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Synthesis and Conformation of Aromatic Cyclic Dipeptides. Cyclo(phenylalanyl)$_2$, Cyclo(1-naphthylalanyl)$_2$, and Cyclo(2-naphthylalanyl)$_2$

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Cyclic dipeptides of aromatic amino acids, cyclo(L-phenylalanyl)$_2$, cyclo(L-1-naphthylalanyl)$_2$, and cyclo(L-2-naphthylalanyl)$_2$ were synthesized and subjected to spectroscopic analyses using ^{1}H NMR, absorption, circular dichroism (CD), fluorescence, and fluorescence-detected circular dichroism (FDCD). The ^{1}H NMR data suggested that the 2,5-piperazinedione rings of the three cyclic dipeptides are in planar or nearly planar bowsplit boat-type conformation. The aromatic side groups of cyclo(1- and 2-naphthylalanyl)$_2$'s were found to take asymmetric configurations, one naphthyl group being folded onto the 2,5-piperazinedione ring, the other being unfolded. Strong exciton couplet was observed in CD spectra of the three compounds. The signs of the exciton splitting were opposite in the two naphthyl cyclic dipeptides. Fluorescence spectra of the two naphthyl cyclic dipeptides showed no excimer emission. The absence of strong interchromophoric interaction in the lowest excited state was also suggested by the virtual coincidence of CD spectrum with FDCD spectrum. From the above spectroscopic data, probable conformations were proposed for the naphthyl cyclic dipeptides.

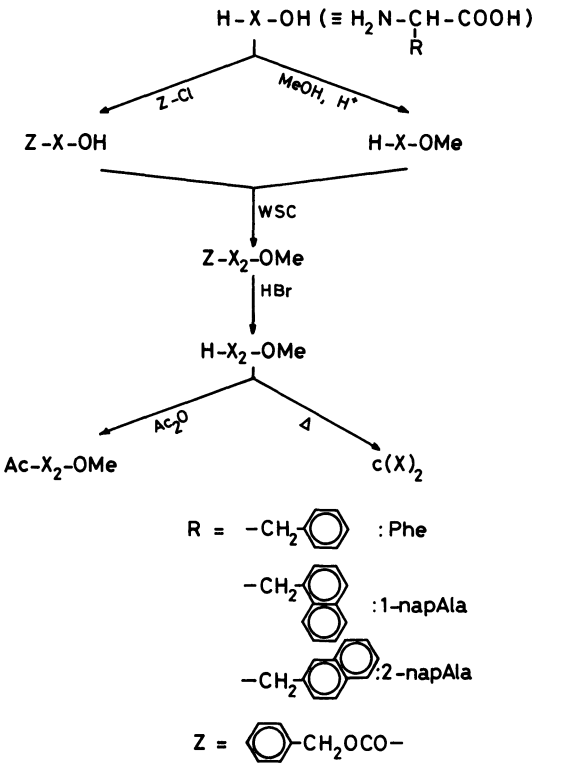
Bichromophoric systems in which conformational freedom of the two chromophores are highly restricted, have been studied and basic information on electronic properties of spatially fixed chromophoric systems has been accumulated.[1] In this respect, cyclic compounds carrying aromatic groups are especially interesting because of the rigidity of the chromophore arrangement. Bichromophoric cyclophanes,[1] cyclobutanes,[2,3] and crown ethers[4] have been reported in the past. However, few *chiral* bichromophoric cyclic compound has been reported so far.[1] The chiral bichromophoric systems are advantageous, since chiroptical spectroscopy, such as circular dichroism (CD), circularly polarized fluorescence (CPF),[5,6] and fluorescence-detected circular dichroism (FDCD)[7] provides more information on the electronic properties than that from conventional spectroscopy.

In this study, syntheses of aromatic cyclic dipeptides carrying phenyl, 1-naphthyl, and 2-naphthyl chromophores were undertaken and their conformations in solution were investigated. Cyclic dipeptides consisting of natural amino acids i.e., phenylalanine (Phe), tyrosine (Tyr), histidine (His), and tryptophan (Trp) have been studied by ^{1}H NMR, ^{13}C NMR, CD, and X-ray crystallography.[8–15] However, the aromatic groups of the natural amino acids are not suited for photochemical and photophysical investigations. In this study, artificial aromatic amino acids carrying 1- or 2-naphthyl group, L-1- and L-2-naphthylalanine (1- or 2-napAla) are employed and their linear and cyclic dipeptides are prepared.

Experimental

Meterials. Linear and cyclic dipeptides of Phe, 1-napAla, and 2-napAla were prepared by the procedure shown in Scheme 1. Optically active 1- and 2-napAla's were prepared by the optical resolution of their acetyl derivatives with acylase,[16,17] which were synthesized by the acetamidomalonate ester method. In the following, syntheses of linear and cyclic dipeptides of 2-napAla are described as typical examples.

***N*-Benzyloxycarbonyl-L-2-naphthylalanine (*Z*-2-napAla).**



Scheme 1.

