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Mechanical Control of Enantioselectivity of Amino Acid Recognition by Cholesterol-Armed Cyclen Monolayer at the Air-Water Interface

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Chiral molecular recognition (CMR) plays an important role in many biological events.[1] Inspired by this fact, control of molecular chirality or macromolecular and supramolecular helicity by various external stimuli such as light, temperature, solvent, redox, pH, and chiral agents has been attempted, and some artificial molecular systems have been prepared which regulate perfectly the chirality or helicity in solution.[2] However, only a few of these are capable of CMR, that is, external control of enantioselective molecular recognition.[3] Furthermore, since biological processes occur in cell membranes, a more appropriate medium than solution is required for a deeper understanding of molecular recognition phenomena in living systems. The air−water interface is such an appropriate medium, and pioneering work on discrimination of diastereomeric interactions of naturally occurring biomolecules and their derivatives[4] implicates its use as a biomembrane model. The most notable advantage of the air−water interface is that both molecular conformation and intermolecular interactions of the host molecule can be tuned by mechanical compression of the monolayer.[5] Previously, we reported dynamicity in molecular recognition by compressing monolayers of a steroid-armed cyclophane.[6] The presence of a flexible spacer in the host molecule is essential for an efficient conformational change by lateral pressure application. Here we employed an excellently designed polycholesteryl-substituted cyclen complex host molecule, and report for the first time the successful inversion of enantioselectivity in molecular recognition controlled by lateral pressure applied to the monolayer at the air−water interface.

The cyclen host is a unique supramolecular platform and forms complexes with a variety of metal ions.[7] The octacoordinate Na^+ complex **1** has two possible quadruple helicate structures (Figure 1). Helicity is influenced by the chirality of the side arms especially when ordered or aggregated at the supramolecular level. Accommodation of chiral guest molecules within the hydrophobic cavities also affects the helicity of **1**.[8] Importantly, **1** is composed of hydrophobic cholesterol moieties and a charged hydrophilic metal complex and is thus suitable for formation of a chiral host monolayer at the air−water interface. Application of lateral pressure should affect the helix structure and, consequently, the diastereomeric stability of complexes with guest molecules.

The π-*A* isotherm of **1** indicates formation of a stable Langmuir monolayer with a limiting molecular area of ∼1.57 nm^2 and a collapse pressure of ∼50 mN m^{-1} (Figure 2). The experimentally determined molecular area is similar to the calculated value (∼1.6 nm^2) for the four cholesterol moieties of **1** in a closed conformation.[8b] It should be noted that the area of the ester-armed hydrophilic cyclen moiety is only 0.35 nm^2, leaving sufficient space between the

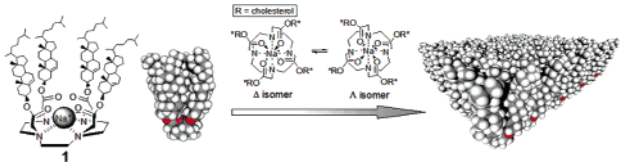

Figure 1. Structure of the cholesterol-armed cyclen Na^+ complex **1** as a host monolayer. Schematic illustrations of the two stereoisomers and self-assembled monolayer are included.

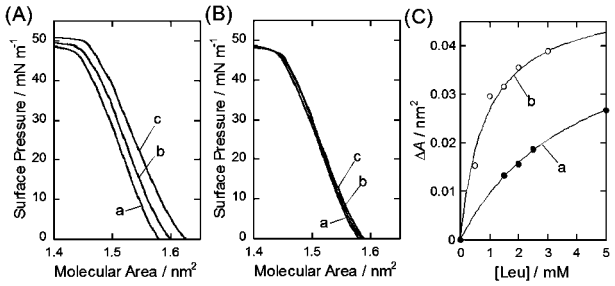

Figure 2. π-*A* Isotherms of **1** at 20.0 ± 0.2 °C: (A) a, on pure water; b, on 1.5 mM aqueous L-leucine; c, on 1.5 mM aqueous D-leucine and (B) a, on pure water; b, on 1 mM aqueous L-valine; c, on 1 mM aqueous D-valine; (C) examples of binding curves of a, L-leucine; b, D-leucine at the surface pressure 20 mN m^{-1}. ΔA represents the difference in the molecular area values between on aqueous leucine and on pure water.

molecules for accommodation of guest species. When amino acids such as leucine or valine were added to the subphase, the isotherms were shifted to larger molecular areas with increasing amino acid concentration (Figure 1 in Supporting Information). The extent of the shift is related to the size of the amino acids. Leucine has an additional methylene unit to valine, leading to a larger expansion than valine (Figures 2A and 2B). Furthermore, the isotherms on aqueous D-leucine are shifted to larger molecular areas than on aqueous L-leucine of the same concentration. In contrast, the difference between the isotherms on aqueous L- and D-valines is insignificant. These results suggest a greater and negligible enantioselectivity for leucine and valine, respectively, according to the conventional interpretation.[9] However, a remarkable chiral discrimination could be obtained, even for valine, when the binding constant (*K*) is estimated from the molecular area values at a certain surface pressure using a Langmuir-type equation under the assumption that an increase in the molecular area values of the π-*A* isotherm is proportional to the amount of amino acid adsorbed. Curve fitting of the data provided *K* values with a correlation coefficient of >0.99 (Figure 2C). The values tended to increase with the surface pressure (Table 1 in Supporting Information). Since chiral discrimination is caused by the pairwise packing of adjacent chiral centers, stronger selectivity should be expected in highly ordered, well-packed systems such as a Langmuir monolayer. Intermolecular interactions between cholesterol arms, which are the

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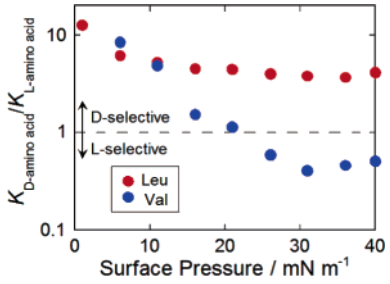

Figure 3. Plots of the surface pressure of the monolayer and the ratio of the binding constants with enantiomeric leucine and valine.

