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Self-assembly of thermotropic liquid-crystalline folic acid derivatives: hydrogen-bonded complexes forming layers and columns†

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Folic acid derivatives having 2-(3,4-dialkoxyphenyl)ethyl moieties have been found to exhibit thermotropic liquid-crystalline behavior. Smectic and discotic phases are observed for these compounds over wide temperature ranges. X-Ray diffraction and infrared measurements show that the formation of the smectic and discotic phases is due to the ribbon- and disk-like structures of the pterin rings of folic acid, respectively. The smectic phase is changed to a hexagonal columnar phase by the addition of alkali metal salts. This behavior is attributed to the change of the hydrogen-bonded structures from ribbon to disk induced by the ion–dipolar interactions.

Introduction

The use of molecular self-organization processes is a useful strategy for the development of novel functional materials having nanometre or micrometre scale order.[1] Therefore, molecules capable of forming self-assembled and self-organized structures have attracted a great deal of attention in materials chemistry.[1] Biomolecules are a treasury of hydrogen-bonded molecules.[2,3] The wide diversity, high selectivity, and dynamic properties of the hydrogen bonding play a crucial role in providing self-assembling, self-replicating, and reproducing abilities to organisms. To obtain functional materials such as liquid crystals,[4] the formation of hydrogen-bonded assemblies is one of the most important approaches.[5,6] For example, the hydrogen bonding between pyridines and carboxylic acids has been shown to be advantageous for spontaneous formation of supramolecular calamitic liquid crystals.[5] Dynamic structures exhibiting association and dissociation of the hydrogen bonding can be achieved for these liquid crystals.[5a–e] Hydrogen bonding has also been applied to form discotic liquid-crystalline assemblies.[7]

Here, we intend to introduce calamitic and/or discotic anisotropy into biomolecules. We focused on folic acid as a building block for new thermotropic hydrogen-bonded liquid crystals. Folic acid is an important biologically active molecule.[8] Its alkali metal salts are known to show lyotropic liquid-crystalline phases in water.[9] The generation of a lyotropic hexagonal columnar phase is attributed to the hydrogen-bonded discotic tetramer formation of the pterin (2-aminopteridin-4-ol) moieties.[9] The pterin ring of folic acid also has the potential to show two hydrogen-bonded self-assembling patterns as shown in Fig. 1.[10,11] If we can control the nature of the spontaneous formation of the two hydrogen-bonded patterns, novel materials with dynamic functions will be obtained. These materials are expected to respond to external stimuli or to the atmosphere by dynamic change of their self-assembled structures.

In the present study, we use the self-assembling abilities of folic acid for the development of novel thermotropic liquid crystals. To induce thermotropic liquid crystallinity, we have introduced 2-(3,4-dialkoxyphenyl)ethyl groups into the L-glutamic acid moiety of folic acid.[12] We describe the

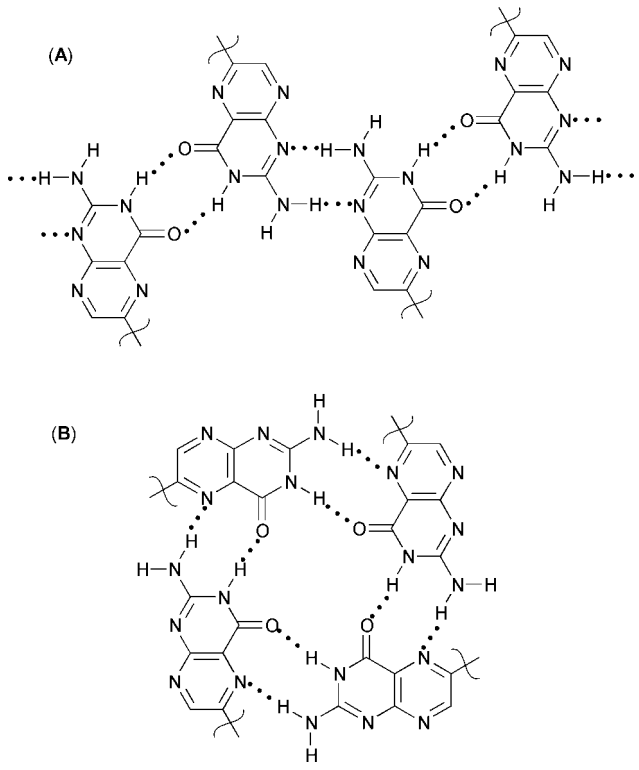
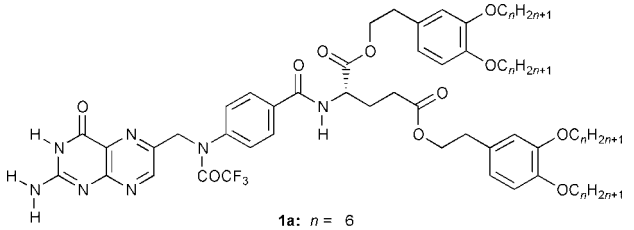


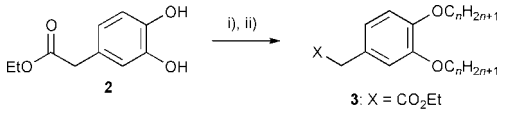
Fig. 1 Hydrogen-bonded ribbon-like (A) and disk-like (B) aggregations of the pterin ring of folic acid.

†Basis of a presentation given at Materials Discussion No. 4, 11–14 September 2001, Grasmere, UK.



1a: n = 6
1b: n = 11
1c: n = 14
1d: n = 18

Chart 1



3: X = CO_2Et
4: X = CH_2OH

3a, **4a**: n = 6
3b, **4b**: n = 11
3c, **4c**: n = 14
3d, **4d**: n = 18

Scheme 1 *Reagents and conditions*: i) $C_nH_{2n+1}Br$ (2.2 mol), K_2CO_3 (4.0 mol), DMF, 80 °C, 1 d, 75–91%; ii) $LiAlH_4$ (1.1 mol), THF, 0 °C, 3 h, 92–100%.

synthesis, thermotropic liquid-crystalline behavior, and structural change of folic acid derivatives.

Results and discussion

Molecular design and synthesis of folic acid derivatives

We have designed and synthesized folic acid derivatives **1a–d** as shown in Chart 1.[12] Thermotropic liquid crystallinity for folic acids has been induced by introducing lipophilic moieties. The 2-(3,4-dialkoxyphenyl)ethyl moieties were introduced onto the glutamic acid part of folic acid. Phenethyl moieties instead of a benzyl counterpart were chosen to increase the side-chain flexibility, which was suitable for the induction of mesomorphic behavior. We synthesized 2-(3,4-dialkoxyphenyl)ethyl alcohols **4** starting from ethyl 3,4-dihydroxyphenylacetate (**2**) by etherification followed by the reduction of the corresponding ester **3** as shown in Scheme 1. Hexyloxy-, undecyloxy-, tetradecyloxy-, and octadecyloxy-substituted compounds **1a–d** were prepared to examine the effects of the length of the alkyl chains on the thermal properties.

Generally, direct esterification[13] or alkylation[14] of folic acid to give α,γ-difunctionalized folate derivatives is not easy because of their insolubility in most organic solvents. Furthermore, the formation of inseparable complex mixtures containing α-conjugate, γ-conjugate, and the desired α,γ-conjugate is a serious problem. Practical regioselective introduction of functional groups into folic acid[15] was achieved by amidations of pteroic acid derivatives‡ with the functionalized glutamic acid derivatives. As a key step for an efficient synthesis of the target molecule **1**, we selected a condensation reaction of N^{10}-(trifluoroacetyl)pteroic acid (**7**)[16] with α,γ-bis[2-(3,4-dialkoxyphenyl)ethyl] L-glutamate **6** by a mixed anhydride method.[15a] The synthetic procedure for the preparation of **1a–d** is shown in Scheme 2. The isolated yields are summarized in Table 1.

Initially, alcohols **4** were condensed with *N*-benzyloxycarbonyl-L-glutamic acid to give the corresponding *N*-benzyloxycarbonyl-L-glutamates **5** by using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP). To obtain **6**, the benzyloxycarbonyl group of **5** was successively hydrogenated with 10% palladium activated on carbon (Pd/C) under a hydrogen atmosphere. In this step, to suppress side reactions such as intramolecular amidation and/or ester-exchange, the reaction was carried out at 50 °C within 3 h. In some cases, especially for **5d**, the hydrogenation did not proceed effectively. The addition of formic acid into the reaction mixture solved the problem.[17] The details for the hydrogenation are summarized in the Experimental section. An *N,N*-dimethylformamide (DMF) solution of **7** was treated with isobutyl chloroformate in the presence of triethylamine to prepare mixed anhydride **8**. The mixture was added to a THF solution of **6** and reacted in the dark under an argon atmosphere for 4 days. Purification of the crude mixture by flash column chromatography on silica gel followed by recycling preparative gel permeation chromatography (GPC) afforded the desired compounds **1a–d** as analytically pure forms. The introduction of the trifluoroacetyl group on the N^{10} atom of the pteroic acid improved the solubility in organic solvents and accelerated nucleophilic substitution of the nitrogen atom of the glutamate at the carboxy carbon.

We also synthesized racemic compounds DL-**1b** and DL-**1d** starting from DL-glutamic acid to study the effects of the chirality of the glutamic acid part on the liquid crystallinity of **1a–d**. Sodium folate showed lyotropic cholesteric phases in *aqueous* media.[9] The induction for the cholesteric structure was based on the chirality of the glutamic acid.

Table 1 Isolated yields of compounds **1**, **5**, and **6**

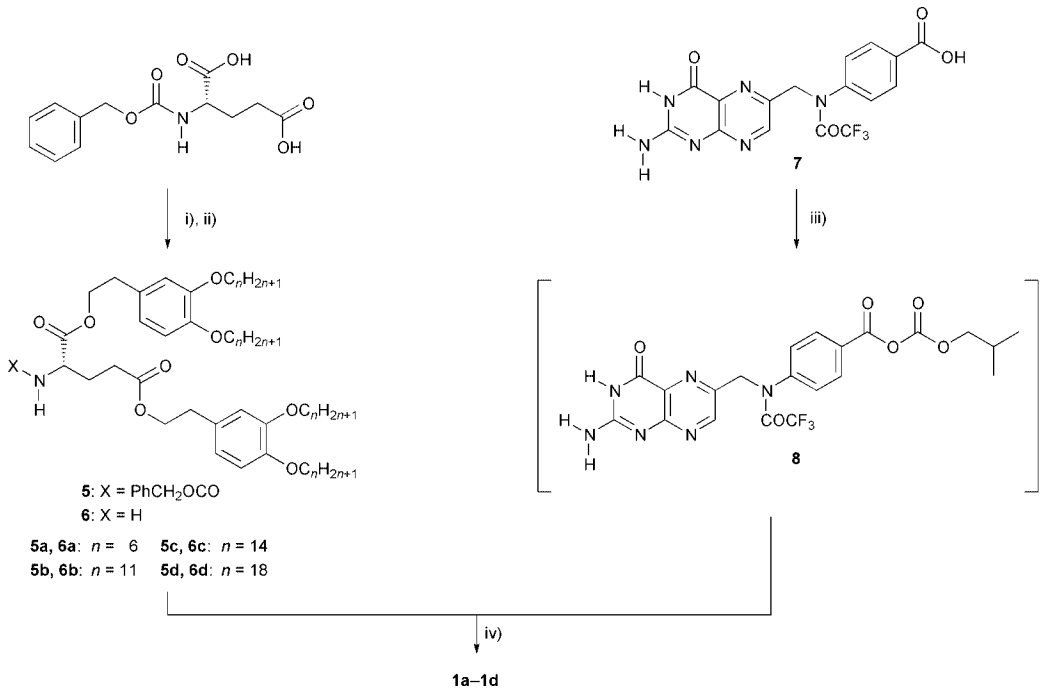
	Isolated yields(%)		
n	**5**	**6**	**1**
6	70 (**5a**)	66 (**6a**)	65 (**1a**)
11	80 (**5b**)	56 (**6b**)	40 (**1b**)
	74 (DL-**5b**)	80 (DL-**6b**)	24 (DL-**1b**)
14	80 (**5c**)	16[a] (**6c**)	42 (**1c**)
18	86 (**5d**)	61[b] (**6d**)	29 (**1d**)
	85 (DL-**5d**)	54 (DL-**6d**)	49 (DL-**1d**)

[a]The reaction was carried out in benzene in lieu of EtOAc–EtOH. [b]Reaction conditions: CH_2Cl_2–EtOH–HCO_2H = 25 : 5 : 1 (wt/wt/wt).