2-NapAla (200 mg) was dissolved in 1 M† NaOH aqueous solution (1 ml) and cooled by ice. Benzyloxycarbonyl chloride (0.15 ml) and 1 M NaOH were added dropwise concurrently under vigorous stirring. The stirring was continued overnight and then the pH of the solution was adjusted to about 3. The organic component was extracted with ethyl acetate and the extract was dried and evaporated. The crude crystals remained were recrystallized from an ether–hexane mixed solvent. Yield 90%, mp 165—170 °C. *Z*-l-napAla: Yield 95%, mp 150—152 °C. *Z*-Phe: Yield 71%, mp 86—89 °C.

L-2-Naphthylalanine Methyl Ester Hydrochloride (2-napAla-OMe·HCl). The amino acid (200 mg) was dissolved in methanol (20 ml) containing 2 ml of 1 M HCl and refluxed for 1 h. The solvent was evaporated and the residue was recrystallized from a methanol–ethyl acetate mixed solvent. Yield 87%, mp 165 °C (gradually sublimed above 130 °C). 1-NapAla-OMe·HCl: Yield 98%, mp 143—145 °C (partially sublimed). Phe-OMe·HCl: Yield 95%, mp 159—161 °C.

***N*-Benzyloxycarbonyl-L-2-naphthylalanyl-L-2-naphthylalanine Methyl Ester [*Z*-(2-napAla)$_2$-OMe].** *Z*-2-NapAla (133 mg) was dissolved in dichloromethane (2 ml) and 2-napAla-OMe·HCl (100 mg) and triethylamine (58 μl) were added. After cooling with an ice–water bath, water-soluble carbodiimide (WSC) [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] (80 mg) and 1-hydroxybenzotriazole (56 mg) were added. After stirring overnight the solvent was evaporated and ethyl acetate was added. The solution was washed with 10% citric acid, aq NaCl solution, 10% $NaHCO_3$, and water and dried over sodium sulfate. The residue remained after evaporation was recrystallized from an ethyl acetate–ether mixed solvent. Yield 83%, mp 163 °C. *Z*-(1-napAla)$_2$-OMe: Yield 73%, mp 136 °C. *Z*-(Phe)$_2$-OMe: Yield 40%, mp 106—109 °C.

Cyclo(L-2-naphthylalanyl-L-2-naphthylalanyl) [c(2-napAla)$_2$]. *Z*-(2-NapAla)$_2$-OMe (177 mg) was dissolved in 25% HBr–acetic acid (3 ml) and stirred for 30 min at room temperature. The solution was concentrated under reduced pressure and a small amount of acetic acid was added again. The solution was poured into ether and the precipitate was collected and dried under vacuum. The HBr salt was then dispersed in ethyl acetate and shaked with aqueous $NaHCO_3$ solution. The organic layer was dried over sodium sulfate and the solvent was evaporated. 1-Butanol (50 ml) was added to the residue remained and the solution was refluxed for 2 d. The crystal which appeared after cooling the reaction mixture in refrigerator, was collected and washed with methanol. The cyclic dipeptide was only slightly soluble in such polar aprotic solvents as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and trimethyl phosphate (TMP). No appropriate solvent was found for recrystallization. Yield 55%, mp>300 °C. Found: C, 79.39; H, 5.85; N, 7.22%. Calcd for $C_{26}H_{24}N_2O_2$: C, 79.17; H, 5.62; N, 7.10%. c(1-napAla)$_2$: Yield 47%, mp 272—274 °C. Anal. Found: C, 79.30; H, 5.58; N, 7.27%. c(Phe)$_2$: Yield 32%, mp>300 °C. Found: C, 73.61; H, 6.11; N, 9.43%. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%.

† 1 M=1 mol dm^{-3}.

***N*-Acetyl-L-2-naphthylalanyl-L-2-naphthylalanine Methyl Ester [Ac-(2-napAla)$_2$-OMe].** The benzyloxycarbonyl group of *Z*-(2-napAla)$_2$-OMe was removed by 25% HBr–acetic acid. The HBr salt of the dipeptide methyl ester was dissolved in acetic anhydride–triethylamine (1:1) mixture and stirred overnight. The volatile component was removed under reduced pressure and the solid remained was dissolved in ethyl acetate. The solution was washed with 1 M HCl, 10% $NaHCO_3$, and water and dried over Na_2SO_4. Evaporation gave a crude crystal which was recrystallized from an ethyl acetate–hexane mixed solvent. Mp 200—205 °C. Found: C, 73.37; H, 5.96; N, 5.98%. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98%. Ac-(1-napAla)$_2$-OMe: Mp 208—212 °C. Found: C, 74.37; H, 5.99; N, 6.32%.

