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To cite this Article Ihara, Hirotaka , Shudo, Ken , Hirayama, Chuichi , Hachisako, Hiroshi and Yamada, Kimiho(1996) 'Functional organic gels. Enantioselective elution using chiral gels from amino acid-derived lipids', Liquid Crystals, 20: 6, 807 — 809
To link to this Article: DOI: 10.1080/02678299608033175
URL: http://dx.doi.org/10.1080/02678299608033175

LIQUID CRYSTALS, 1996, VOL. 20, NO. 6, 807–809

Functional organic gels. Enantioselective elution using chiral gels from amino acid-derived lipids

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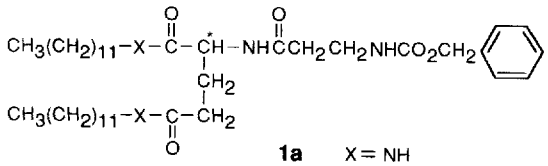
(*Received 6 April 1995; in final form 12 January 1996; accepted 15 January 1996*)

The L-glutamic acid-derived lipids form organic gels in benzene, which show enantioselective elution of *N*-dansyl L-phenylalanine from organic gels to aqueous phases. Differential scanning calorimetry and circular dichroism measurements demonstrate that this enantioselectivity occurred through highly-oriented structures of aggregated lipids like those of aqueous lipid membrane systems.

1. Introduction

Organic gels (organogels and lipogels) are being used as organic media for chemical reactions, selective transport, drug delivery and controlled-release, and enzyme immobilization in non-aqueous systems. Very recently, it has been found that some special lipids form organic gels in organic solvents [1–4]. This organic gel is very attractive due to the fact that the gelation is induced through the formation and morphological development of highly-oriented aggregates like those of aqueous lipid membranes. Throughout these studies, we have had a great interest in how biomembrane function can be reproduced in organic solution systems. For example, we have clarified that lipid aggregates in benzene show phase separation behaviour [1] and chirality induction for achiral low-molecular weight substances [2], which are usually observed in aqueous lipid membrane systems.

In this communication, we report the first example of enantioselective elution behaviour in organic gel systems. We also describe how this enantioselectivity is effectively induced through the formation of highly-oriented structures due to self-assembling of lipids.



1a X = NH

1b X = O

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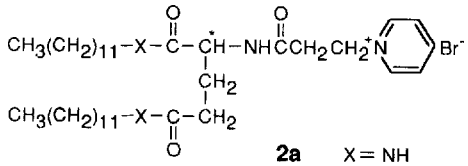
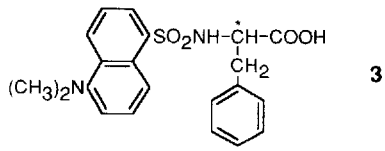


2a X = NH

2b X = O



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2. Results and discussion

2.1. *Formation of an organic gel in benzene*

Lipids **1** and **2** were derived from L-glutamic acid [1, 5]. Lipids **1a** and **2a** are unique in the fact that a head group and two long chain alkyl groups are introduced through amide bonds (shown as *X* in the structures). For example, lipid **2b**, in which the long chain alkyl groups were introduced through ester bonds, forms multi-lamellar vesicles (like liposomes from phospholipids) in aqueous solutions, but lipid **2a** preferentially produces tubular aggregates [5]. The tubular aggregates are generated through the development of helical ribbon-like aggregates formed from single-walled bilayer membranes. We confirmed by a MOPAC calculation [6, 7] that the three amide bonds of lipid **2a** provided a steric configuration effective in forming intermolecular hydrogen bonds: the centre-to-centre distance (2·45 Å) between the oxygen and hydrogen atoms combining to

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α-carbonyl and amino groups, respectively, is very close to the centre-to-centre distance (2·39 Å) between the oxygen and hydrogen atoms combining to the γ-amide bond. This configuration cannot be obtained with **1b**.