Thermotropic liquid crystallinity and phase transition behavior of the folic acid derivatives

Folic acid derivatives **1a–d** exhibit thermotropic liquid-crystalline behavior. The phase transition temperatures as well as the phase transition enthalpy changes of **1a–d** determined using a differential scanning calorimeter (DSC) on heating are summarized in Table 2. It is noteworthy that the phase behavior of **1a–d** is greatly dependent on the length of the alkyl chains. Folic acid derivative **1d** with 2-[3,4-bis(octadecyloxy)phenyl]-ethyl groups forms discotic phases. Three endothermic peaks at 62, 207, and 223 °C are observed in a DSC thermogram of **1d**. The enthalpy changes of these transitions are 81, 5, and 8 kJ mol^{-1}, respectively. Polarizing microscope observation shows that these peaks are attributed to the mesophase–mesophase transitions and the mesophase–isotropic transition. Similar liquid-crystalline behavior is observed for compound **1c** which has tetradecyl chains. On the other hand, for **1a** and **1b**, oily streak textures, which are characteristic of smectic phases,[18] are seen over wide temperature ranges up to about 240 °C. The enthalpy changes of the smectic–isotropic transitions of **1a**,**b** are about 35 kJ mol^{-1}. The representative texture of **1b** observed by a polarizing microscope at 200 °C is shown in Fig. 2. Similar textures are also seen in **1a**. For compound **1a**, neither exothermic crystallization nor glass transition behavior is seen on cooling below −50 °C on DSC measurement. The

‡Pteroic acid = *p*-[(2-amino-4-hydroxypteridin-6-ylmethyl)amino]benzoic acid.



Scheme 2 Synthesis of folic acid derivatives **1**. *Reagents and conditions*: i) compound **4** (2.1 mol), EDC (2.2 mol), DMAP (0.2 mol), CH_2Cl_2, rt, 1 d; ii) 10% Pd/C, H_2, EtOAc–EtOH, 50 °C, 3 h; iii) isobutyl chloroformate (1.1 mol), Et_3N (1.2 mol), DMF, rt, 1 h; iv) THF–DMF, 40 °C, 4 d, dark.

melting temperature of the chiral compound of **1b** is lower by 8 °C than that of the racemic compound of DL-**1b**. For the isotropization temperatures, we observe no differences between the chiral and racemic compounds.

Table 2 Thermal behavior of folic acid derivative **1**

Compound	*n*	Phase transition behavior[a]						
1a	6			S			238 (37)	Iso
1b	11	Cr	−13 (10)	S			235 (33)	Iso
DL-**1b**		Cr	−5 (12)	S			235 (34)	Iso
1c	14	D_{ho}	36 (40)	D_{hd}	226 (9)	N_C	232 (9)	Iso
1d	18	D_{ho}	62 (81)	D_{hd}	207 (5)	N_C	223 (8)	Iso
DL-**1d**		D_{ho}	63 (84)	D_{hd}	207 (6)	N_C	225 (11)	Iso

[a]Transition temperatures (°C) and enthalpy changes of transitions (kJ mol^{-1}, in parentheses). Cr: crystalline: S: semectic; D_{ho}: ordered discotic hexagonal columnar; D_{hd}: disordered discotic hexagonal columnar; N_C: nematic columnar; Iso: isotropic.

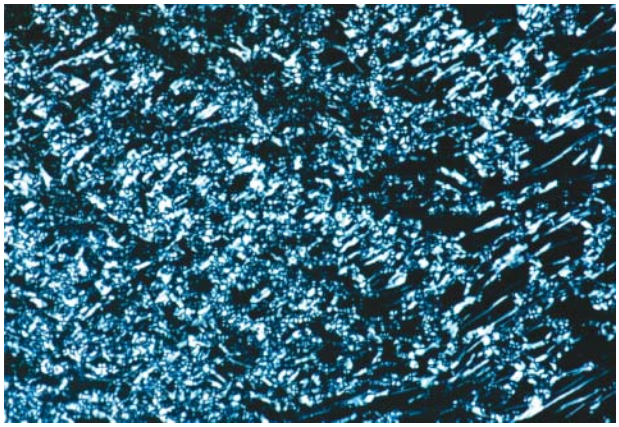


Fig. 2 Polarized photomicrograph of **1b** at 200 °C.

X-Ray diffraction measurements were carried out to examine the phase structures of **1a–d**. These results are shown in Fig. 3. For smectic liquid-crystalline **1a** and **1b**, only one sharp peak and a broad halo are observed at 25 °C (Fig. 3, (a) and (b)). These diffraction patterns also support the formation of the smectic phases. The layer spacings of the smectic phases for **1a** and **1b** are 37.8 and 41.9 Å, respectively. The structures for **1a** and **1b** could be induced by the ribbon-like aggregation of the pterin ring as shown in Fig. 1 (A). In contrast, the X-ray diffraction pattern of **1d** at 25 °C shows the formation of an ordered discotic hexagonal columnar (D_{ho})

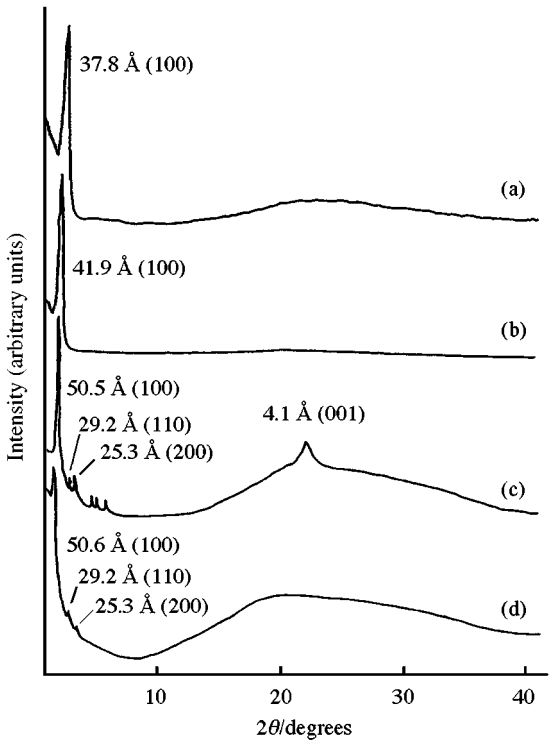


Fig. 3 X-Ray diffraction patterns of folic acid derivatives **1**: (a) **1a** at 25 °C; (b) **1b** at 25 °C; (c) **1d** at 25 °C; (d) **1d** at 100 °C.

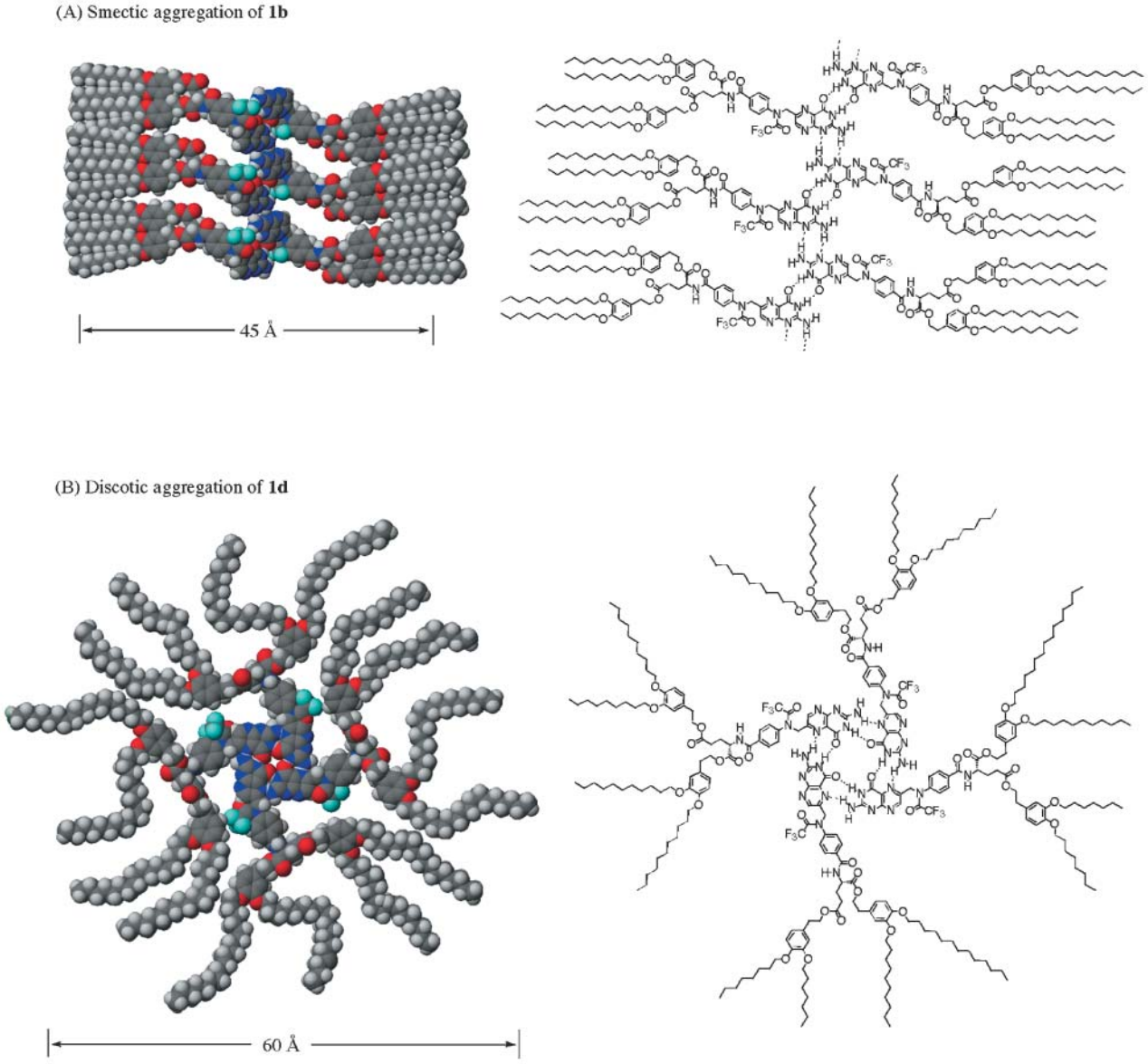


Fig. 4 Self-assembled smectic (A) and discotic (B) structures of folic acid derivatives **1b** and **1d**.

phase (Fig. 3, (c)). For example, the diffraction peaks at 50.5, 29.2, and 25.3 Å are attributed to the (100), (110), and (200) lattices of the hexagonal packing, respectively. In the wide-angle area, a sharp peak at 4.1 Å due to the distance between disks, and a broad halo at 4.2 Å resulting from the disorder of the aliphatic chains, are observed. At 100 °C (Fig. 3, (d)), the peaks at 50.6, 29.2, and 25.3 Å correspond to the (100), (110), and (200) lattices, respectively. A diffused halo is also observed at 4.3 Å. This pattern is characteristic of a disordered discotic hexagonal columnar phase (D_{hd}). The disappearance of the peaks due to the (110) and (200) lattices at 210 °C indicates that **1d** shows a nematic columnar (N_C) phase from 207 to 223 °C.[19] For hexagonal columnar phases, the lattice constant reflects the diameter of the column.[20] Thus, the diameters of the self-assembled discotic aggregate of **1d** at 25 and 100 °C are 58.3 and 58.4 Å, respectively. The relationships between the layer spacings and the self-assembled structures of **1b** and **1d** have been examined by molecular modeling. One of the most plausible layer structures of **1b** is shown in Fig. 4 (A). The layer spacing can be estimated to be about 45 Å, which is similar to the spacing observed by X-ray diffraction measurement of **1b**. For compound **1d**, the diameter of the discotic aggregate can be arranged to be 60 Å as shown in Fig. 4 (B). The distance is consistent with the results of the X-ray diffraction. The generation of the smectic and discotic phases of **1b** and **1d** is attributed to the formation of hydrogen-bonded ribbon- and disk-like self-assembled structures as shown in Fig. 4.