Measurements. ^{1}H NMR (90 MHz) was recorded on a JEOL FX90Q Fourier Transform spectrometer in *N*,*N*-dimethylformamide (DMF)-d_7 over the temperature range of 50—100 °C for c(Phe)$_2$ and c(2-napAla)$_2$ and over the temperature range of −40—100 °C for c(1-napAla)$_2$. Residual peaks of the solvent were eliminated by a 180°-τ-90° pulse sequence. The peak assignment reported by Kobayashi et al.[18] was adopted. The amide NH peaks of the naphthyl dipeptides overlapped with the peaks of aromatic protons. Therefore, the coupling parameter $J_{NH-C^{\alpha}H}$, was measured from the splitting of $C^{\alpha}H$ proton band under irradiating the $C^{\beta}H$ proton. Octets were observed in the region of $C^{\beta}H$ protons for the three cyclic dipeptides, indicating the two nonequivalent $C^{\beta}H$ protons [$C^{\beta}H$(S) and $C^{\beta}H$(R)] couple with each other and with the $C^{\alpha}H$ proton. The coupling constants, $J_{C^{\alpha}H-C^{\beta}H(S)}$ and $J_{C^{\alpha}H-C^{\beta}H(R)}$, were directly read from the peak separations of the octets.

Circular dichroism (CD) was recorded on a JASCO J-20 spectropolarimeter. Fluorescence-detected circular dichroism (FDCD) was also measured on the JASCO J-20 machine, equipped with a cutoff filter for excitation light, a Hamamatsu R268 photomultiplier tube, and a preamplifier.[7] Fluorescence spectra were recorded on a Hitachi MPF-4 instrument under an autocorrection mode. The dipeptides in DMF ([Aryl group]=1.0×10^{-5} mol l^{-1}) were put into a quartz tube of diameter 5 mm, and the tube was immersed into a Dewer vessel with quartz windows. The Dewer vessel was filled with a temperature-controlled methanol. The DMF solution was bubbled with nitrogen gas for 20 min before each measurement.

Results and Discussion

^{1}H NMR Spectra. The proton NMR spectra of the three cyclic dipeptides were measured in DMF-d_7. The spectra for c(1- and 2-napAla)$_2$ are shown in Fig. 1.

Coupling parameters obtained from the spectra are collected in Tables 1 and 2. They were virtually constant over the temperature range of 50—100 °C for c(Phe)$_2$ and c(2-napAla)$_2$ and −40—100 °C for c(1-napAla)$_2$, indicating a temperature independence of the skeletal conformations of the 2,5-piperazinedione rings and of the conformer populations of the side chains for the three cyclic dipeptides.

Table 1 lists the coupling constants $J_{NH-C^{\alpha}H}$, which are related to the dihedral angle $\theta_{NH-C^{\alpha}H}$ between C^{α}–N–H plane and H–C^{α}–N plane. $\theta_{NH-C^{\alpha}H}$ is approximately equal to $\phi(N-C^{\alpha})-60°$, where ϕ is the rotational angle around N–C^{α} bond as defined by the IUPAC-IUB nomenclature committee.[19] The dihedral angles were calculated from the coupling constants by using three different equations proposed by Bystrov et al.,[20] Ramachandran et al.,[21] and Chung et al.,[22] and are listed in the same table. It is seen that the angles estimated by using the three equations differ considerably.

Skeletal conformation of cyclic dipeptides in solution is often assumed to be symmetric and have planar amide bonds. Under these assumptions, the skeletal conformation is expressed by a single angle β, which is defined as a complementary angle between the two amide planes.[12,13] A skeletal conformation with positive β is called as a bowsplit boat-type one in which the two C^{β} atoms are in extended positions out of the 2,5-piperazinedione ring. The conformation of negative β is called as a flagpole boat-type one in which the two C^{β} atoms approach with each other above the 2,5-piperazinedione ring. β is zero for a planar 2,5-piperazinedione ring. The smallest β has been reported for cyclo(*N*-methyl-L-Val)$_2$[15] to be $-41°$, while the largest β has been found in cyclo(L-proline)$_2$[23] to be 38°. Larger or smaller β leads to unacceptably small bond angles at the C^{α} atom.

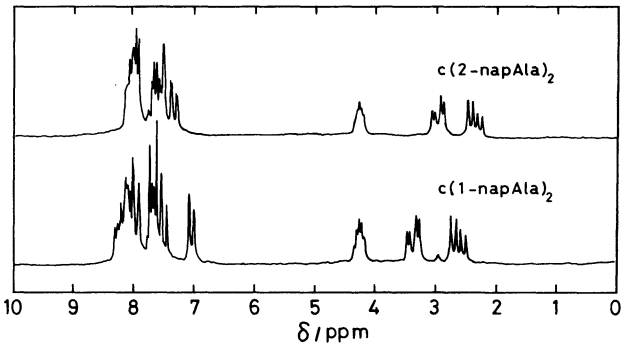


Fig. 1. Proton NMR spectra of c(1- and 2-napAla)$_2$ in DMF-d_7. Concentration=2.0 mg/0.4 ml. Temperature=30 °C for c(1-napAla)$_2$, 50 °C for c(2-napAla)$_2$.

