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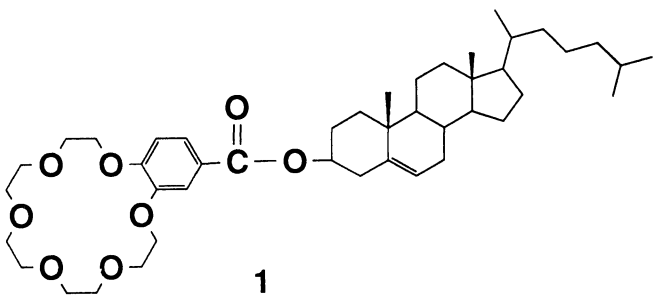
Chiral Recognition of α-Amino Acid Derivatives by a Steroidal Crown Ether at the Air-Water Interface

Hirosuke KAWABATA and Seiji SHINKAI*
Chemirecognics Project, ERATO, Research Development Corporation of Japan,
Aikawa 2432-3, Kurume, Fukuoka 830

4'-(Cholesteryloxycarbonyl)benzo-18-crown-6 forms a stable monolayer at the air-water interface and the π-A isotherms respond to α-amino acid derivatives in an asymmetric manner. This is a novel amino acid sensing system using a monolayer assembly.

It is of recent, growing concern to apply monolayers formed at the air-water interface to molecular recognition.[1-3] Of particular interest is the potential application to chiral discrimination: chiral guest molecules in the subphase interact with chiral amphiphilic compounds forming the monolayer and the resultant "diastereomeric complexes" change the π-A isotherm in an asymmetric manner.[4,5] We have been interested in chiral discrimination of α-amino acid derivatives and the "reading-out" of the recognition process.[6] We thus considered that the monolayer system might be useful for this purpose. It was recently demonstrated that certain cholesterol derivatives (natural chiral source) form beautiful monolayers.[7] In this paper, we address that a cholesterol derivative **1** which combines a 18-crown-6 moiety as an NH_3^+ - binding site within a molecule provides an interesting monolayer system for chiral discrimination of α-amino acid derivatives. In a sense, this is a novel example for chiral discrimination of naturally-originating compounds (α-amino acids) by naturally-originating compounds (cholesterols).

Compound **1** was synthesized from cholesterol and 4'-carboxymonobenzo-18-crown-6.[8] Pressure-area isotherms (π-A curves) of **1** were measured with a computer-controlled film balance (USI System Co., model USI-110) at 20 ± 0.1 °C and a barrier speed of 8.0 cm min^{-1}. Benzene as spreading solvent was allowed to evaporate within 10 minutes. Water was ion exchanged and bidistilled.



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As shown by π-A curves on pure water (Fig. 1), **1** gave a stable condensed phase: the limiting molecular area (A_0) is 0.67 nm^2 $molecule^{-1}$ and collapse pressure is 65.0 mN m^{-1}. The A_0 of cholesterol is estimated from the π-A curve to be 0.40 nm^2 $molecule^{-1}$,[9] and the plane area of 18-crown-6 is estimated from the CPK molecular model to be 1.20 nm^2 $molecule^{-1}$. The results suggest that the crown ring is not parallel to the water surface but stands up to form the stacked monolayer.

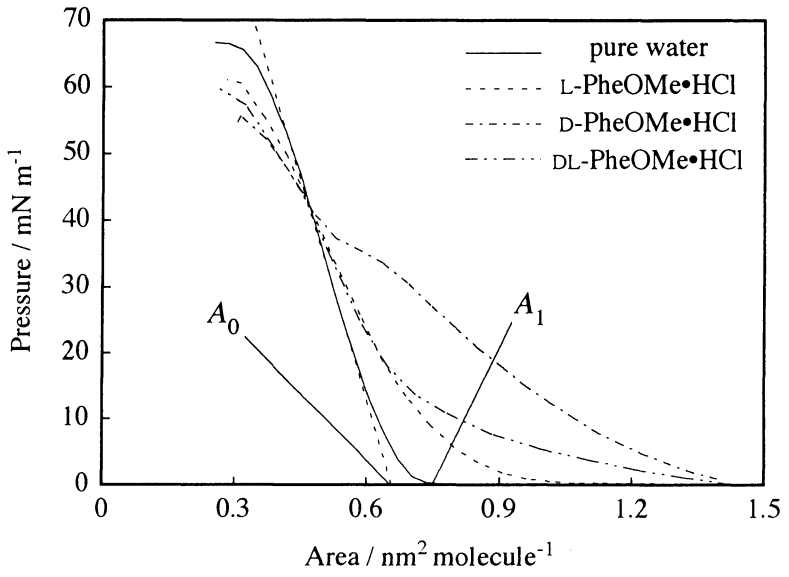

Fig. 1. Surface pressure-area isotherms of **1** at 20 °C on 100 mM phenylalanine methyl ester hydrochlorides. A_0 indicates the limiting area defined by extrapolating the solid-like region to zero pressure and A_1 indicates the lift-off area defined as the first point of the π-A isotherm where a monolayer shows detectable resistance to compression. A_0 and A_1 shown in this figure correspond to those for the π-A isotherm on pure water.