Atomic force microscopy (AFM) is a useful method for the observation of two-dimensional molecular assemblies on surfaces. For example, hydrogen-bonded materials on substrates have been examined by this method.[21] Self-assembled structures of **1b** and **1d** in thin film states on a silicon substrate were examined by AFM. The surface images of **1b** and **1d** are shown in Fig. 5. For compound **1b**, layer structures are observed. The average distance of the periodical strands for **1b** is 50 Å, which is wider than the layer spacing (41.9 Å) of the smectic phases determined by X-ray diffraction. The average distances may be based on the ribbon-like aggregated structure as shown in Fig. 4 (A). In contrast, compound **1d**, which forms a disk-like aggregated structure in the bulk liquid-crystalline state, exhibits no stripe image on the surface.

The difference between the ribbon- and disk-like hydrogen-bonded structures of **1** has been examined by infrared (IR) spectroscopy. The IR spectra of the samples of **1a**, **1b**, and **1d** at room temperature are shown in Fig. 6. The peak patterns are dependent on the liquid-crystalline phase structures. In the case

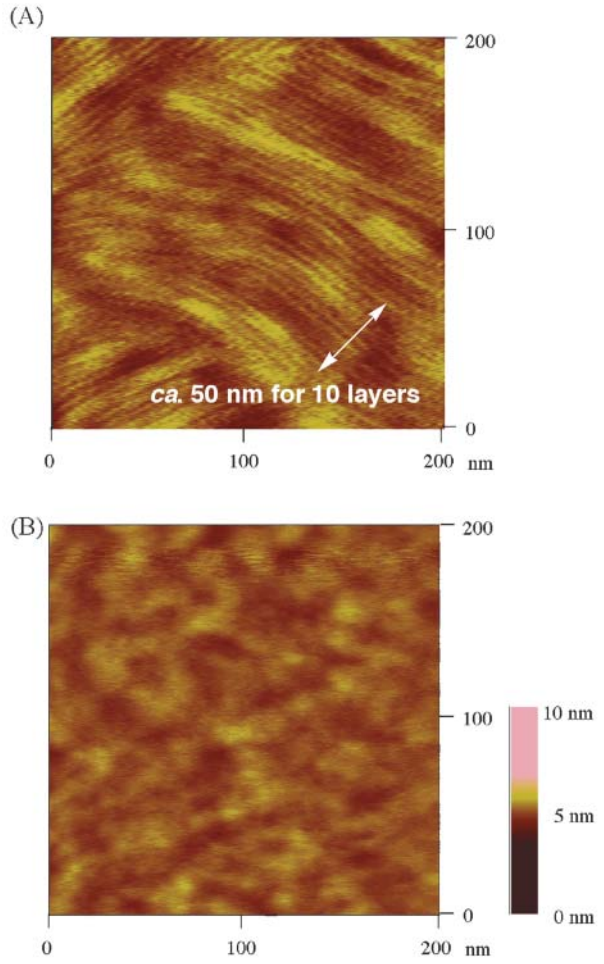


Fig. 5 AFM images of **1b** (A) and **1d** (B) on silicon surfaces.

of smectic compounds **1a** and **1b**, the peaks corresponding to the N–H stretching appear at 3351 and 3341 cm^{-1}, respectively. However, for discotic compound **1d**, the peaks are split into 3304 and 3251 cm^{-1}. These two patterns of the spectra can be attributed to the ribbon- and disk-like hydrogen-bonded structures for **1a**,**b** and **1c**,**d**, respectively, shown in Figs. 1 and 4. Similar hydrogen-bonded ribbon- and disk-like structures

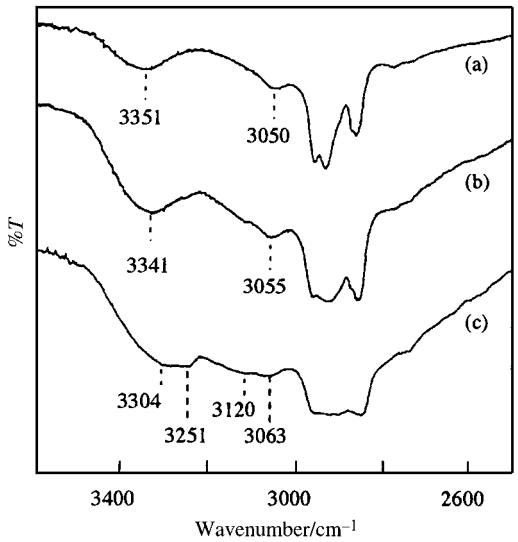


Fig. 6 Infrared spectra of folic acid derivatives **1** at room temperature on KBr: (a) **1a**; (b) **1b**; (c) **1d**.

were also observed for guanosine derivatives by Gottarelli[10] and Sessler,[11] respectively. The enthalpy difference between the smectic–isotropic transition of **1a**,**b** (33–37 kJ mol^{-1}) and the discotic–isotropic transition of **1c**,**d** (8–11 kJ mol^{-1}) listed in Table 2 is due to the difference of ribbon- and disk-like aggregation patterns.

Complexation of the folic acid derivatives with alkali metal triflates

We have succeeded in inducing a phase change from smectic to hexagonal columnar (Col_h) phase by the addition of alkali metal salts to **1b**. For the metal salts, we selected sodium triflate (NaOTf) due to the high co-solubility with organic molecules in organic solvents. The phase diagram of **1b** with NaOTf is shown in Fig. 7. Initially, the isotropization temperatures decrease drastically from 235 °C to 179 °C with increase of the molar ratio of NaOTf : **1b** from 0 : 1 to 0.3 : 1 in the mixtures. Further addition of NaOTf results in the increase of the isotropization temperatures. Fan-like textures characteristic of the Col_h phases are observed for the mixtures containing NaOTf more than 0.5 mol. A polarized photomicrograph of the mixture of the NaOTf and **1b** in the ratio of 1.8 : 1 (mol/mol) at 100 °C is shown in Fig. 8. The addition of the salt may generate ion–dipolar interactions between the pterin ring and the metal cation, resulting in the change from ribbon-like aggregate to the disk-like tetramer. To our knowledge, the induction of structural changes of specific hydrogen-bonded patterns leading to liquid-crystalline phase changes has not yet been reported, although the formation of the hexagonal columnar mesophases by the addition of metal salts was

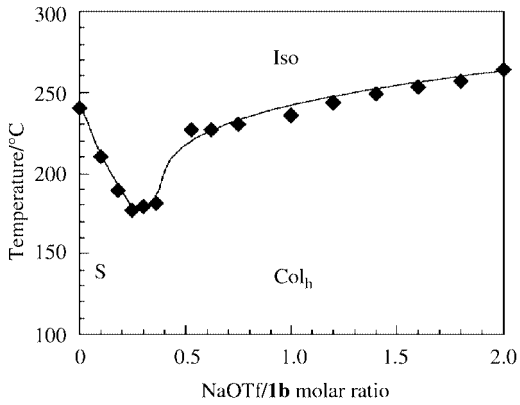


Fig. 7 Isotropization temperatures of the complexes of NaOTf and **1b**. S: smectic; Col_h: hexagonal columnar; Iso: isotropic.

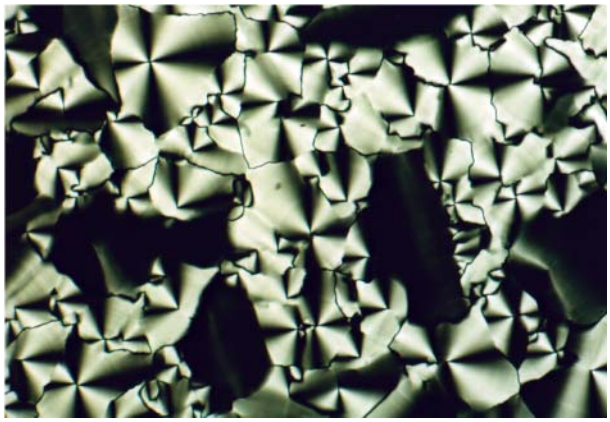


Fig. 8 Polarized photomicrograph of NaOTf : **1b** = 1.8 : 1 at 100 °C.

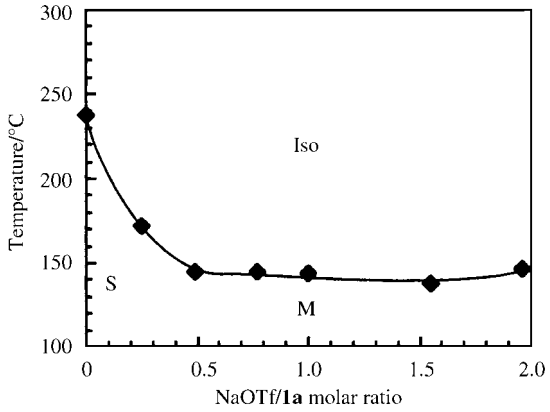


Fig. 9 Isotropization temperatures of the complexes of NaOTf and **1a**. S: smectic; M: mesomorphic; Iso: isotropic.

studied.[22] The addition of more than 2.5 mol of NaOTf to **1b** induces the phase separation of the sodium salt from the mixture.

We mixed NaOTf with **1a** which has hexyl chains. The isotropization temperatures of the mixtures are shown in Fig. 9. The addition of 0.25 mol of NaOTf to **1a** results in a decrease of the isotropization temperatures from 238 °C to 172 °C. The formation of a Col_h phase is not observed for the mixtures. Only mesomorphic sandy textures are seen for all of the mixtures. For the induction of the Col_h phases for compounds **1** by the complexation with the metal salts, the length of the alkyl chains should be appropriate to form a stable outer region in the column.

For alkali metal folates, the sodium cation is more suitable for the formation of octamers than the potassium cation.[9] On the other hand, two guanine tetramers effectively bind potassium[23] and lead(II)[24] to form octamers. To examine the effects of the cation, we prepared mixtures of LiOTf and KOTf with **1b**. The phase behaviors of the mixtures as a function of the molar ratio are similar to that of the mixtures containing NaOTf. The columnar phases are also induced by the addition of the potassium and lithium salts of **1b**. In the case of **1a**, the addition of these salts leads to phase destabilization; none of the columnar phases are induced.