If one allows a variation of β between ±45°, the allowed range of $\theta_{NH-C^{\alpha}H}$ is between $-20°$ and $-100°$. Hence, among the four values of $\theta_{NH-C^{\alpha}H}$ obtained as solutions of each equation of Table 1, only one is in the allowed range, which is indicated in the parentheses. If one adopts $\theta=-102°$ for c(Phe)$_2$, the bond angle $\angle$(N,C,C′) will be 97°. Similarly, if one takes $\theta=-115°$ for c(2-napAla)$_2$, the bond angle will be 85°. These small bond angles around C^{α} atom are unacceptable.

As the result of the above consideration, it was concluded that the $\theta_{NH-C^{\alpha}H}$ values lie between $-58°$ and $-39°$ for the two c(napAla)$_2$'s and between $-72°$ and $-57°$ for c(Phe)$_2$. These ranges of $\theta_{NH-C^{\alpha}H}$ correspond to the range of β between 0° and 20° for the two c(napAla)$_2$'s and between $-10°$ and 5° for c(Phe)$_2$. Therefore, the two c(napAla)$_2$'s have planar or nearly planar bowsplit boat-type skeletal conformations and c(Phe)$_2$ is in a planar conformation in DMF solution.

Little has been reported on the skeletal conformations of aromatic cyclic dipeptides. Snow and Hooker[13] calculated conformation energy and theoretical CD for c(Tyr)$_2$ and concluded that its β value was around 20°. This value is within the possible range of β for the two c(napAla)$_2$'s. On the other hand, Benedetti et al.[15] reported a result of X-ray crystallography of c(*N*-methyl-Phe)$_2$ and found that $\beta=-19°$. The large negative value may reflect the effect of *N*-methyl substituents and cannot be directly

Table 1. The Coupling Constant $J_{NH-C^{\alpha}H}$, and the Dihedral Angle $\theta_{NH-C^{\alpha}H}$, of Aromatic Cyclic Dipeptides in *N*,*N*-Dimethylformamide-d_7

Amino acid	$J_{NH-C^{\alpha}H}$[a]	$\theta_{NH-C^{\alpha}H}$/degree		
		Bystrov[c]	Ramachandran[d]	Chung[e]
Phe	≲1.0[b]	±102, ±72 (−72)[f]	[g]	±102, ±57 (−57)
1-napAla	2.9	±117, ±55 (−55)	±112, ±52 (−52)	±116, ±39 (−39)
2-napAla	2.5	±115, ±58 (−58)	±109, ±56 (−56)	±113, ±43 (−43)

a) Measured at 30 °C for c(1-napAla)$_2$ and at 50 °C for c(2-napAla)$_2$ and c(Phe)$_2$, ±0.2 Hz. b) Estimated from the linewidth of C^{α} proton signal under irradiating the C^{β} protons. c) $J_{NH-C^{\alpha}H}=9.4\cos^2\theta-1.1\cos\theta+0.4$. (Ref. 20). d) $J_{NH-C^{\alpha}H}=7.9\cos^2\theta-1.5\cos\theta+1.35\sin^2\theta$. (Ref. 21). e) $J_{NH-C^{\alpha}H}=4.3\cos^2\theta-2.9\cos\theta+4.3$. (Ref. 22). f) Value which corresponds to the allowed range of β(±45 °). g) The Ramachandran equation affords no solution.

compared with the present results.

Coupling constants $J_{C^{\alpha}H-C^{\beta}H(R)}$ and $J_{C^{\alpha}H-C^{\beta}H(S)}$ afford information on the rotamer population around C^{α}–C^{β} bond (χ_1), if the rotation is fast enough compared with the NMR time scale. Although the bulky aromatic groups is expected to retard the rotation considerably, no evidence for the restricted rotation was detected in the ^1H NMR spectra over the temperature range of −40—100 °C for c(1-napAla)$_2$ and 50—100 °C for c(2-napAla)$_2$ and c(Phe)$_2$. The coupling constants are listed in Table 2, together with the rotamer populations calculated according to the empirical equation reported by Pachler.[24]

The population of trans conformation is smaller than 20% for the three cyclic dipeptides. The small contribution of trans form is explained by a repulsive interaction between aromatic ring and the carbonyl oxygen. g^+ indicates a folded conformation in which the aromatic ring is overlapped onto the 2,5-piperazinedione ring. It should be noted that the population of the folded conformation is larger than 40% for the two c(napAla)$_2$'s and even larger for c(Phe)$_2$. The predominance of the folded conformation may be, at least partially, ascribed to an aromatic-amide interaction which has been detected by NMR spectroscopy.[25]

A CPK model examination and a preliminary result of empirical potential energy calculation for c(napAla)$_2$'s[26] suggested that the two side chains cannot take the folded conformation concurrently. Therefore, the high population of the folded conformation indicates that one side chain takes a folded conformation whereas the other is in unfolded conformations, t and g^- with a predominance of g^-. Incidentally, Benedetti et al.[15] reported that the side chains of c(*N*-methyl-L-Phe)$_2$ are in an asymmetric conformation, one being in a folded, the other in an unfolded conformation in the solid state.

To summarize the ^1H NMR results, the three aromatic cyclic dipeptides take similar skeletal and side-chain conformations. The skeletal conformation is planar (β=0°) or nearly planar bowsplit boat-type one (β<20°). The side-chains rotate rapidly within the NMR time scale and its rotamer population favors folded (g^+)–unfolded (g^->t) asymmetric conformations.