Here, we examined the influence of added α-amino acid esters on the π-A isotherms. Very interestingly, the monolayer expanded only to a smaller extent when L-PheOMe•HCl (L-phenylalanine methyl ester hydrochloride) was added, whereas the addition of D-PheOMe•HCl induced a large expansion of the monolayer (Fig. 1). As summarized in Table 1, the A_0 increases from 0.67 nm^2 $molecule^{-1}$ in the absence of D-PheOMe•HCl to 0.91 nm^2 $molecule^{-1}$ in the presence of 100 mM D-PheOMe•HCl and the lift-off area (A_1 defined as the first point of the π-A isotherm where a monolayer shows detectable resistance to compression) increases from 0.75 nm^2 $molecule^{-1}$ to 1.44 nm^2 $molecule^{-1}$. In the presence of L-PheOMe•HCl, on the other hand, the increase in these parameters is much smaller. In the π-A curves of D-PheOMe•HCl (and also of other D-isomers) an intermediary phase appears around 35.0 mN m^{-1}. When racemic DL-PheOMe•HCl was used, the π-A curve appeared between L- and D-PheOMe•HCl. The π-A isotherms for AlaOMe•HCl are shown in Fig. 2. Although the A_0 for D-AlaOMe•HCl

Table 1. Limiting area (A_0) and lift-off area (A_1) for **1** on several concentrations of PheOMe•HCl

conc. / mM	A_0 / nm^2 $molecule^{-1}$	A_1 / nm^2 $molecule^{-1}$
0	0.67	0.75
1 / L-isomer	0.70	0.82
/ D-isomer	0.72	0.87
10 / L-isomer	0.71	0.82
/ D-isomer	0.85	1.06
100 / L-isomer	0.72	1.06
100 / D-isomer	0.91	1.44

($0.79\ nm^2\ molecule^{-1}$) is a little smaller than that for L-AlaOMe•HCl ($0.82\ nm^2\ molecule^{-1}$) because of the appearance of the intermediary phase, the large expansion was observed for D-AlaOMe•HCl. In fact, the A_1 for D-AlaOMe•HCl ($1.44\ nm^2\ molecule^{-1}$) is much greater than that for L-AlaOMe•HCl ($1.20\ nm^2\ molecule^{-1}$).

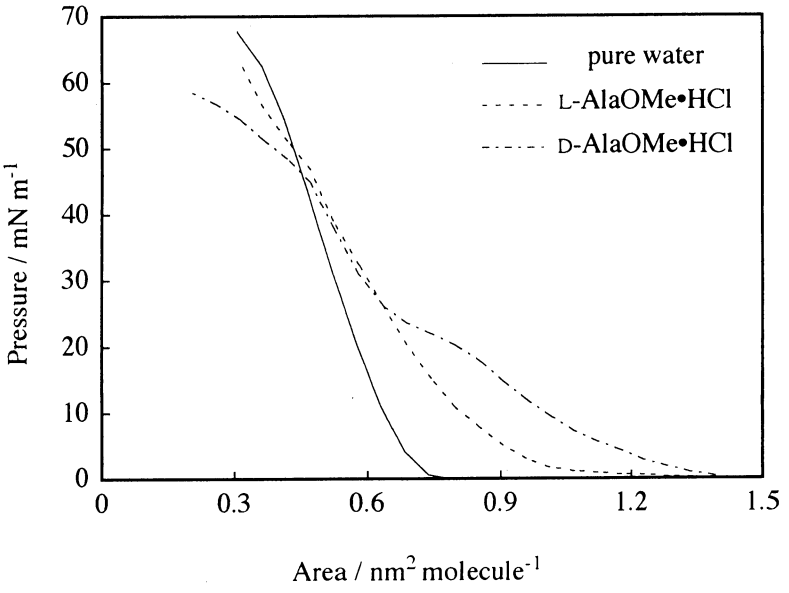

Fig. 2. Surface pressure-area isotherms of **1** at 20 °C on 100 mM alanine methyl ester hydrochlorides.

As summarized in Table 2, chiral discrimination was achieved for other α-amino acid derivatives but the largest difference was observed for PheOMe•HCl. Why is such chiral discrimination of α-amino acid derivatives that is difficult with conventional chiral amphiphilic compounds readily realized in a cholesterol-based monolayer system? It is undoubted that the NH_3^+ moiety is bound to the 18-crown-6 ring. As the α-amino acid residue CH_2R is more hydrophobic than the CO_2Me group, this group should be trapped in the hydrophobic cholesterol stacks. In this binding mode, the cholesterol skeleton with a wide chiral plane can more advantageously enforce the orientation of α-amino acid derivatives than conventional chiral amphiphiles with simple point chirality. Thus, the α-amino acid derivatives are recognized at two points (NH_3^+ by the crown ring and CH_2R by the cholesterol plane) by the **1** monolayer (as in Fig. 3). We previously found that cholesteric liquid crystals containing **1** can asymmetrically recognize α-amino acid derivatives: L-isomers stabilize the liquid crystal phase to shorten the pitch length whereas D-isomers destabilize the liquid crystal phase to elongate the pitch length.[6] Although the monolayer phase is different from the liquid crystal phase, the microscopic environment where one amino acid residue is flanked by two cholesterol planes should be similar to each other. Important is the fact that in both systems D-isomers disorder the cholesterol-based organized phases more efficiently than L-isomers. Presumably, the space formed between two cholesterols fits the asymmetrical shape of L-isomers.