X-Ray diffraction measurements have been performed to examine the change of the self-assembled structures of the folic acid derivatives by the addition of alkali metal triflates. The diffraction patterns of the sodium salt complexes of **1b** and **1a** are shown in Fig. 10 (A) and (B), respectively. As shown in Fig. 10 (A), the diffraction at 41.9 Å becomes weaker on the addition of 0.25 mol of the sodium salt. The diffraction peaks attributable to the (110) lattice of the columnar mesophases are observed for compound **1b** containing 1.0 and 1.8 mol of the sodium salt. These patterns are characteristic of the disordered Col_h phases. For the equimolar mixture of **1a**, the intensity of the diffraction at 38.8 Å is smaller than that of **1a**. None of the peaks corresponding to the (110) lattice appear. The addition of sodium salt to **1a** induces only destabilization of the mesophases. The smectic–columnar phase change is only observed for compound **1b**. An IR spectroscopic study for the mixtures of **1b** with the sodium salt was carried out to examine the hydrogen-bonded structural change from ribbon to disk. Fig. 11 shows the results for the mixtures of **1b** with 0.25 (b) and 1.2 (c) mol of the salts as well as the single component of **1b** (a). The peak pattern in Fig. 11(c) is similar to that of **1d** shown in Fig. 6(c) exhibiting the D_h phase. The result indicates that the change of the hydrogen-bonded structures from ribbon to disk is induced for **1b** by the addition of 1.2 mol of the sodium salt. It seems that the spectral features of **1b** with 0.25 mol of NaOTf in Fig. 11(b) are between those in Fig. 11(a) and (c).

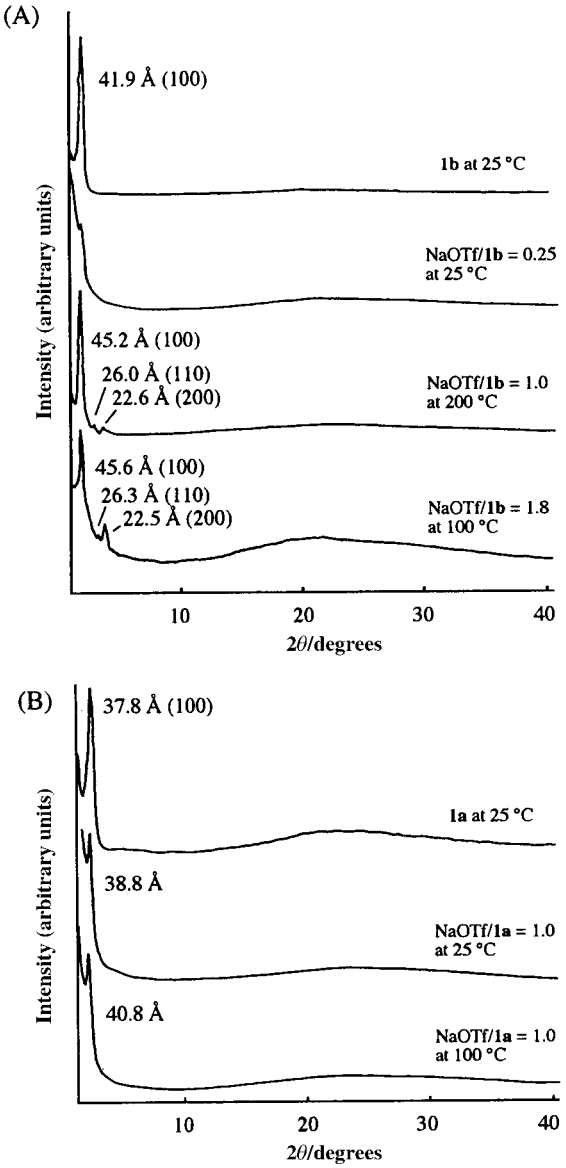


Fig. 10 X-Ray diffraction patterns of the sodium salts complexes of **1b** (A) and **1a** (B).

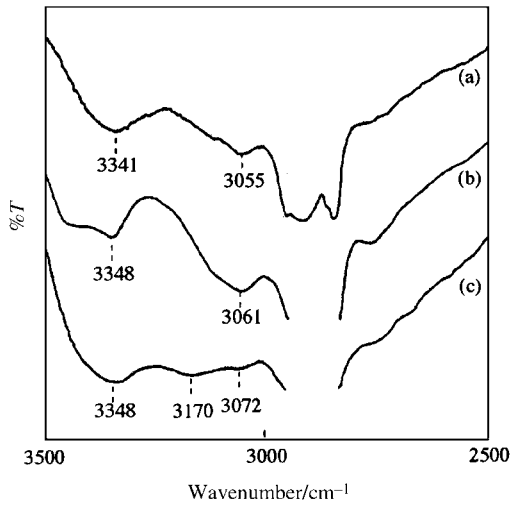
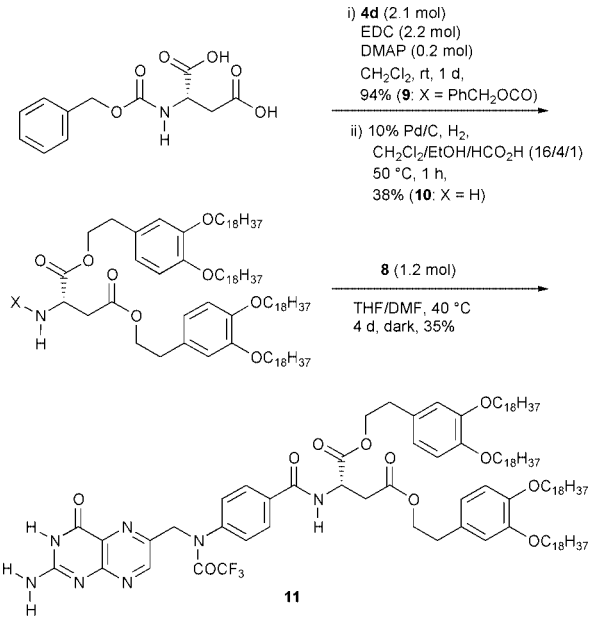


Fig. 11 Infrared spectra of **1b** and the sodium triflate complexes of **1b** at room temperature on KBr: (a) **1b**; (b) NaOTf : **1b** = 0.25 : 1; (c) NaOTf : **1b** = 1.2 : 1.

Thermotropic behavior of a pteroylaspartate

The liquid-crystalline structures of **1a–d** depend on the length of the alkyl chains. The effect of the glutamic acid moiety on the liquid crystallinity is also of interest. Our synthetic procedure for **1** enables us to introduce a variety of functionalized amino acids to the pteroic acid moiety. We synthesized pteroylaspartate **11** with octadecyl chains. The synthetic route to **11** is shown in Scheme 3. Compound **11** shows thermotropic discotic liquid crystallinity from room temperature to 223 °C. The transition temperatures and phase structures are as follows: D_{ho} 64 D_{hd} 193 N_C 223 Iso. The D_{hd}–N_C transition temperature of **11** is lower by 14 °C than that of **1d**, which suggests that the glutamic acid moiety is preferred for the stabilization of the hexagonal columnar structure.



Scheme 3 Synthesis of pteroyl-L-aspartate **11**.

Conclusions

We have prepared thermotropic liquid-crystalline folic acid derivatives **1a–d** by introducing long alkyl chains. Compounds **1a**,**b** having shorter alkyl chains show smectic phases, while discotic phases are observed for compounds **1c**,**d** having longer alkyl chains. We have found that the smectic phase exhibited by **1b** is changed to the hexagonal columnar phase when more than 0.5 mol of alkali metal salts such as LiOTf, NaOTf, and KOTf are added. The change of the hydrogen-bonded structures from ribbon to disk induced by the ion–dipolar interaction between the pterin ring and the metal cation is a key for this process. However, this phase change is not induced for **1a**. The appropriate length of the alkyl chain is necessary to induce such structural change. These supramolecular materials reported here have great potential for dynamically functional materials responsive to external stimuli and to the change of atmosphere if we can control the shapes and interactions of molecules.

Experimental section

General techniques

All reagents of the highest commercial quality and solvents were purchased from Aldrich Chemical, Kanto Chemicals, Tokyo Kasei, or Wako Pure Chemicals, and were used as received. 10% Pd/C was purchased from Kojima Chemicals. Unless otherwise noted, all of the reactions were carried out under an argon atmosphere in a dry solvent purchased from Kanto Chemicals. Completion of the reactions was monitored by thin-layer chromatography using 0.25 mm E. Merck silica gel plates (Silica Gel F_{254}), visualized under UV light and/or by dipping the plates in an ethanolic sodium phosphomolybdate followed by heating. Silica gel from Kanto Chemicals (Silica Gel 60, spherical, 40–50 μm) was used for flash column chromatography. Recycling preparative GPC was carried out using a Japan Analytical Industry LC-908 chromatograph. Measurements of melting points and phase transition temperatures and determinations of liquid-crystalline phases were carried out with an Olympus BH-2 optical polarizing microscope equipped with a Mettler FP82 HT hot-stage. Thermal characterization was conducted with a Mettler DSC 30 system (scanning rate 10 °C min^{-1}). IR measurements were conducted on a JASCO FT/IR-8900μ in KBr unless otherwise noted. NMR spectra were measured in a $CDCl_3$ solution unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-270 and a JEOL JNM-LA400. ^{19}F NMR spectra were recorded on a Varian Mercury-300 at 282 MHz. Chemical shifts of ^1H, ^{13}C, and ^{19}F NMR signals were quoted to internal standard Me_4Si ($\delta = 0.00$), $CDCl_3$ ($\delta = 77.00$), and $CFCl_3$ ($\delta = 0.00$), respectively, and expressed as chemical shifts in ppm (δ), multiplicity, coupling constant (Hz), and relative intensity. Mass spectra were recorded on a Shimadzu GC/MS QP-5000 spectrometer (70 eV). Matrix associated laser desorption ionization–time of flight mass spectra (MALDI-TOF MS) were taken on a PerSeptive Biosystems Voyager-DE™ STR spectrometer. Elemental analyses were carried out on a Perkin-Elmer CHNS/O 2400 apparatus. X-Ray diffraction measurements were carried out on a Rigaku X-ray Rad 2B system with a heating stage using Ni-filtered CuKα radiation.

Synthesis of ethyl 3,4-dihydroxyphenylacetate (2). A deaerated ethanolic solution (300 mL) of 3,4-dihydroxyacetic acid (20 g, 119 mmol) and conc. H_2SO_4 (1 mL) was heated to reflux with stirring under an argon atmosphere for 4 h. The reaction mixture was then cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (300 mL) and poured into H_2O (300 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc three times (total 500 mL). The combined organic extracts were washed with successive, 5% aq. $NaHCO_3$ (300 mL) and sat. aq. NaCl (300 mL). The resulting extracts were dried over anhydrous magnesium sulfate, filtered through a pad of Celite, and concentrated *in vacuo* to give **2** in a quantitative yield as pale yellow solids. Further purification was not necessary for the next step. $R_f = 0.47$ (hexane–EtOAc = 1 : 1). IR (neat) 3394, 2984, 1701, 1609, 1522, 1449, 1374, 1287, 1030, 970, 850, 798 cm^{-1}; ^1H NMR (400 MHz) $\delta = 6.79$ (s, 1 H), 6.78 (d, $J = 8$ Hz, 1 H), 6.69 (d, $J = 8$ Hz, 1 H), 5.58 (s, 1 H), 5.36 (s, 1 H), 4.16 (q, $J = 7$ Hz, 2 H), 3.50 (s, 2 H), 1.29 (t, $J = 7$ Hz, 3 H); ^{13}C NMR (100 MHz) $\delta = 173.4$, 143.8, 143.1, 125.9, 121.5, 116.2, 115.3, 61.3, 40.6, 14.0; MS *m*/*z* (rel intensity) 197 ($M^+ + 1$, 3), 196 (M^+, 22), 167 (5), 149 (15), 124 (12), 123 (100), 105 (11), 97 (15), 91 (12), 88 (13), 73 (32), 70 (77), 64 (30). Found: C, 60.20; H, 6.41%. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16%.

