CHEMISTRY LETTERS, pp. 1481-1484, 1987.

Synthetic Peptide Lipids Having Axial Chirality. Preparation and Aggregate Morphology

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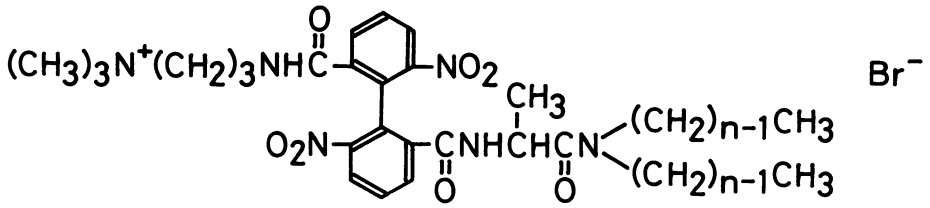
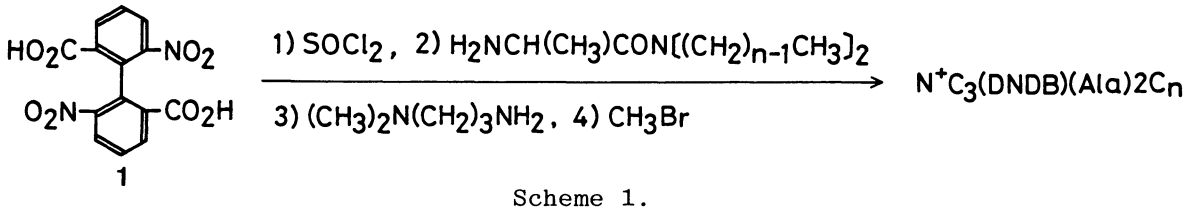
The (R)-(+)- and (S)-(-)-3,3'-dinitro-2,2'-dibenzoyl moieties were used as axial chirality components, and peptide lipids were prepared by introducing either of them into the single chain portion adjacent to the alanyl residue. Their aggregate morphology was examined in aqueous media by various physical methods.

Dynamic functions of synthetic bilayer membranes, which may provide unique reaction fields with high molecular organization, have been attracting current attention.[1] Up to the present time, several enzymatic reactions have been successfully simulated by employing functionalized bilayer membranes as enzyme models.[2-4] However, studies on chiral recognition ability of bilayer aggregates have been limited to hydrolysis reactions, and single central chirality provided by an α-amino acid residue or accumulated central chirality by multiple combination of them through the peptide bond linkage has been utilized for stereospecific discrimination toward substrates.[3,4] We have previously shown that synthetic peptide lipids formed with a polar head moiety, a hydrophobic double-chain segment, and α-amino acid residue(s) interposed between them afforded stable bilayer membranes exhibiting chiral recognition in aqueous media.[4] Aiming at development of the superior chiral bilayer catalyst, we now designed peptide lipids having an axially chiral moiety in addition to the previously employed molecular segments. In this communication, we report on preparation and aggregate morphology of N,N-dialkyl-N^{α}-[2'-[N-[3-(trimethylammonio)propyl]carbamoyl]-6,6'-dinitro-1,1'-biphenyl-2-carbonyl]alaninamide bromide [$N^{+}C_3$(DNDB)(Ala)2C_n]; DNDB and Ala denote the 3,3'-dinitro-2,2'-dibenzoyl and alanyl moieties, respectively.

3,3'-Dinitro-2,2'-dibenzoic acid (**1**) was prepared[5] and resolved into pure



$N^{+}C_3$(DNDB)(Ala)2C_n



Scheme 1.

(R)-(+) $[[\alpha]_D^{27}$ +134° (c 1.0, ethanol)] and (S)-(-) $[[\alpha]_D^{27}$ -134° (c 1.0, ethanol)] enantiomers in a manner similar to that reported by Ingersoll and Little.[6] The corresponding lipids were prepared according to Scheme 1. Each optically pure enantiomer or the racemic species of **1** was converted into the corresponding acid chloride with thionyl chloride, and the resulting acid chloride underwent reaction with an N,N-dialkylalaninamide[7] (**2**) (a molar ratio, 3:1) at 80 °C in dry benzene containing triethylamine. To the reaction mixture was added an excess amount of N,N-dimethyl-1,3-propanediamine, and quaternization was carried out with methyl bromide. Purification by gel-filtration chromatography on a column of Sephadex LH-20 with methanol as an eluant gave N^+C_3(DNDB)(Ala)$2C_n$ in an overall yield of ca. 20% based on **2**.[8]