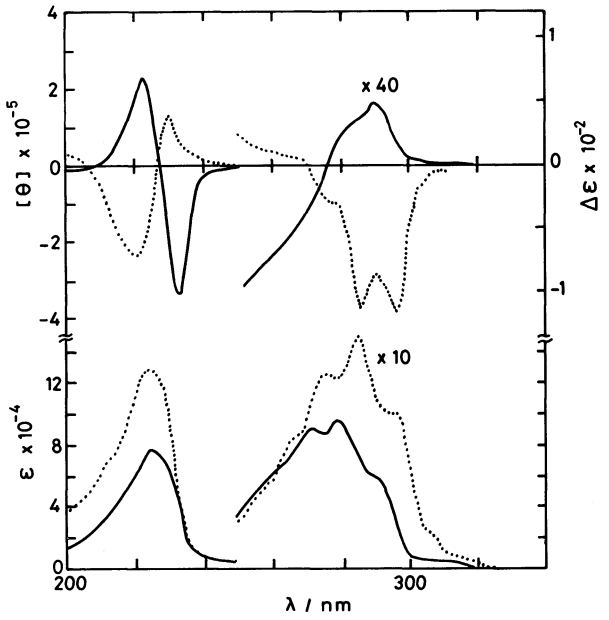
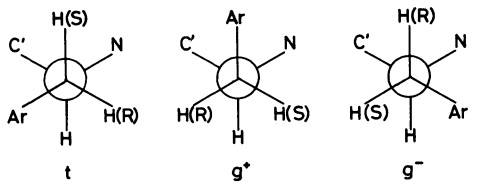


Fig. 2. CD (top) and absorption (bottom) spectra of c(1-napAla)$_2$ (·····) and c(2-napAla)$_2$ (——) in trimethyl phosphate at 25 °C. [θ] and ε are calculated with respect to two naphthyl chromophores.

Table 2. The Coupling Constant $J_{C^{\alpha}H-C^{\beta}H}$, and the Rotamer Populations around C^{α}–C^{β} Bond in *N*,*N*-Dimethylformamide-d_7

Amino acid	$J_{C^{\alpha}H-C^{\beta}H(S)}$	$J_{C^{\alpha}H-C^{\beta}H(R)}$[a]	Rotamer polulations[b]		
			t	g^-	g^+
Phe	4.1	6.9	0.14	0.39	0.47
1-napAla	4.5	7.2	0.17	0.42	0.41
2-napAla	4.6	7.1	0.18	0.41	0.41

a) These coupling parameters (in Hz) were constant over the temperature range of 30—100 °C. The estimated error is ±0.1 Hz for 1- and 2-napAla's and ±0.5 Hz for Phe. b) Calculated on the basis of the Pachler's empirical equation (Ref. 24): $J_{C^{\alpha}H-C^{\beta}H(S)} = 10.96\,t + 2.60$, $J_{C^{\alpha}H-C^{\beta}H(R)} = 10.96\,g^- + 2.60$. The configurations of the three rotamers are shown below.



Absorption Spectra and Circular Dichroism. Figure 2 shows absorption and CD spectra of c(1- and 2-napAla)$_2$'s in TMP. The two cyclic dipeptides exhibit marked exciton couplets at the ^1B_b absorption band with opposite signs. The molar ellipticities are: $[\theta]_{229}=1.4\times10^5$, $[\theta]_{221}=-2.4\times10^5$ ($\Delta\tilde{\nu}=1581$ cm^{-1}) for c(1-napAla)$_2$ and $[\theta]_{233}=-3.5\times10^5$, $[\theta]_{222}=2.3\times10^5$ ($\Delta\tilde{\nu}=2127$ cm^{-1}) for c(2-napAla)$_2$. According to the exciton coupling rule,[27] the sign of exciton coupling in c(1-napAla)$_2$ indicates that the screw sense of the arrangement of ^1B_b absorption transition moment is right-handed in the conformation which contributes most significantly to the CD spectrum observed. The sign of exciton couplet in c(2-napAla)$_2$ indicates that the screw sense is left-handed in the most significant conformer.

The marked exciton couplet also suggests strong interchromophore interaction between naphthyl groups in the cyclic dipeptides. A preliminary conformational calculation[26] indicated that the center-to-center distances between two naphthyl groups in the two cyclic dipeptides are between 6—7 Å in the folded(g$^+$)-unfolded(g$^-$) side-chain conformations. The interchromophore distance is short enough to induce strong exciton couplet in the CD spectra.