General procedure for the preparation of ethyl 3,4-dialkoxyphenylacetate (3)

A DMF (200 mL) suspension of **2** (19.6 g, 0.100 mol), 1-bromoalkane (0.22 mol), and K_2CO_3 (54 g, 0.40 mol) in a round-bottomed flask (1 L) equipped with a stirring bar was deaerated under reduced pressure, and the flask was filled with argon. The deaeration was repeated three times to remove oxygen in the flask, thoroughly. After the resulting mixture was heated at 80 °C for 1 day with vigorous stirring, the mixture

was poured into a mixture of warm water and EtOAc (40 °C, 500 mL of each). The organic phase was separated, and the aqueous phase was extracted with EtOAc three times (total 500 mL). The combined organic extracts were washed with equal-volume portions of warm water, 10% NH_4Cl aq. solution, and sat. aq. NaCl, successively. The resulting warm organic phase was dried over $MgSO_4$, filtered through a pad of Celite before cooling, and concentrated under reduced pressure. The residue was recrystallized from ethanol to give **3**. The yields and the spectroscopic data are summarized as follows.

Ethyl 3,4-bis(hexyloxy)phenylacetate (3a). This compound was purified by silica gel flash-column chromatography (hexane–EtOAc = 10 : 1) instead of recrystallization. Yield 79%, colorless oil; $R_f = 0.54$ (hexane–EtOAc = 5 : 1). IR (neat) 2932, 2861, 1734, 1517, 1508, 1473, 1457, 1262, 1143, 1033, 794 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.77$–6.93 (m, 3 H), 4.14 (q, $J = 7$ Hz, 2 H), 3.92–4.03 (m, 4 H), 3.52 (s, 2 H), 1.72–1.86 (m, 4 H), 1.21–1.57 (m, 12 H), 1.25 (t, $J = 7$ Hz, 3 H), 0.90 (t, $J = 6$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 171.8$, 149.0, 148.1, 126.6, 121.4, 114.7, 113.7, 69.2, 69.1, 60.7, 40.9, 31.5, 29.2, 25.6, 22.6, 14.1, 14.0; MS *m*/*z* (rel intensity) 366 ($M^+ + 2$, 0.1), 365 ($M^+ + 1$, 1), 364 (M^+, 5), 280 (3), 197 (6), 196 (55), 168 (2), 149 (30), 123 (100), 105 (6), 77 (8), 71 (10). Found: C, 72.31; H, 10.02%. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95%.

Ethyl 3,4-bis(undecyloxy)phenylacetate (3b). Yield 91%. Colorless solid, mp = 40.5–42.4 °C; $R_f = 0.57$ (hexane–EtOAc = 5 : 1). IR 2923, 2850, 1738, 1526, 1469, 1265, 1191, 1138, 1031, 1003, 876, 791 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.70$–6.83 (m, 3 H), 4.14 (q, $J = 7$ Hz, 2 H), 3.91–4.03 (m, 4 H), 3.52 (s, 2 H), 1.69–1.88 (m, 4 H), 1.18–1.59 (m, 35 H), 0.88 (t, $J = 6$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 172.0$, 149.1, 148.0, 126.6, 121.4, 114.8, 113.8, 69.3, 69.1, 60.7, 40.9, 31.9, 29.6, 29.4, 29.34, 29.26, 26.0, 22.7, 14.2, 14.1; MS *m*/*z* (rel intensity) 506 ($M^+ + 2$, 0.4), 505 ($M^+ + 1$, 2), 504 (M^+, 6), 350 (2), 197 (8), 196 (71), 168 (2), 135 (7), 124 (10), 123 (100), 97 (6), 83 (10), 69 (28). Found: C, 76.47; H, 11.40%. Calcd for $C_{32}H_{56}O_4$: C, 76.14; H, 11.18%.

Ethyl 3,4-bis(tetradecyloxy)phenylacetate (3c). Yield 75%. Colorless solid, mp = 51.1–51.9 °C; $R_f = 0.59$ (hexane–EtOAc = 5 : 1). IR 2954, 2919, 2849, 1739, 1525, 1469, 1331, 1265, 1189, 1138, 1033, 722 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.78$–6.91 (m, 3 H), 4.14 (q, $J = 7$ Hz, 2 H), 3.96–4.10 (m, 4 H), 3.52 (s, 2 H), 1.64–1.91 (m, 4 H), 1.03–1.61 (m, 47 H), 0.88 (t, $J = 8$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 171.9$, 149.0, 148.1, 126.6, 121.4, 114.8, 113.8, 69.2, 69.1, 60.7, 40.9, 31.9, 29.7, 29.6, 29.42, 29.36, 29.26, 26.0, 22.7, 14.2, 14.1; MS *m*/*z* (rel intensity) 591 ($M^+ + 2$, 2), 590 ($M^+ + 1$, 8), 589 (M^+, 18), 515 (0.4), 392 (4), 197 (12), 196 (100), 163 (3), 150 (2), 135 (5), 123 (77), 97 (8), 83 (15), 71 (20), 69 (33). Found: C, 77.63; H, 11.76%. Calcd for $C_{38}H_{68}O_4$: C, 77.50; H, 11.64%.

Ethyl 3,4-bis(octadecyloxy)phenylacetate (3d). Yield 86%. Colorless solid, mp = 53.9–54.5 °C; $R_f = 0.59$ (hexane–EtOAc = 5 : 1). IR 2956, 2918, 2850, 1735, 1518, 1468, 1431, 1270, 1235, 1143, 1034, 721 cm^{-1}; ^1H NMR (400 MHz) $\delta = 6.74$–6.90 (m, 3 H), 4.14 (q, $J = 7$ Hz, 2 H), 3.92–4.05 (m, 4 H), 3.51 (s, 2 H), 1.75–1.94 (m, 4 H), 1.15–1.57 (m, 61 H), 0.88 (t, $J = 7$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 171.9$, 149.3, 148.1, 126.7, 121.5, 114.8, 113.8, 69.3, 69.2, 60.7, 40.9, 31.9, 29.70, 29.66, 29.43, 29.36, 29.26, 26.0, 22.7, 14.2, 14.1; MS *m*/*z* (rel intensity) 703 ($M^+ + 2$, 1), 702 ($M^+ + 1$, 6), 701 (M^+, 11), 449 (4), 197 (13), 196 (100), 137 (5), 124 (12), 123 (92), 97 (17), 83 (24), 71 (30), 69 (41). Found: C, 78.93; H, 12.29%. Calcd for $C_{46}H_{84}O_4$: C, 78.80; H, 12.08%.

Preparation of 2-(3,4-dialkoxyphenyl)ethanol 4: general procedure

To a stirred suspension of lithium aluminium hydride (LAH, 3.6 g, 96 mmol) in THF (50 mL) was added a solution of **3** (80 mmol) in THF (100 mL) at 0 °C over a period of 10 min. The mixture was stirred at room temperature for 3 h, quenched by slow addition of Pr^iOH (3 mL), H_2O (5 mL), and 30% aq. NaOH (5 mL) at 0 °C, successively. The resulting mixture was stirred at room temperature for 3 h before mixing with Celite, anhydrous $MgSO_4$, and diethyl ether (300 mL). The insoluble materials were filtered off through a pad of Celite by using a suction funnel, and the filter cake was washed with diethyl ether (50 mL, 4 times) and CH_2Cl_2 (50 mL, 4 times), successively. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from hexane to give **4**. The isolated yields and spectral properties of **4** are as follows.

2-[3,4-Bis(hexyloxy)phenyl]ethanol (4a). This compound was purified by flash column chromatography (hexane–EtOAc = 5 : 1) in lieu of recrystallization. Yield 100%. A colorless oil; $R_f = 0.32$ (hexane–EtOAc = 5 : 2). IR (neat) 3363, 2931, 2861, 1590, 1516, 1472, 1426, 1387, 1260, 1233, 1139, 1047, 798 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.72$–6.85 (m, 3 H), 3.98 (t, $J = 7$ Hz, 2 H), 3.96 (t, $J = 7$ Hz, 2 H), 3.80–3.86 (m, 2 H), 2.79 (t, $J = 6$ Hz, 2 H), 1.74–1.83 (m, 4 H), 1.27–1.46 (m, 12 H), 0.88 (t, $J = 7$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 149.2$, 147.8, 130.9, 121.1, 114.7, 114.1, 69.4, 69.2, 63.7, 38.7, 31.6, 29.3, 25.7, 22.6, 14.0; MS *m*/*z* (rel intensity) 323 ($M^+ + 1$, 3), 322 (M^+, 15), 238 (10), 154 (61), 124 (10), 123 (100), 77 (6). Found: C, 74.16; H, 10.78%. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63%.

2-[3,4-Bis(undecyloxy)phenyl]ethanol (4b). Yield 92%. Colorless solid, mp 44.8–45.2 °C; $R_f = 0.44$ (hexane–EtOAc = 5 : 2). IR 3460, 2919, 2850, 1518, 1471, 1428, 1261, 1232, 1138, 1026, 807, 720 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.72$–6.85 (m, 3 H), 3.98 (t, $J = 7$ Hz, 2 H), 3.97 (t, $J = 7$ Hz, 2 H), 3.79–3.86 (m, 2 H), 2.79 (t, $J = 6$ Hz, 2 H), 1.74–1.83 (m, 4 H), 1.27–1.46 (m, 32 H), 0.88 (t, $J = 7$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 149.2$, 147.7, 131.0, 121.1, 114.7, 114.1, 69.4, 69.2, 63.7, 38.7, 31.9, 29.6, 29.4, 29.34, 29.30, 26.0, 22.7, 14.1; MS *m*/*z* (rel intensity) 464 ($M^+ + 2$, 2), 463 ($M^+ + 1$, 10), 462 (M^+, 32), 308 (9), 155 (8), 154 (94), 124 (11), 123 (100), 97 (8), 83 (11), 71 (15), 69 (27). Found: C, 78.18; H, 11.69%. Calcd for $C_{30}H_{54}O_3$: C, 77.87; H, 11.76%.

2-[3,4-Bis(tetradecyloxy)phenyl]ethanol (4c). Yield 100%. Colorless solid, mp 56.7–57.4 °C; $R_f = 0.50$ (hexane–EtOAc = 5 : 2). IR 3447, 2918, 2849, 1519, 1472, 1263, 1233, 1138, 1022, 809, 720 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.68$–6.87 (m, 3 H), 3.89–4.02 (m, 4 H), 3.77–3.99 (m, 2 H), 2.79 (t, $J = 6$ Hz, 2 H), 1.69–1.90 (m, 4 H), 1.10–1.59 (m, 45 H), 0.88 (t, $J = 7$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 149.2$, 147.8, 131.0, 121.1, 114.7, 114.1, 69.4, 69.2, 63.7, 38.7, 31.9, 29.7, 29.6, 29.43, 29.36, 29.31, 26.0, 22.7, 14.1; MS *m*/*z* (rel intensity) 549 ($M^+ + 3$, 2), 548 ($M^+ + 2$, 10), 547 ($M^+ + 1$, 12), 350 (6), 154 (88), 152 (12), 137 (13), 124 (15), 123 (100), 107 (3), 97 (12), 85 (11), 83 (21), 71 (27), 70 (11), 69 (44). Found: C, 79.56; H, 12.34%. Calcd for $C_{36}H_{66}O_3$: C, 79.06; H, 12.16%.