These peptide lipids formed multiwalled bilayer aggregates in the aqueous dispersion state (Fig. 1A) and single-walled vesicles in a diameter range of 200—500 Å upon sonication of the dispersion samples (Fig. 1B). Circular dichroism (CD) spectra of the single-walled vesicles formed with N^+C_3(R-DNDB)(S-Ala)$2C_{16}$ and N^+C_3-(S-DNDB)(S-Ala)$2C_{16}$ are shown in Fig. 2. These CD spectra are symmetrical and asymmetrical to each other in the wavelength regions longer and shorter than 310 nm, respectively. In addition, single-walled vesicles composed of an equimolar mixture of these diastereomeric lipids showed no CD band in the wavelength region above 310 nm (Fig. 2). Thus, the CD bands for vesicles of each diastereomer reflect chirality due to the DNDB moiety and that due to both DNDB and Ala moieties in the wavelength regions above and below 310 nm, respectively. It is noteworthy that CD spectra of the single-walled vesicles formed with N^+C_3(DNDB)(R-Ala)$2C_{16}$ and N^+C_3(DNDB)(S-Ala)$2C_{14}$, prepared from the racemic species of **1** by using (R)-**2** and

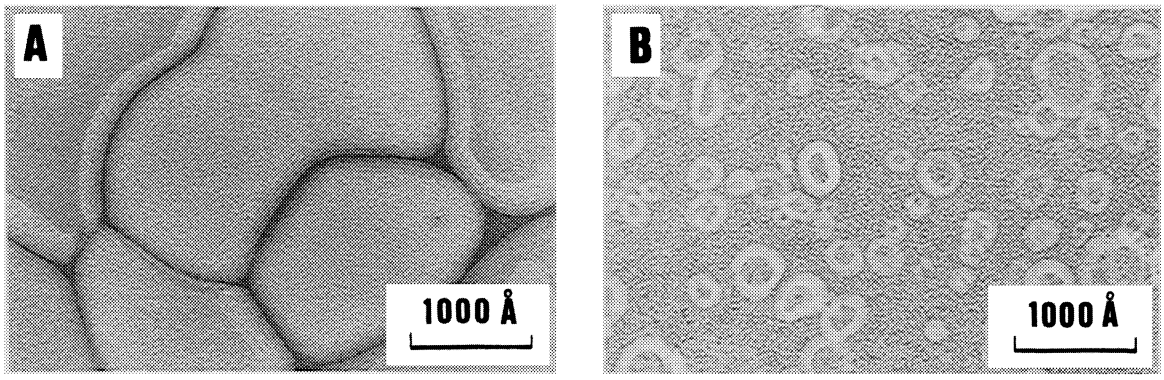


Fig. 1. Electron micrographs negatively stained with uranyl acetate: A, 1.0 mmol dm^{-3} aqueous dispersion of N^+C_3(R-DNDB)(S-Ala)$2C_{16}$; B, 0.5 mmol dm^{-3} aqueous solution of N^+C_3(R-DNDB)(S-Ala)$2C_{16}$ sonicated for 5 min with a probe-type sonicator at 30 W.

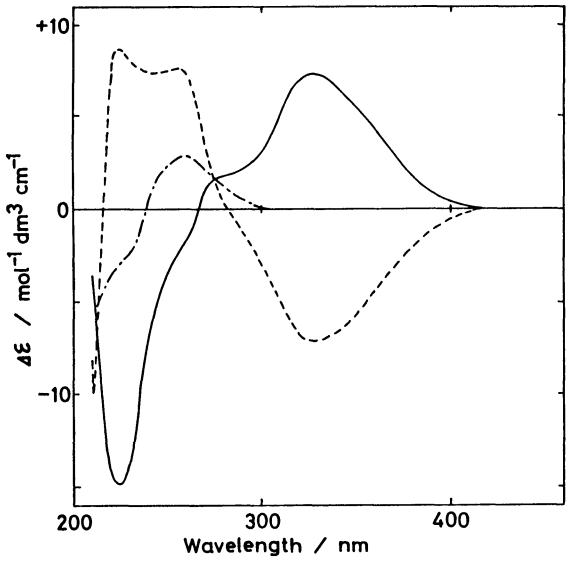


Fig. 2. CD spectra of single-walled vesicles formed with N^+C_3(R-DNDB)(S-Ala)$2C_{16}$ (——), N^+C_3(S-DNDB)(S-Ala)$2C_{16}$ (----), and their equimolar homogeneous mixture (— - —) at 30.0 °C.

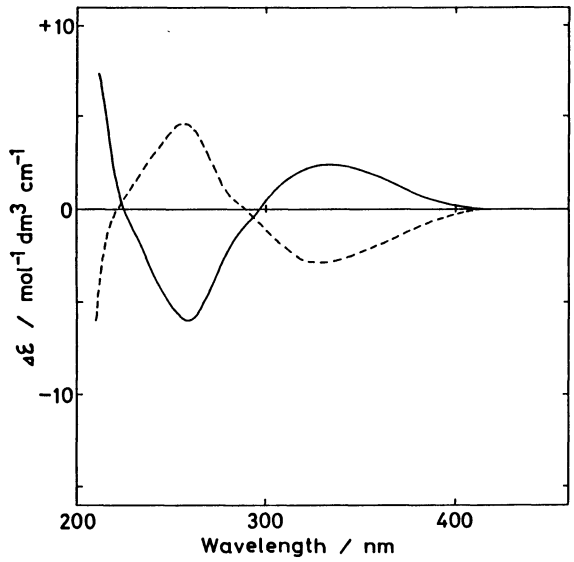


Fig. 3. CD spectra of single-walled vesicles formed with N^+C_3-(DNDB)(R-Ala)$2C_{16}$ (——) and N^+C_3-(DNDB)(S-Ala)$2C_{14}$ (----) at 30.0 °C.