The CD intensity at the ^1B_b absorption band is much more intense in the cyclic dipeptides than in the corresponding linear dipeptides which are shown in Fig. 3. No exciton couplet is seen in Ac-(1-napAla)$_2$-OMe and very weak CD is observed in Ac-(2-napAla)$_2$-OMe. The weak CD indicates a weaker interchromophore interaction in the linear dipeptides due to longer average interchromophore distances and/or an averaging of positive and negative CD spectra of a variety of conformations allowed for the linear dipeptides in solution. Absorption coefficients of the two cyclic dipeptides (Fig. 2) are smaller than those of the linear dipeptides (Fig. 3), especially for the 2-naphthyl derivatives. The hypochromicity indicates a stronger interchromophore interaction in the cyclic dipeptides than in the linear ones, suggesting that the weak CD of linear dipeptides is caused not by the averaging of positive and negative CD curves but by a weak interchromophore interaction in the linear dipeptides.

The weak chromophoric interaction in the linear dipeptides suggests that the dipeptides are in extended conformations in TMP. Rizzo and Jäckle[28] reported that linear aromatic dipeptides, such as Ac-(Trp)$_2$-NHMe, Ac-(Phe)$_2$-NHMe, and Ac-(Tyr)$_2$-NHMe, are in folded conformations in a protic solvent, 2,2,2-trifluoroethanol, and in extended ones in an aprotic solvent, tetrahydrofuran. Although it is impossible to test the above rule in the present case due to the limited solubility, the extended conformations suggested for the linear dipeptides of napAla's in TMP, which is an aprotic solvent, do not contradict the above rule.

Figure 4 shows absorption and CD spectra of c(Phe)$_2$ in TMP. A moderately strong exciton couplet is observed around 195 nm, which corresponds to the ^1B_b absorption band of the phenyl group. The interpretation of the sign of the exciton couplet of c(Phe)$_2$ is somewhat difficult due to the complexity in the direction of the ^1B_b transition moment.[29]

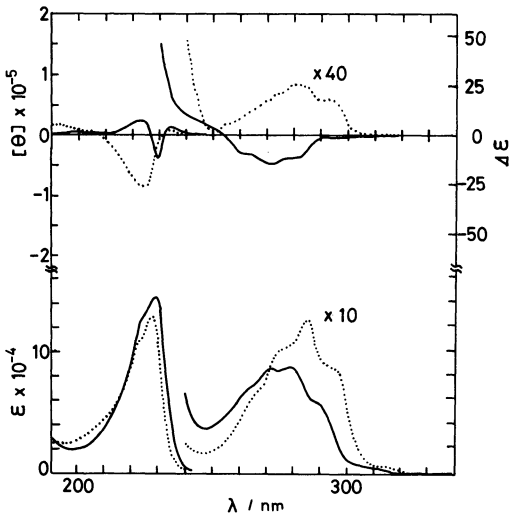


Fig. 3. CD (top) and absorption (bottom) spectra of Ac-(1-napAla)$_2$-OMe (·····) and Ac-(2-napAla)$_2$-OMe (——) in trimethyl phosphate at 25 °C. [θ] and ε are calculated with respect to two naphthyl chromophores.

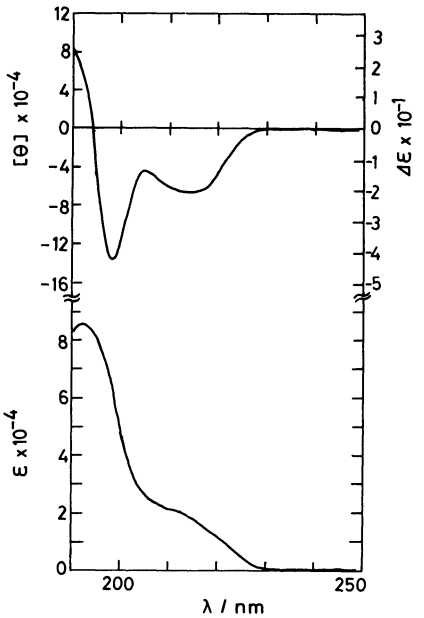


Fig. 4. CD (top) and absorption (bottom) spectra of c(Phe)$_2$ in trimethyl phosphate at 25 °C. [θ] and ε are calculated with respect to two phenyl chromophores.

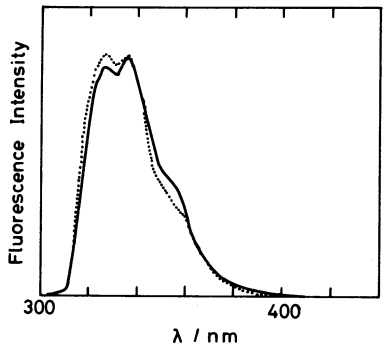


Fig. 5. Fluorescence spectra of c(1-napAla)$_2$ (·····) and c(2-napAla)$_2$ (——) in N_2-bubbled *N,N*-dimethylformamide at 25 °C. Excitation wavelength=285 nm.

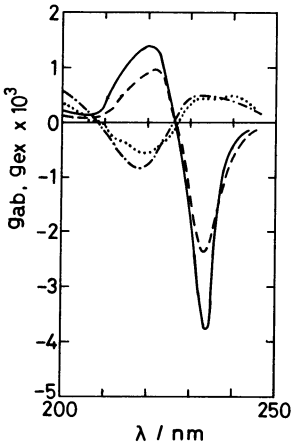


Fig. 6. FDCD spectra (g_{ex}) of c(1-napAla)$_2$ (·····) and c(2-napAla)$_2$ (----), and absorption CD spectra (g_{ab}) of c(1-napAla)$_2$ (—·—) and c(2-napAla)$_2$ (——) in trimethyl phosphate at 25 °C.