2-[3,4-Bis(octadecyloxy)phenyl]ethanol (4d). Yield 97%. Colorless solid, mp 66.5–67.4 °C; $R_f = 0.54$ (hexane–EtOAc = 5 : 2). IR 3420, 2918, 2850, 1518, 1468, 1265, 1234, 1139, 1048, 806, 721 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.71$–6.85 (m, 3 H), 3.98 (t, $J = 7$ Hz, 2 H), 3.96 (t, $J = 7$ Hz, 2 H), 3.80–3.86 (m, 2 H), 2.79 (t, $J = 6$ Hz, 2 H), 1.74–1.85 (m, 4 H), 1.26–1.48 (m, 60 H), 0.88 (t, $J = 7$ Hz, 6 H); ^{13}C NMR (100 MHz) $\delta = 149.2$, 147.7, 131.0, 121.1, 114.7, 114.2, 69.4, 69.2, 63.7, 38.7, 31.9, 29.7, 29.6, 29.44,

29.36, 29.33, 26.1, 22.7, 14.1; MALDI-TOF MS (indole-3-acrylic acid (IAA)) *m/z* 681.8 ($M+Na^+$, $C_{44}H_{82}O_3$ requires 681.6). Found: C, 80.40; H, 12.59%. Calcd for $C_{44}H_{82}O_3$: C, 80.18; H, 12.54%.

General method for synthesis of bis[2-(3,4-dialkoxyphenyl)ethyl] *N*-benzyloxycarbonyl-L-glutamate 5

To a mixture of 2-(3,4-dialkoxyphenyl)ethanol (**4**, 18 mmol), *N*-benzyloxycarbonyl-L-glutamic acid (2.5 g, 8.8 mmol), and DMAP (0.43 g, 3.5 mmol) in CH_2Cl_2 (80 mL), EDC (4.5 g, 24 mmol) was added portionwise at room temperature over 10 min. The reaction mixture was stirred overnight at the same temperature, and the resulting mixture was poured into an aq. NH_4Cl solution (200 mL). The insoluble material was dissolved in $CHCl_3$ (300 mL), and the organic phase was separated. The aqueous phase was extracted three times with $CHCl_3$ (total 500 mL). The combined organic extracts were washed with sat. aq. NH_4Cl solution (200 mL) and sat. aq. NaCl solution (200 mL). The resulting organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: hexane–EtOAc = 5 : 1) to give **5**.

Bis{2-[3,4-bis(hexyloxy)phenyl]ethyl} *N*-benzyloxycarbonyl-L-glutamate (5a). Yield 70%. Colorless solid, mp 41.7–42.5 °C; $R_f = 0.53$ (hexane–EtOAc = 5 : 2). IR 3326, 2956, 2931, 2859, 1729, 1687, 1590, 1519, 1468, 1428, 1393, 1262, 1236, 1140, 1068, 1048, 802, 732 cm^{-1}; ^1H NMR (270 MHz) $\delta = 7.26$–7.41 (m, 5 H), 6.65–6.83 (m, 6 H), 5.35 (d, $J = 8$ Hz, 1 H), 5.09 (s, 2 H), 4.32–4.43 (m, 1 H), 4.13 (t, $J = 7$ Hz, 2 H), 4.31 (t, $J = 7$ Hz, 2 H), 3.89–4.01 (m, 8 H), 2.77–2.91 (m, 4 H), 2.22–2.43 (m, 2 H), 2.10–2.21 (m, 1 H), 1.87–2.04 (m, 1 H), 1.71–1.87 (m, 8 H), 1.20–1.57 (m, 24 H), 1.90 (t, $J = 6$ Hz, 12 H); ^{13}C NMR (100 MHz) $\delta = 172.6$, 171.7, 155.8, 149.13, 149.07, 147.9, 147.8, 136.0, 130.1, 129.7, 128.5, 128.2, 128.1, 121.0, 114.6, 114.5, 113.9, 69.3, 69.2, 67.0, 66.2, 65.4, 53.3, 34.54, 34.48, 31.6, 30.0, 29.3, 27.5, 25.7, 22.6, 14.0; MALDI-TOF MS (IAA) *m/z* 912.9 ($M+Na^+$, $C_{53}H_{79}NO_{10}$ requires 912.6). Found: C, 71.83; H, 9.12; N, 1.60%. Calcd for $C_{53}H_{79}NO_{10}$: C, 71.51; H, 8.94; N, 1.57%.

Bis{2-[3,4-bis(undecyloxy)phenyl]ethyl} *N*-benzyloxycarbonyl-L-glutamate (5b). Yield 80%. Colorless solid, mp = 49.3–50.0 °C; $R_f = 0.62$ (hexane–EtOAc = 5 : 2). IR 3317, 2922, 2852, 1732, 1687, 1540, 1520, 1467, 1264, 1234, 1173, 1140, 1057, 999, 802 cm^{-1}; ^1H NMR (400 MHz) $\delta = 7.26$–7.38 (m, 5 H), 6.64–6.82 (m, 6 H), 5.36 (d, $J = 9$ Hz, 1 H), 5.08 (s, 2 H), 4.33–4.43 (m, 1 H), 4.30 (t, $J = 7$ Hz, 2 H), 4.22 (t, $J = 7$ Hz, 2 H), 3.82–4.00 (m, 8 H), 2.84 (t, $J = 7$ Hz, 2 H), 2.82 (t, $J = 7$ Hz, 2 H), 2.25–2.42 (m, 2 H), 2.08–2.21 (m, 1 H), 1.86–1.98 (m, 1 H), 1.72–1.85 (m, 8 H), 1.08–1.26 (m, 64 H), 0.86 (t, $J = 7$ Hz, 12 H); ^{13}C NMR (100 MHz) $\delta = 172.5$, 171.6, 155.8, 149.1, 149.0, 147.86, 147.78, 136.1, 130.1, 129.6, 128.4, 128.1, 128.0, 120.1, 114.6, 114.5, 113.9, 69.22, 69.16, 66.9, 66.1, 65.3, 53.3, 34.5, 31.8, 30.0, 29.6, 29.4, 29.3, 27.4, 26.0, 22.6, 14.0; MALDI-TOF MS (IAA) *m/z* 1193.7 ($M+1+Na^+$, $C_{73}H_{119}NO_{10}$ requires 1193.9). Found: C, 74.82; H, 10.43; N, 1.39%. Calcd for $C_{73}H_{119}NO_{10}$: C, 74.89; H, 10.25; N, 1.20%.

Bis{2-[3,4-bis(tetradecyloxy)phenyl]ethyl} *N*-benzyloxycarbonyl-L-glutamate (5c). Yield 80%. Colorless solid, mp = 59.7–60.6 °C; $R_f = 0.66$ (hexane–EtOAc = 5 : 2). IR 3319, 2920, 2851, 1732, 1686, 1519, 1468, 1265, 1235, 1171, 1139, 1055, 794, 721 cm^{-1}; ^1H NMR (400 MHz) $\delta = 7.26$–7.40 (m, 5 H), 6.62–6.83 (m, 6 H), 5.37 (d, $J = 8$ Hz, 1 H), 5.10 (s, 2 H), 4.34–4.43 (m, 1 H), 4.31 (t, $J = 7$ Hz, 2 H), 4.23 (t, $J = 7$ Hz, 2 H), 3.89–4.00 (m, 8 H), 2.87 (t, $J = 7$ Hz, 2 H), 2.84 (t, $J = 7$ Hz, 2 H), 2.26–2.44 (m, 2 H), 2.09–2.19 (m, 1 H), 1.86–1.98 (m, 1 H), 1.73–1.82 (m, 8 H), 1.19–1.53 (m, 88 H), 0.88 (t, $J = 7$ Hz, 12 H); ^{13}C NMR (100 MHz) $\delta = 172.5$, 171.6, 155.8, 149.11, 149.06, 147.9, 147.8, 136.1, 130.1, 129.6, 128.4, 128.1, 128.0, 121.0, 114.6, 114.5, 113.9, 69.24, 69.17, 66.9, 66.1, 65.3, 53.3, 34.5, 31.9, 30.0, 29.7, 29.6, 29.4, 29.3, 27.4, 26.0, 22.6, 14.0; MALDI-TOF MS (IAA) *m/z* 1361.9 ($M+Na^+$, $C_{85}H_{143}NO_{10}$ requires 1361.1). Found: C, 76.71; H, 11.05; N, 0.98%. Calcd for $C_{85}H_{143}NO_{10}$: C, 76.24; H, 10.76; N, 1.05%.

Bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} *N*-benzyloxycarbonyl-L-glutamate (5d). Yield 86%. Colorless solid, mp = 68.8–70.0 °C; $R_f = 0.69$ (hexane–EtOAc = 5 : 2). IR 3316, 2919, 2850, 1734, 1518, 1468, 1265, 1235, 1165, 1140, 1068, 804, 721 cm^{-1}; ^1H NMR (400 MHz) $\delta = 7.23$–7.45 (m, 5 H), 6.62–6.89 (m, 6 H), 5.33 (d, $J = 9$ Hz, 1 H), 5.10 (s, 2 H), 4.31–4.45 (m, 1 H), 4.31 (t, $J = 7$ Hz, 2 H), 4.23 (t, $J = 7$ Hz, 2 H), 3.85–4.08 (m, 8 H), 2.85 (t, $J = 7$ Hz, 2 H), 2.87 (t, $J = 7$ Hz, 2 H), 2.28–2.45 (m, 2 H), 2.10–2.25 (m, 1 H), 1.82–1.99 (m, 1 H), 1.70–1.82 (m, 8 H), 1.12–1.58 (m, 120 H), 0.88 (t, $J = 7$ Hz, 12 H); ^{13}C NMR (100 MHz) $\delta = 172.5$, 171.7, 155.9, 149.16, 149.11, 147.93, 147.86, 136.0, 130.1, 129.7, 128.5, 128.14, 128.06, 121.0, 114.7, 114.5, 114.0, 69.3, 69.2, 67.0, 66.2, 65.4, 53.3, 34.5, 31.9, 29.7, 29.6, 29.4, 29.3, 27.5, 26.0, 22.7, 14.1; MALDI-TOF MS (IAA) *m/z* 1586.5 ($M+1+Na^+$, $C_{101}H_{175}NO_{10}$ requires 1586.3). Found: C, 77.88; H, 11.47; N, 1.03%. Calcd for $C_{101}H_{175}NO_{10}$: C, 77.59; H, 11.28; N, 0.90%.

Bis{2-[3,4-bis(undecyloxy)phenyl]ethyl} *N*-benzyloxycarbonyl-DL-glutamate (DL-5b). Yield 74%. Spectroscopic data of DL-**5b** were identical to those of **5b**.

Bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} *N*-benzyloxycarbonyl-DL-glutamate (DL-5d). Yield 85%. Spectroscopic data of DL-**5d** were the same as those of **5d**.