Table 2. Limiting area A_0 and lift-off area A_1 of **1** on 100 mM amino acid methyl ester hydrochlorides

	A_0 / nm^2 $molecule^{-1}$		A_1 / nm^2 $molecule^{-1}$	
Amino acid	L-Isomer	D-Isomer	L-Isomer	D-Isomer
Phe	0.72	0.91	1.06	1.44
Ala	0.82	0.79	1.20	1.44
Trp	0.81	0.84	1.34	1.33
Val	0.71	0.77	1.04	1.14

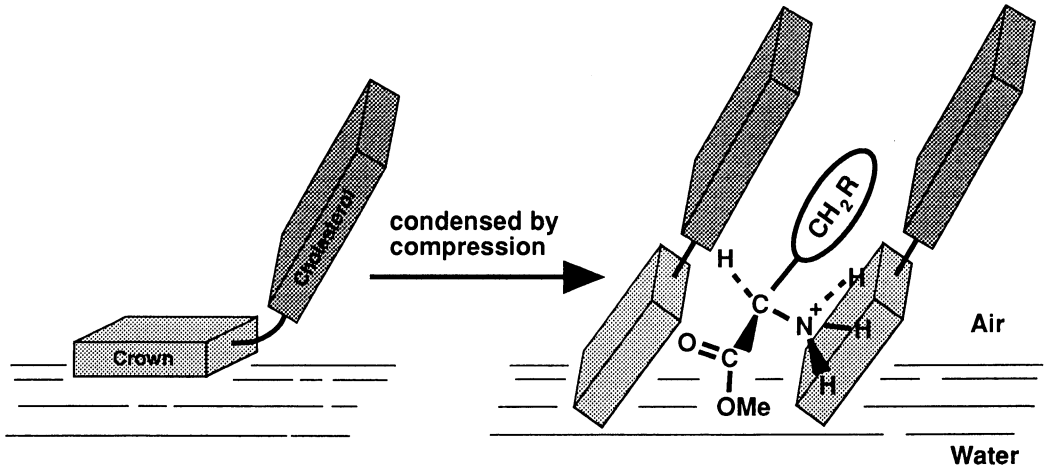

Fig. 3. Recognition of an α-amino acid derivative by a cholesterol monolayer.

In conclusion, compound **1** provides a unique monolayer system which responds to α-amino acid derivatives in an asymmetric manner. The results will be further elaborated as a new sensory system for α-amino acids using cholesterol-based monolayers.

References

1) K. Kurihara, K. Ohto, Y. Tanaka, Y. Aoyama, and T. Kunitake, *J. Am. Chem. Soc.*, **113**, 444 (1991); K. Kurihara, K. Ohto, Y. Honda, and T. Kunitake, *ibid.*, **113**, 5077 (1991); Y. Ikeura, K. Kurihara, and T. Kunitake, *ibid.*, **113**, 7342 (1991).

2) Y. Ishikawa, T. Kunitake, T. Matsuda, T. Otsuka, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1989**, 1937.

3) H. Kawabata and S. Shinkai, *Chem. Expr.*, **8**, 765 (1993).

4) E. M. Arnett, N. G. Harvey, and P. L. Rose, *Acc. Chem. Res.*, **22**, 131 (1989); N. G. Harvey, D. Mirajovsky, P. L. Rose, R. Verbiar, and E. M. Arnett, *J. Am. Chem. Soc.*, **111**, 1115 (1991).

5) P. Qian, M. Matsuda, and T. Miyashita, *J. Am. Chem. Soc.*, **115**, 5624 (1993).

6) T. Nishi, A. Ikeda, T. Matsuda, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1991**, 339.

7) T. Nishi and S. Shinkai, *Chem. Expr.*, **8**, 173 (1993).

8) S. Shinkai, G. -X. He, T. Matsuda, K. Shimamoto, N. Nakashima, and O. Manabe, *J. Polym. Sci., Polym. Lett. Ed.*, **27**, 209 (1989); S. Shinkai, T. Nishi, A. Ikeda, T. Matsuda, K. Shimamoto, and O. Manabe, *J. Chem. Soc., Chem. Commun.*, **1990**, 303.

9) R. Maoz and J. Sagiv, *J. Colloid Interface Sci.*, **100**, 465 (1984).

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