(S)-**2**, respectively, show the stereoselective formation of N^+C_3(R-DNDB)(R-Ala)$2C_{16}$ and N^+C_3(S-DNDB)(S-Ala)$2C_{14}$, respectively, with relatively high diastereomeric purity (33% d.e. for the former and 39% d.e. for the latter) (Fig. 3). Such stereochemically induced reaction courses seem to indicate superiority of the biaryl moiety as a chiral recognition site.

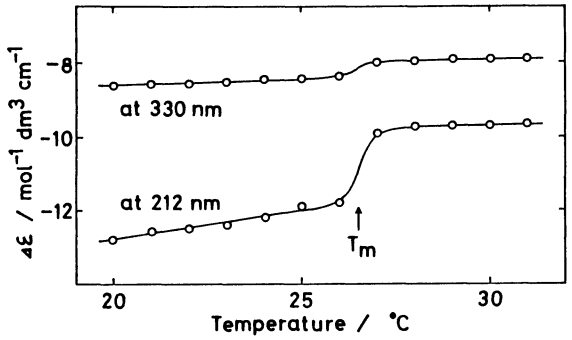


Fig. 4. Temperature dependence of CD intensities for multiwalled bilayer aggregates formed with N^+C_3-(S-DNDB)(S-Ala)$2C_{16}$.

Although the CD pattern for the multiwalled bilayer membrane was analogous to that for the corresponding single-walled one at 30.0 °C, the CD intensities for the former aggregate formed with N^+C_3(S-DNDB)(S-Ala)$2C_{16}$ increased with a decrease in temperature, exhibiting a clear inflection point at 26.5 °C (Fig. 4).[9] This value was in good agreement with the peak temperature for gel to liquid-crystalline phase transition (T_m) evaluated by differential scanning calorimetry (DSC) (Table 1). The phase transition parameters, T_m and the corresponding enthalpy change (ΔH), for N^+C_3(DNDB)(Ala)$2C_n$ obtained by DSC are comparable to those for the peptide lipids lacking the biaryl moiety; N,N-dialkyl-N^{α}-[6-(trimethylammonio)hexanoyl]-(S)-alaninamide bromide[10] [N^+C_5(S-Ala)$2C_n$] (Table 1). Accordingly, the results imply that bulkiness of the biaryl moiety scarcely affects the molecular packing mode of hydrophobic double-chain segments, although the phase

Table 1. Phase transition parameters for various peptide lipids in aqueous dispersion as evaluated by DSC

Peptide lipid	T_m/°C (ΔH/kJ mol^{-1})
N^+C_3(R-DNDB)(S-Ala)$2C_{16}$	25.0 (29.7)
N^+C_3(S-DNDB)(S-Ala)$2C_{16}$	26.9 (27.6)
N^+C_3(DNDB)(R-Ala)$2C_{16}$	27.0 (25.9)
N^+C_3(DNDB)(S-Ala)$2C_{14}$	2.5 (16.7)
N^+C_5(S-Ala)$2C_{16}$	25.5 (32.6)[10]
N^+C_5(S-Ala)$2C_{14}$	2.0 (20.5)[10]

transition gives some perturbation to conformations of the biaryl and α-amino acid moieties placed in the hydrogen-belt domain[7,10] of bilayer membranes.

In conclusion, it became apparent that the synthetic peptide lipids having both central and axial chirality components form morphologically stable bilayer membranes and their phase-transition behavior is primarily controlled by a size of the double-chain segment.

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8) N^+C_3(R-DNDB)(S-Ala)$2C_{16}$ Found: C, 63.22; H, 9.07; N, 7.94%. Calcd for $C_{55}H_{93}BrN_6O_7 \cdot H_2O$: C, 63.02; H, 9.13; N, 8.02%. N^+C_3(S-DNDB)(S-Ala)$2C_{16}$ Found: C, 63.99; H, 9.03; N, 7.92%. Calcd for $C_{55}H_{93}BrN_6O_7$: C, 64.12; H, 9.10; N, 8.16%. N^+C_3(DNDB)(R-Ala)$2C_{16}$ Found: C, 63.99; H, 9.20; N, 7.93%. Calcd for $C_{55}H_{93}BrN_6O_7$: C, 64.12; H, 9.10; N, 8.16%. N^+C_3(DNDB)(S-Ala)$2C_{14}$ Found: C, 61.95; H, 8.78; N, 8.26%. Calcd for $C_{51}H_{85}BrN_6O_7 \cdot H_2O$: C, 61.74; H, 8.84; N, 8.47%.
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(Received April 20, 1987)