Representative procedure for the preparation of bis{2-[3,4-bis(undecyloxy)phenyl]ethyl} L-glutamate (6b)

A suspension of **5b** (5.0 g, 4.3 mmol) and 10% Pd/C (1.0 g) in EtOAc (60 mL) and EtOH (40 mL) was vigorously stirred for 3 h at 50 °C under a hydrogen atmosphere with a slightly positive pressure. The resulting mixture was filtered through a pad of Celite/Wakogel C-100, and the filtrate was concentrated *in vacuo*. Purification of the residue by flash silica gel column chromatography (eluent: CH_2Cl_2–EtOAc = 10 : 1, $R_f = 0.43$) afforded **6b** as a colorless solid in a yield of 56% (2.5 g, 2.4 mmol), mp = 45.2–45.9 °C. IR 3386, 3322, 2921, 2847, 1726, 1606, 1590, 1516, 1472, 1428, 1391, 1330, 1266, 1228, 1182, 1142, 1070, 1028, 998, 980, 945, 857, 814, 721 cm^{-1}; ^1H NMR (400 MHz) $\delta = 6.70$–6.81 (m, 6 H), 4.23–4.31 (m, 4 H), 3.94–3.98 (m, 8 H), 3.42 (dd, $J = 5$, 8 Hz, 1 H), 2.83–2.90 (m, 4 H), 2.43 (t, $J = 8$ Hz, 2 H), 2.00–2.07 (m, 1 H), 1.76–1.84 (m, 9 H), 1.26–1.46 (m, 64 H), 0.88 (t, $J = 7$ Hz, 12 H); ^{13}C NMR (100 MHz) $\delta = 175.5$, 173.1, 149.12, 149.08, 147.89, 147.83, 130.2, 129.9, 121.0, 114.7, 114.6, 114.0, 69.34, 69.26, 65.6, 65.2, 53.7, 34.6, 31.9, 30.5, 29.6, 29.5, 29.4, 29.3, 26.0, 22.7, 14.1; MALDI-TOF MAS (IAA): *m/z* 1037.3 ($M+1$, $C_{65}H_{113}NO_8$ requires 1036.8). Found: C, 75.00; H, 11.14; N, 1.40%. Calcd for $C_{65}H_{113}NO_8$: C, 75.31; H, 10.99; N, 1.35%.

Bis{2-[3,4-bis(hexyloxy)phenyl]ethyl} L-glutamate (6a). Compound **6a** was prepared in 66% yield from **5a**. A pale yellow viscous oil; $R_f = 0.39$ ($CHCl_3$–MeOH = 10 : 1). IR 3210, 2932, 2861, 1740, 1699, 1516, 1469, 1428, 1262, 1234, 1140, 1046, 1019, 804, 726 cm^{-1}; ^1H NMR (270 MHz) $\delta = 6.70$–6.82 (m, 6 H), 4.29 (t, $J = 7$ Hz, 2 H), 4.25 (t, $J = 7$ Hz, 2 H), 3.97 (t, $J = 7$ Hz, 4 H), 3.96 (t, $J = 7$ Hz, 4 H), 3.42 (dd, $J = 5$, 8 Hz, 1 H), 2.82–2.89 (m, 4 H), 2.42 (t, $J = 7$ Hz, 2 H), 1.97–2.10 (m, 1 H), 1.74–1.86 (m, 9 H), 1.26–1.58 (m, 26 H), 0.88 (t, $J = 7$ Hz, 12 H); ^{13}C NMR (100 MHz) $\delta = 175.0$, 172.6, 148.80, 148.76, 147.6, 147.5, 130.0,

129.7, 120.7, 114.35, 114.27, 113.6, 68.9, 68.8, 65.2, 64.8, 53.3, 34.3, 31.3, 29.0, 25.4, 22.3, 13.7; MALDI-TOF MS (IAA) *m/z* 756.6 (M+1, $C_{45}H_{73}NO_8$ requires 756.5). Found: C, 71.54; H, 9.98%. Calcd for $C_{45}H_{73}NO_8$: C, 71.49; H, 9.73%.

Bis{2-[3,4-bis(tetradecyloxy)phenyl]ethyl} L-glutamate (6c). Synthesis of **6c** was carried out in benzene instead of in EtOAc–EtOH. Yield 16%. Colorless solid, mp = 59.1–60.0 °C; R_f = 0.54 ($CHCl_3$–MeOH = 10 : 1). IR 3393, 2919, 1730, 1519, 1471, 1266, 1233, 1140, 1020, 814, 721 cm^{-1}; ^1H NMR (400 MHz) δ = 6.69–6.82 (m, 6 H), 4.21–4.35 (m, 4 H), 3.90–4.05 (m, 8 H), 3.43 (dd, *J* = 5, 6 Hz, 1 H), 2.77–2.90 (m, 4 H), 2.43 (t, *J* = 8 Hz, 2 H), 1.99–2.10 (m, 1 H), 1.73–1.90 (m, 9 H), 1.53 (br s, 2 H), 1.13–1.55 (m, 88 H), 0.88 (t, *J* = 7 Hz, 12 H); ^{13}C NMR (100 MHz) δ = 175.5, 173.0, 149.13, 149.10, 147.9, 147.8, 130.3, 129.9, 121.0, 114.7, 114.6, 114.0, 69.4, 69.3, 65.6, 65.2, 53.7, 34.6, 31.9, 30.5, 29.7, 29.53, 29.46, 29.36, 29.33, 26.1, 22.7, 14.1; MALDI-TOF MS (IAA) *m/z* 1205.5 (M+1, $C_{77}H_{137}NO_8$ requires 1205.0). Found: C, 76.99; H, 11.69; N, 1.18%. Calcd for $C_{77}H_{137}NO_8$: C, 76.75; H, 11.46; N, 1.16%.

Bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} L-glutamate (6d). Obtained in 61% yield from **5d**. The reaction was performed in CH_2Cl_2–EtOH–HCO_2H (25 : 5 : 1, wt/wt/wt) for 1.5 h instead of in benzene. Colorless solid, mp = 70.5–71.1 °C; R_f = 0.61 ($CHCl_3$–MeOH = 10 : 1). IR 3751, 2919, 2851, 1735, 1518, 1468, 1267, 1234, 1141, 1070, 1021, 808, 721 cm^{-1}; ^1H NMR (400 MHz) δ = 6.70–6.82 (m, 6 H), 4.19–4.30 (m, 4 H), 3.88–4.03 (m, 8 H), 3.43 (dd, *J* = 5, 6 Hz, 1 H), 2.76–2.92 (m, 4 H), 2.43 (t, *J* = 7 Hz, 2 H), 1.98–2.10 (m, 1 H), 1.73–1.82 (m, 9 H), 1.55 (br s, 2 H), 1.11–1.53 (m, 120 H), 0.88 (t, *J* = 7 Hz, 12 H); ^{13}C NMR (100 MHz) δ = 172.5, 172.4, 149.2, 149.1, 148.0, 147.8, 129.9, 129.3, 121.0, 114.6, 114.5, 113.9, 69.30, 69.26, 65.6, 64.9, 34.5, 34.3, 31.9, 29.9, 29.5, 29.4, 26.3, 26.1, 22.7, 14.1; MALDI-TOF MS (IAA) *m/z* 1430.0 (M+2, $C_{93}H_{169}NO_8$ requires 1430.3). Found: C, 75.82; H, 11.83; N, 1.19%. Calcd for $C_{93}H_{169}NO_8 \cdot 0.5CHCl_3$: C, 75.42; H, 11.47; N, 0.94%.

Bis{2-[3,4-bis(undecyloxy)phenyl]ethyl} DL-glutamate (DL-6b). Obtained in a yield of 80% by the same procedure for the preparation of **6b**. Spectroscopic data of DL-**6b** were identical to those of **6b**.

Bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} DL-glutamate (DL-6d). Yield 54%. The chemical structure of DL-**6d** was assigned by the comparison of the spectroscopic data of **6d**.

Representative procedure for the preparation of 1: bis{2-[3,4-bis-(undecyloxy)phenyl]ethyl} *N*-[N^{10}-(trifluoroacetyl)pteroyl]-L-glutamate (1b)

N^{10}-(Trifluoroacetyl)pteroic acid‡[15a] (0.67 g, 1.65 mmol) was charged in an oven-dried, 100 mL, two-necked, round-bottomed flask, equipped with a rubber septum and magnetic stirring bar and dried over P_2O_5 for 24 h at 40 °C. Then anhydrous DMF (5 mL) was added into the flask under an argon atmosphere. The resulting suspension was stirred at 40 °C until all the solid dissolved. To the dark red solution was slowly added dropwise triethylamine (0.27 mL, 1.98 mmol) and, subsequently, isobutyl chloroformate (0.24 mL, 1.82 mmol) at 0 °C. The mixture was protected from light and stirred at room temperature for 1 h before a solution of **6b** (1.89 g, 1.82 mmol) in THF (15 mL) was slowly added dropwise. The resulting mixture was stirred at 40 °C for 3 days, the solvent was removed *in vacuo*, and the residue was dissolved in $CHCl_3$–EtOH–benzene (15 : 1 : 1). The solution was then filtered through a pad of Celite to remove a trace of solid residue. The filtrate was concentrated *in vacuo* and purified by silica gel flash column chromatography (eluent: $CHCl_3$–EtOH–benzene = 13 : 1 : 1) to give **1b** as a mesomorphic yellow waxy solid in a yield of 40%. Phase transition temperature (DSC on heating): Cr −13 S 235 Iso. R_f = 0.40 (CH_2Cl_2–EtOH–benzene = 13 : 1 : 1). IR 2924, 2855, 1698, 1609, 1512, 1466, 1424, 1389, 1343, 1262, 1208, 1157, 1007, 857, 799, 721 cm^{-1}; ^1H NMR (400 MHz) δ = 8.81 (s, 1 H), 7.87 (d, *J* = 8 Hz, 2 H), 7.42 (d, *J* = 8 Hz, 2 H), 6.81–6.69 (m, 6 H), 5.16 (s, 2 H), 4.77–4.72 (m, 1 H), 4.36–4.21 (m, 4 H), 3.99–3.93 (m, 8 H), 2.88 (t, *J* = 7 Hz, 2 H), 2.83 (t, *J* = 7 Hz, 2 H), 2.47–2.35 (m, 2 H), 2.26–2.20 (m, 1 H), 2.11–2.04 (m, 1 H), 1.80–1.76 (m, 8 H), 1.43–1.24 (m, 64 H), 0.86 (t, *J* = 7 Hz, 12 H); ^{19}F NMR (282 MHz) δ = −67.4; MALDI-TOF MS (IAA) *m/z* 1427.7 (M+2, $C_{81}H_{122}F_3N_7O_{11}$ requires 1427.9). Found: C, 68.03; H, 8.58; N, 6.87%. Calcd for $C_{81}H_{122}F_3N_7O_{11}$: C, 68.18; H, 8.62; N, 6.87%.

Bis{2-[3,4-bis(hexyloxy)phenyl]ethyl} *N*-[N^{10}-(trifluoroacetyl)-pteroyl]-L-glutamate (1a). Yield 65%. Yellow mesomorphic solid. Phase transition temperature (DSC on heating): S 238 Iso. R_f = 0.58 ($CHCl_3$–MeOH = 6 : 1). IR 2932, 2860, 1717, 1699, 1517, 1508, 1261, 1212, 1162, 1017, 825, 802 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ = 11.5 (s, 1 H), 8.83 (d, *J* = 7 Hz, 1 H), 8.62 (s, 1 H), 7.87 (d, *J* = 8 Hz, 2 H), 7.63 (d, *J* = 8 Hz, 2 H), 6.59–6.91 (m, 6 H), 6.50–7.20 (br m, 2 H), 5.10 (s, 2 H), 4.39 (m, 1 H), 4.14 (t, *J* = 7 Hz, 2 H), 4.17–4.28 (m, 2 H), 3.75–3.98 (m, 8 H), 2.71–2.82 (m, 4 H), 2.36 (t, *J* = 7 Hz, 2 H), 1.83–2.08 (m, 2 H), 1.54–1.70 (m, 8 H), 1.17–1.50 (m, 24 H), 0.84 (t, *J* = 5 Hz, 12 H); ^{19}F NMR (282 MHz) δ = −67.4; MALDI-TOF MS (IAA) *m/z* 1146.0 (M, $C_{61}H_{82}F_3N_7O_{11}$ requires 1145.6). Found: C, 63.69; H, 7.34; N, 8.55%. Calcd for $C_{61}H_{82}F_3N_7O_{11}$: C, 63.91; H, 7.21; N, 8.55%.