It was observed that lipids **1a** and **2a** show more attractive properties in their dispersion behaviours in benzene solutions. Compound **1a** readily dissolved in benzene at 70°C. When the solution was gradually cooled to room temperature, the typical gelation was observed. Similar gelation was observed with a mixture of **1a** and **2a** (**2a** alone is a little difficult to dissolve in benzene, because it has a polar ionic head group). Electron microscopy showed that these gels contained a formation of well-developed micro-fibrous aggregates (with more than 50 nm and 1 μm in diameter and length, respectively). In addition, it is estimated that the aggregates in the gel provided highly oriented structures at room temperature, since the differential scanning calorimetry (DSC) of these gels showed typical endothermic peaks at temperatures around 67°C (see figure 1 (*a*)). On the other hand, no similar gelation, aggregate formation or phase transition was observed for **1b** or **2b**. Therefore, the unique dispersion behaviours of **1a** and **2a** are also attributable to the three amide bonds.

2.2. *Induction of enantioselectivity*

At first, the elution of benzene from the benzene gel of **1a** to an aqueous phase was investigated. The elution rate was followed by monitoring the absorbance (Abs_{250}) at 250 nm. The time of the change of Abs_{250} showed that the elution of benzene remarkably decreased to about 1/5 in the presence of 10 mM of **1a**. This result clearly indicates that gel formation due to **1a** suppresses elution.

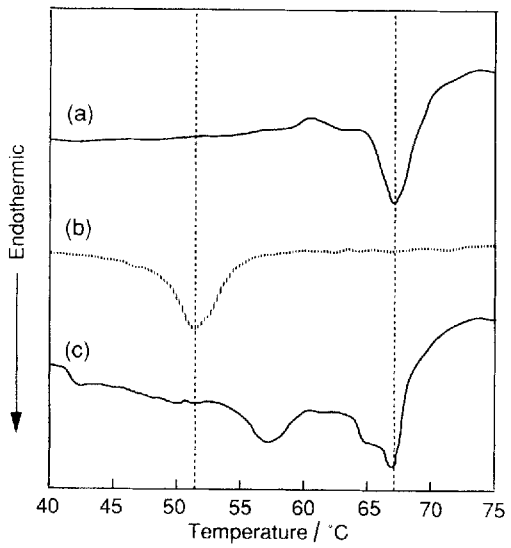

Figure 1. DSC thermograms of lipids **1a** and **1b** in benzene; (*a*) the gel with 10 mM of **1a**; (*b*) the dispersion with 10 mM of **2a**; (*c*) the mixed gel with 10 mM of **1a** and 2 mM of **2a**.

Similarly, elution was examined by adding enantiomers of *N*-dansyl phenylalanines (L-**3** or D-**3**) to the **1a**-containing benzene gel. The dansyl group not only enables solubilization of phenylalanine to benzene, but also provides a more spectrophotometrically detectable upper wavelength absorption (λ_{max}, 310 nm) than benzene (λ_{max}, 252 nm). When 1·0 M of aqueous NaOH solution was used as the aqueous phase, in order to promote the elution of **3**, the absorption at 310 nm due to **3** increased gradually in the aqueous phase and became constant at about 12 h. However, no significant difference was observed in the elution rate (E_D and E_L) for the L- and D-isomers. This lack of selectivity is explained by the fact that lipid **1a** is a nonionic compound and thus an electrostatic interaction with the anionic compound **3** cannot be expected.

On the contrary, when the mixed gel containing **1a** and **2a** was used as an organic medium, distinct enantioselectivity was observed. As shown in figure 2, the selectivity (E_D/E_L) was 1·5 in the presence of 17 mol % of **2a** [8]. It is assumed that this selectivity is induced through the ionic property of **2a** and highly oriented structures from **1a**. The following results support this estimation:

(1) The elution rate decreased with an increase of **2a** as shown in figure 2. This indicates that the interaction (which is probably electrostatic because **2a** has a cationic head group) between **2a** and **3** suppresses the elution of **3** from the organic to aqueous phases.

(2) This interaction can be detected using a circular dichroism (CD) measurement. As shown in figure 3, the mixed gel of **1a** and **2a** provided induced CD spectra for L-**3** and D-**3**. No similar induced CD was observed in the absence of **2b**. Therefore, it is concluded that **2b** provides chiral binding sites for **3**.

