proline) II conformation:* a) $\Delta = 0.5$ eV. b) $\Delta = 1.2$ eV. c) $\Delta = 2.0$ eV. d) $\Delta = 2.8$ eV. I'_n is everywhere 27.10 eV. Assumed bandwidths: $\Delta(\pi\text{-}\pi^*) = 16.0$ nm, $\Delta(\text{n-}\pi^*) = 14.5$ nm. As Δ grows, the distinction between (π-π^*) and (n-π^*) gets blurred.

Appendix

Sum rule for the rotatory strengths

The use of approximate wavefunctions. - The sum rule for the rotatory strengths is well-known:

$$\sum_{b \neq a} \mathrm{Im}\,\{\langle a|\vec{\mu}|b\rangle\langle b|\vec{m}|a\rangle\} = \mathrm{Im}\,\{\langle a|\vec{\mu}\cdot\vec{m}|a\rangle - \langle a|\vec{\mu}|a\rangle\cdot\langle a|\vec{m}|a\rangle\} = 0. \qquad (\mathrm{A.1})$$

Im $\{\ldots\}$ designates the imaginary part of the quantity in brackets. This expression vanishes, because the diagonal elements of a hermitian operator must be real. Both $\vec{\mu}$ and $\vec{m}$, the electric dipole and magnetic dipole operator, are hermitian. The product $\vec{\mu}\cdot\vec{m}$ is also hermitian, because the components commute pairwise, *i.e.*, μ_x with m_x, etc. One often designates by $|a\rangle$ the ground state and by $|b\rangle$ (collectively) the excited states of the molecule in question. In this case these functions are eigenfunctions of the molecular hamiltonian and they form a complete orthonormal set. To establish (A.1) one uses the fact that the functions form a complete set, in which $\vec{\mu}$ and $\vec{m}$ can be represented, but one does not use the fact that they are eigenfunctions of the hamiltonian. The relation (A.1) will therefore be valid for any complete (orthonormal) set of functions in which $\vec{\mu}$ and $\vec{m}$ may be represented.

Consider $|a\rangle$ to be a *Hartree-Fock* ground state Φ_0 defined in a quasi-infinite basis of SCF MO's. The totality of configurations defined within these MO's form a complete set in the sense mentioned above. There are, however, only nonvanishing matrix elements of $\vec{\mu}$ and $\vec{m}$ between Φ_0 and singly excited configurations Φ_i^k. Therefore the sum rule holds exactly for $|a\rangle = \Phi_0$, $|b\rangle = \Phi_i^k$. The sum rule will likewise also hold exactly between $|a\rangle = \Phi_0$ and single-excitation CI wavefunctions, which may be viewed as the result of a unitary transformation of the Φ_i^k among themselves. Evidently the sum rule holds when $|a\rangle$ and $|b\rangle$ are full-CI wavefunctions. In the intermediate case between single-excitation CI and full-CI, the sum rule is not automatically exactly fulfilled [22].

In our computations we use single-excitation CI, but with a limited basis and with additional, drastic approximations. The sum rule is then approximately fulfilled.

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