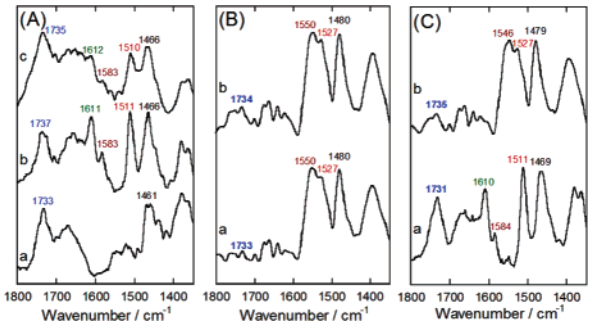

Figure 4. FT-IR-RAS spectra (1300−1800 cm^{-1}) of LB films (10 layers) of **1**: a monolayer transferred from (A) a, pure water; b, 3 mM aqueous L-leucine; c, 3 mM aqueous D-leucine, at surface pressure of 30 mN m^{-1}; (B) a, 5 mM aqueous L-valine; b, 5 mM aqueous D-valine, at surface pressure of 10 mN m^{-1}; (C) a, 5 mM aqueous L-valine; b, 5 mM aqueous D-valine, at surface pressure of 30 mN m^{-1}.

origin of the monolayer chirality, are supposed to be amplified by guest incorporation.[10] This tendency is more significant for the L-isomer than for the corresponding D-form. The L-enantiomers show a continuous increase in *K* values upon compression, whereas the increase for D-enantiomers is noticeable only above 15 mN m^{-1}. This difference results in an inversion of the magnitude of *K* values between L- and D-enantiomers (Figure 3). The *K* values of D-leucine are always greater than those of L-leucine, indicating that monolayers of **1** have a stronger interaction with D-leucine. Conversely, the values of L-valine are smaller than those of D-valine at low surface pressure but exceed them at 22∼23 mN m^{-1}. In other words, chiral recognition in monolayers of **1** with valine changes from the D- to L-form upon compression. That the small difference in the chemical structure between leucine and valine can be distinguished by the dynamic process of monolayer formation is remarkable.

FT-IR spectra of LB films of monolayers of **1**, transferred at different surface pressures, were measured. Additional peaks characteristic of COO^- and NH_3^+ (or NH_2) when compared to the film from pure water, indicate that amino acids are accommodated in the films (Figure 4A). When the surface pressure of LB film preparation was increased from 10 to 20 and to 30 mN m^{-1}, the relative peak intensities at 1406−1409 and 1578−1586 cm^{-1} (ν_{COO^-}) decreased, whereas the peak intensity at 1735−1741 cm^{-1} (overlapping $\nu_{C=O(ester)}$ and $\nu_{C=O(carboxylic\ acid)}$) increased (Figure 2 in Supporting Information).[11] This suggests that the amino acids are zwitterionic in the vicinity of the air−water interface, but are neutral when accommodated deeply in the films. Variations in the peak intensities at 1511 and 1606−1611 ($\delta_{NH_3^+}$) and ∼3304 cm^{-1} (ν_{NH}) support this (Figure 2 in Supporting Information). FT-IR spectra of LB films transferred from aqueous L- or D-valine at 10 mN m^{-1} contain peaks characteristic of the zwitterionic and neutral forms at 1527 and 1550 cm^{-1} and 1733−1734 cm^{-1}, respectively (Figure 4B). The more intense lower frequency peaks imply considerable interactions of NH_3^+ and COO^- groups with the host monolayer. The higher frequency peak intensities are associated with the amount of neutral amino acid, reflecting the larger *K* value of D-valine at 10 mN m^{-1}. Conversely, at 30 mN m^{-1} while the spectrum for D-valine is similar to that of the film transferred at 10 mN m^{-1}, that from L-valine shows a significant increase in the peak intensity at 1731 cm^{-1} so that its spectrum is similar to those from leucine (Figure 4C). This indicates that a large quantity of neutral L-valine is accommodated within monolayers of **1**, analogously to leucine where larger *K* values result from greater hydrophobicity. This substantial difference in the IR spectra between L- and D-valine is consistent with the *K* values obtained from the π-*A* isotherms.

In conclusion, mechanical control of enantioselectivity in amino acid recognition has been for the first time realized using the helical host molecule **1** at the air−water interface. At the air−water interface, chiral recognition was proven to be more strongly modulated than in solutions.[8b] Remarkably, a small difference in the amino acid structure resulted in differing selectivities, a feature comparable to the delicate functions of enzymes and receptors in living organism. A detailed recognition mechanism will be elucidated by control experiments using various guest molecules as well as by modeling techniques.

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Supporting Information Available: Experimental details on calculation of binding constants and FT-IR-RAS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The strong peak at 1460−1480 cm^{-1}, which is derived from the cyclen **1**, was used as a reference peak to compare the peak intensities.

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