Fluorescence Spectra and Fluorescence-Detected Circular Dichroism. Figure 5 shows fluorescence spectra of c(1- and 2-napAla)$_2$'s in DMF. No excimer emission was observed in the two cyclic dipeptides, indicating the inaccessibility of the two naphthyl groups connected to the 2,5-piperazinedione ring. Excimer emission was not detected even at low temperatures down to −50 °C for the two c(napAla)$_2$'s. This contrasts the case of *cis*-1,2-di(2-naphthyl)cyclobutane,[3] in which excimer emission has not been detected at room temperature, but observed at low temperatures (−20—−80 °C). The absence of excimer emission in the cyclic dipeptides indicates the rigidity of the skeletal and side-chain conformations and excludes the possibility of the folded(g$^+$)–folded(g$^+$) symmetrical side-chain conformation in the cyclic dipeptides.

No excimer was found also in linear dipeptides of 1- and 2-napAla's in DMF, suggesting, again, the extended conformation of the linear dipeptides in such aprotic solvents as TMP and DMF.

The absence of excimers in cyclic dipeptides does not contradict the observation of strong exciton couplet in CD spectra. In the latter case, one naphthyl group in the ^1B_b excited Franck-Condon state interacts with another naphthyl group, which is in the ground state, mainly by a dipole–dipole mechanism. In the case of excimer, one naphthyl group in the lowest ^1L_b excited state interacts with another naphthyl group by a mechanism including an electron-exchange interaction. The excimer formation requires a considerable distortion of molecular configuration to keep the two chromophores close to each other within ca. 3.5 Å.

The absence of strong interchromophore interaction in the lowest excited state is also evident from FDCD spectra shown in Fig. 6. FDCD spectroscopy measures a difference in fluorescence intensities (I_L^{ex}, I_R^{ex}) when excited by left- and right-circularly polarized lights, respectively, and are represented by the Kuhn's excitation dissymmetry factor g_{ex}.[7]

$$g_{ex} = 2(I_L^{ex} - I_R^{ex})/(I_L^{ex} + I_R^{ex})$$

The excitation dissymmetry factor should be compared with the absorption dissymmetry factor g_{ab}, calculated from CD and absorption spectra of the same sample.

$$g_{ab} = 2(\varepsilon_L - \varepsilon_R)/(\varepsilon_L + \varepsilon_R)$$

ε_L and ε_R are the absorption coefficients for left- and right-circularly polarized lights, respectively.

In Fig. 6, the absorption and the excitation dissymmetry factors of c(napAla)$_2$ coincides with each other within an experimental error, indicating the absence of any particular conformation which fluoresces predominantly. In other words, all conformers of c(1-napAla)$_2$ fluoresce equally. This, in turn, suggests the absence of any particular interaction between the naphthyl groups in the lowest excited state. The conclusion should be somewhat modified in the case of c(2-napAla)$_2$. In this case the excitation dissymmetry factor is a little smaller than the absorption dissymmetry factor, especially at the negative lobe. The smaller g_{ex} may indicate that the conformation which shows an intense CD, fluoresces less strongly than other conformers. Presumably, a conformation in which the two naphthyl groups are close to each other induces a strong exciton couplet but fluoresces little due to an enhanced nonradiative process caused by some interchromophoric interactions. However, the interaction is so small that the whole profile of the FDCD spectrum remains unchanged.

Conclusions

Possible conformations of c(1- and 2-napAla)$_2$'s are illustrated in Fig. 7. The folded(g$^+$)–unfolded(g$^-$)

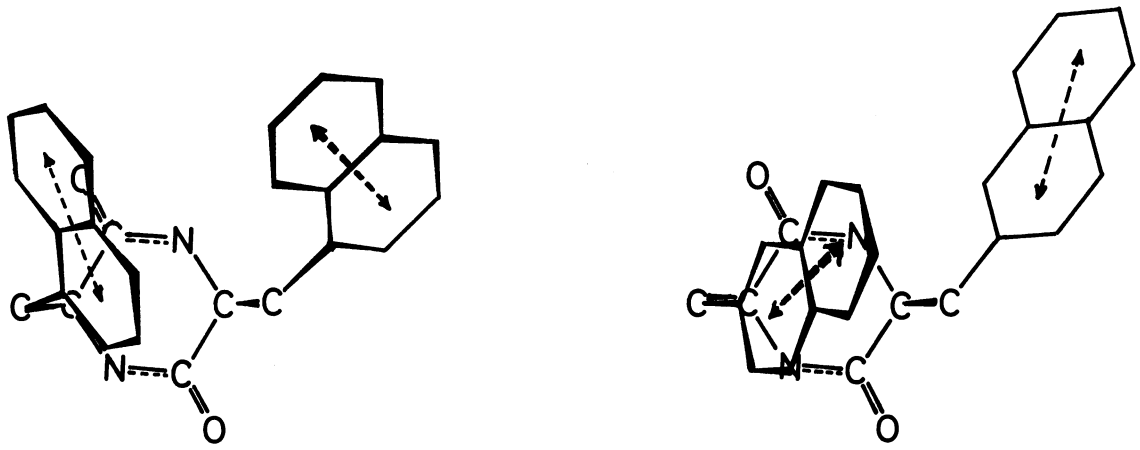


Fig. 7. Possible conformations of c(1-napAla)$_2$ (left) and c(2-napAla)$_2$ (right). The dashed arrows indicate directions of the ^1B_b transition moments.