(3) Figure 3 shows Cotton effects with an opposite sign between the enantiomers and the degree, θ, is twice as large in the D-isomer as in the L-isomer. This may explain the stronger interaction of **2a** with D-**3** than with L-**3**.

(4) No enantioselectivity was observed when **1b** was used instead of **1a**. Lipid **1b** does not show highly oriented aggregation or gelation in benzene solution. This indicates that the highly oriented structures from **1a** play an important role in enantioselectivity, while **2a** provides a binding site.

(5) The mixed gels containing **1a** (10 mM) and **1b** (1·0 mM) provided a DSC thermogram with two peak maxima at 67 and 57°C (see figure 1 (*c*)). The former transition agrees with that of **1a** aggregates in benzene (see figure 1 (*a*)). The latter transition is higher by five degrees than that for **2a** alone in benzene (see

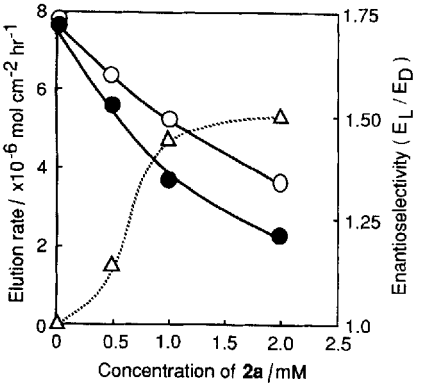

Figure 2. Concentration dependences of **2a** on the elution rate of **3** and on the enantioselectivity (E_D/E_L) at 25°C. [**1a**] = 10 mM, [**3**] = 0·25 mM. —○—, Elution rate for L-**3** (E_L); —●—, elution rate for D-**3** (E_D); —△—, enantioselectivity (E_D/E_L).

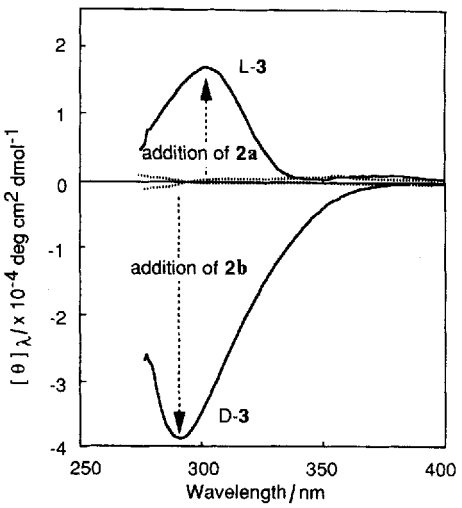

Figure 3. CD spectra of L-**3** and D-**3** (0·25 mM) in the benzene gels of **1a** (1·0 mM) at 25°C, —, in the presence of **2a** (0·10 mM) and ·····, in the absence of **2a**.

figure 1 (*b*)). This result indicates that **1a** and **2a** are phase-separated in the aggregates at room temperature and the **2a** domain is perturbed by **1a**.

(6) This phase separation shows that the enantioselectivity depends on the molar ratio of **2a** added (see figure 2). If the selectivity were induced by monomeric **2a** but not aggregated **2a** in the **1a** aggregates, then it would be independent of the molar ratio.

In conclusion, this study has demonstrated a typical example of enantioselective elution phenomena using chiral organic gels. In this paper, we emphasize that this selectivity is induced by lipids which produce highly oriented structures in organic solutions such as aqueous lipid membranes.

We are grateful to Dr H. Goda of Sumitomo Fine Chemicals Co., Ltd. for his help with the MOPAC calculation. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan.

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[6] This was carried out by calculation with the MOPAC 6·00 program (MATERIA) using the PM3 option [7].
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[8] The elution rate (E_D or E_L, mol cm^{-2} h^{-1}) was determined by using the absorbance change of the initial 2 h. The enantioselectivity is represented by the ratio (E_D/E_L) of elution rate for D- and L-enantiomers.