asymmetric conformation is suggested by the ^1H NMR data and by the absence of excimer emission. The screw sense of the arrangement of the ^1B_b absorption transition moments of the two naphthyl groups is right-handed for c(1-napAla)$_2$ in a conformation which contributes most significantly to CD spectrum. It is left-handed for c(2-napAla)$_2$. The center-to-center interchromophoric distances are 6—7 Å. No particular interaction in the lowest excited state has been detected in the fluorescence and the FDCD spectra.

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References

1) S. N. Semerak and C. W. Frank, *Adv. Polym. Sci.*, **54**, 31 (1983).
2) H. Masuhara, H. Shioyama, N. Mataga, T. Inoue, N. Kitamura, T. Tanabe, and S. Tazuke, *Macromolecules*, **14**, 1738 (1981).
3) S. Ito, M. Yamamoto, and Y. Nishijima, *Bull. Chem. Soc. Jpn.*, **57**, 3295 (1984).
4) P. Tundo and J. H. Fendler, *J. Am. Chem. Soc.*, **102**, 1760 (1980).
5) F. S. Richardson and J. P. Riehl, *Chem. Rev.*, **77**, 773 (1977).
6) M. Sisido, S. Egusa, A. Okamoto, and Y. Imanishi, *J. Am. Chem. Soc.*, **105**, 3351 (1983).
7) S. Egusa, M. Sisido, and Y. Imanishi, *Macromolecules*, **18**, 882 (1985).
8) K. D. Kopple and D. H. Murr, *J. Am. Chem. Soc.*, **89**, 6193 (1967).
9) K. D. Kopple and M. Ohnishi, *J. Am. Chem. Soc.*, **91**, 962 (1969).
10) H. Edelhoch and R. E. Lippoldt, *J. Biol. Chem.*, **243**, 4799 (1968).
11) E. H. Strickland, M. Wilchek, J. Horwitz, and C. J. Billups, *J. Biol. Chem.*, **245**, 4168 (1970).
12) P. E. Grebow, and T. M. Hooker, Jr., *Biopolymers*, **14**, 1863 (1975).
13) J. W. Snow and T. M. Hooker, Jr., *Biopolymers*, **16**, 121 (1977).
14) W. Radding, B. Donzel, N. Ueyama, and M. Goodman, *J. Am. Chem. Soc.*, **102**, 5999 (1980).
15) E. Benedetti, R. E. Marsh, and M. Goodman, *J. Am. Chem. Soc.*, **98**, 6676 (1976).
16) M. Sisido, S. Egusa, and Y. Imanishi, *J. Am. Chem. Soc.*, **105**, 1041 (1983).
17) M. Sisido, S. Egusa, and Y. Imanishi, *J. Am. Chem. Soc.*, **105**, 4077 (1983).
18) J. Kobayashi, T. Higashijima, S. Sekido, and T. Miyazawa, *Int. J. Pept. Protein Res.*, **17**, 486 (1981).
19) IUPAC-IUB Committee, *Biochemistry*, **18**, 3471 (1970).
20) V. F. Bystrov, V. T. Ivanov, S. L. Portonava, T. A. Balashova, and Y. A. Ovchinnikov, *Tetrahedron*, **29**, 873 (1973).
21) G. N. Ramachandran, R. Chandrasekaran, and K. D. Kopple, *Biopolymers*, **10**, 2113 (1971).
22) M. T. Chung, M. Marraud, and J. Neel, *Macromolecules*, **7**, 606 (1974).
23) E. Benedetti, M. Goodman, R. E. Marsh, H. Rapoport, and J. A. Musich, *Cryst. Struct. Commun.*, **4**, 641 (1975).
24) K. G. R. Pachler, *Spectrochim. Acta*, **20**, 581 (1964).
25) J. V. Hatton and R. E. Richards, *Mol. Phys.*, **3**, 253 (1960).
26) M. Sisido and Y. Imanishi, unpublished work.
27) N. Harada and K. Nakanishi, "Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry," University Sci. Books, N. Y. and Tokyo Kagaku Dojin, Tokyo (1982).
28) V. Rizzo and H. Jäckle, *J. Am. Chem. Soc.*, **105**, 4195 (1983).
29) K. Shingu, S. Imajo, H. Kuritani, S. Hagishita, and K. Kuriyama, *J. Am. Chem. Soc.*, **105**, 6966 (1983).