Bis{2-[3,4-bis(tetradecyloxy)phenyl]ethyl} *N*-[N^{10}-(trifluoroacetyl)-pteroyl]-L-glutamate (1c). Yield 42%. Yellow waxy solid. Phase transition temperature (DSC on heating): D_{ho} 36 D_{hd} 226 N_C 232 Iso. R_f = 0.59 ($CHCl_3$–MeOH = 6 : 1). IR 3421, 2922, 2853, 1734, 1717, 1700, 1534, 1517, 1508, 1457, 1264, 1212, 1161, 854, 802 cm^{-1}; ^1H NMR (400 MHz) δ = 8.81 (s, 1 H), 7.77–7.92 (m, 2 H), 7.32–7.50 (m, 2 H), 6.60–6.75 (m, 6 H), 5.17 (s, 2 H), 4.69–4.78 (m, 1 H), 4.17–4.45 (m, 4 H), 3.88–4.02 (m, 8 H), 2.88 (t, *J* = 7 Hz, 2 H), 2.83 (t, *J* = 6 Hz, 2 H), 2.27–2.55 (m, 2 H), 2.02–2.18 (m, 1 H), 2.20–2.31 (m, 1 H), 1.69–1.80 (m, 8 H), 0.97–1.46 (m, 88 H), 0.87 (t, *J* = 6 Hz, 12 H); ^{19}F NMR (282 MHz) δ = −67.5; MALDI-TOF MS (IAA) *m/z* 1595.1 (M+1, $C_{93}H_{82}F_3N_7O_{11}$ requires 1595.1). Found: C, 70.01; H, 9.39; N, 6.16%. Calcd for $C_{93}H_{146}F_3N_7O_{11}$: C, 70.02; H, 9.23; N, 6.15%.

Bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} *N*-[N^{10}-(trifluoroacetyl)-pteroyl]-L-glutamate (1d). Yield 29%. Yellow waxy solid. Phase transition temperature (DSC on heating): D_{ho} 62 D_{hd} 207 N_C 223 Iso. R_f = 0.62 ($CHCl_3$–MeOH = 6 : 1). IR 2919, 2851, 1718, 1701, 1541, 1508, 1265, 1212, 1161, 852, 802 cm^{-1}; ^1H NMR (400 MHz) δ = 8.81 (s, 1 H), 7.88 (d, *J* = 8 Hz, 2 H), 7.43 (d, *J* = 8 Hz, 2 H), 6.60–6.79 (m, 6 H), 5.17 (s, 2 H), 4.69–4.78 (m, 1 H), 4.13–4.23 (m, 4 H), 3.38–4.08 (m, 8 H), 2.75–2.95 (m, 4 H), 2.30–2.52 (m, 2 H), 2.17–2.33 (m, 1 H), 1.99–2.11 (m, 1 H), 1.67–1.82 (m, 8 H), 0.95–1.52 (m, 120 H), 0.86 (t, *J* = 7 Hz, 12 H); ^{19}F NMR (282 MHz) δ = −67.4; MALDI-TOF MS (IAA) *m/z* 1820.9 (M+2, $C_{109}H_{178}F_3N_7O_{11}$ requires 1820.4). Found: C, 69.67; H, 9.67; N, 5.25%. Calcd for $C_{109}H_{178}F_3N_7O_{11} \cdot 0.5CHCl_3$: C, 69.98; H, 9.57; N, 5.22%.

Bis{2-[3,4-bis(undecyloxy)phenyl]ethyl} *N*-[N^{10}-(trifluoroacetyl)-pteroyl]-DL-glutamate (DL-1b). Compound DL-**1b** was obtained in a yield of 24% by the same procedure as for the preparation of **1b** as a yellow waxy solid. Phase transition temperatures (DSC on heating): Cr −5 S 235 Iso. Spectroscopic data of DL-**1b** were consistent with **1b**.

Bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} *N*-[N^{10}-(trifluoroacetyl)-pteroyl]-DL-glutamate (DL-1d). Preparation of DL-**1d** was carried

out by the same procedure as for the synthesis of **1d**. Yield 49%. Yellow waxy solid. Phase transition temperatures (DSC on heating): D_{ho} 63 D_{hd} 207 N_C 225 Iso. Assignment of the structure of DL-**1d** was carried out by comparison of the spectroscopic data with those of **1d**.

Synthesis of bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} *N*-benzyloxycarbonyl-L-aspartate (9)

Compound **9** was prepared by a similar procedure to that for the preparation of **5** as a colorless solid in a yield of 94%. Mp 88.5–88.8 °C. R_f = 0.47 (hexane–EtOAc = 5 : 1). IR 3321, 2956, 2918, 2850, 1726, 1685, 1541, 1521, 1469, 1294, 1264, 1234, 1159, 1141, 999, 721 cm^{-1}; ^1H NMR (400 MHz) δ = 7.23–7.48 (m, 5 H), 6.62–6.80 (m, 6 H), 5.71 (d, J = 8 Hz, 1 H), 5.12 (s, 2 H), 4.57–4.64 (m, 1 H), 4.30 (t, J = 7. Hz, 2 H), 4.21 (t, J = 7. Hz, 2 H), 3.92–4.02 (m, 8 H), 2.95–3.07 (m, 1 H), 2.75–2.90 (m, 5 H), 1.71–1.87 (m, 8 H), 1.02–1.55 (m, 120 H), 0.88 (t, J = 7 Hz, 12 H); ^{13}C NMR (100 MHz) δ = 170.6, 170.5, 155.9, 149.2, 148.0, 147.9, 136.1, 129.9, 129.8, 128.5, 128.2, 128.0, 121.03, 121.00, 114.7, 114.6, 114.1, 69.34, 69.27, 67.1, 66.4, 65.7, 50.4, 36.6, 34.5, 31.9, 29.5, 29.38, 29.36, 26.07, 26.06, 22.7, 14.1; MALDI-TOF MS (IAA) *m*/*z* 1572.5 ($M+1+Na^+$, $C_{100}H_{173}NO_{10}$ requires 1572.3). Found: C, 77.70; H, 11.47%. Calcd for $C_{100}H_{173}NO_{10}$: C, 77.52; H, 11.25%.

Preparation of bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl}-L-aspartate (10)

Preparation of **10** was carried out by the procedure for the preparation of **6**. Yield 38%. Pale yellow solid, mp = 68.2–68.7 °C. R_f = 0.66 (CH_2Cl_2–MeOH = 10 : 1). IR 3446, 2918, 2850, 1733, 1520, 1471, 1267, 1235, 1140, 1070, 1022, 805, 721 cm^{-1}; ^1H NMR (400 MHz) δ = 6.71–6.90 (m, 6 H), 4.18–4.21 (m, 4 H), 3.93–4.07 (m, 8 H), 3.77 (dd, J = 7, 5 Hz, 1 H), 2.81–2.93 (m, 4 H), 2.77 (dd, J = 16, 5 Hz, 1 H), 2.67 (dd, J = 16, 7 Hz, 1 H), 1.79–1.93 (m, 8 H), 1.12–1.60 (m, 120 H), 0.88 (t, J = 7 Hz, 12 H); ^{13}C NMR (100 MHz) δ = 174.0, 171.1, 149.10, 149.09, 147.87, 147.86, 130.0, 129.9, 121.0, 114.6, 114.5, 113.9, 69.3, 69.2, 65.9, 65.5, 51.1, 38.9, 38.8, 4.5, 31.9, 29.7, 29.6, 29.45, 29.36, 29.32, 26.0, 22.7, 14.1. MALDI-TOF MS (IAA) *m*/*z* 1438.3 ($M+1+Na^+$, $C_{92}H_{167}NO_8$ requires 1438.3). Found: C, 77.82; H, 11.77%. Calcd for $C_{92}H_{167}NO_8$: C, 78.07; H, 11.89%.

Bis{2-[3,4-bis(octadecyloxy)phenyl]ethyl} *N*-[N^{10}-(trifluoroacetyl)pteroyl]-L-aspartate (11)

Yield 36%. Pale yellow waxy solid. Phase transition temperature (DSC on heating): D_{ho} 64 D_{hd} 193 N_C 223 Iso. R_f = 0.38 ($CHCl_3$–EtOH = 10 : 1). IR 3421, 2920, 2851, 1733, 1699, 1608, 1516, 1508, 1469, 1264, 1212, 1161, 1072, 721 cm^{-1}; ^1H NMR (400 MHz) δ = 8.34 (s, 1 H), 7.76–7.90 (m, 2 H), 7.36–7.49 (m, 2 H), 6.62–6.86 (m, 6 H), 5.09–5.26 (m, 2 H), 4.94–5.07 (m, 1 H), 4.32–4.42 (m, 2 H), 4.20–4.28 (m, 2 H), 3.89–4.02 (m, 8 H), 3.03–3.12 (m, 1 H), 2.72–3.00 (m, 5 H), 1.65–1.88 (m, 8 H), 0.99–1.51 (m, 120 H), 0.87 (t, J = 7 Hz, 12 H); ^{19}F NMR (282 MHz) δ = −67.5; MALDI-TOF MS (IAA) *m*/*z* 1828.2 ($M+1+Na^+$, $C_{108}H_{176}N_7O_{11}$ requires 1828.3). Found: C, 69.93; H, 9.69; N, 5.14%. Calcd for $C_{108}H_{176}F_3N_7O_{11}\cdot 0.5CHCl_3$: C, 69.86; H, 9.54; N, 5.26%.

AFM measurements of folic acid derivatives on a Si surface

AFM measurements were performed with a commercial atomic force microscope (Digital Instrument Inc., Santa Barbara, CA, Nanoscope IIIa) equipped with a cantilever (NCH-10-T) at room temperature in air. The thin films of **1** were prepared as follows: compound **1** was spin-coated (4000 rpm, 30 s) on a silicon substrate by droplet addition of a solution of **1** in chloroform at a concentration of approximately 1 mg mL^{-1}. After evaporation of the solvent in air, the thin layer of **1** on the substrate was momentarily exposed to a flame to melt. The resulting sample was annealed on a hot stage at 140 °C for 4 h, and then cooled to room temperature overnight under a nitrogen atmosphere.

Infrared measurements for hydrogen-bonded assemblies

The samples for the measurements were prepared as follows: the samples of **1** were sandwiched between two thin pellets of KBr at 140 °C, and the sample was heated to 250 °C followed by cooling to room temperature. The formation of smectic or discotic phases was checked by using a polarizing microscope. Characterization of the hydrogen-bonded patterns of **1** was carried out using a JASCO FT/IR-8900μ equipped with a MICRO-20 microsampling FTIR spectrometer at room temperature.

Complexation of alkali metal salts with folic acid derivatives

All alkali metal salts mixtures of **1** were prepared by slow evaporation from a THF solution containing the requisite amounts of lithium, sodium, or potassium triflate with folic acid derivatives **1** followed by drying overnight *in vacuo*.

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References

1 (*a*) *Molecular Self-Assembly, Organic Versus Inorganic Approaches*, ed. M. Fujita, Springer, Berlin, 2000, *Structure & Bonding*, Vol. 96; (*b*) *Supramolecular Polymers*, ed. A. Ciferri, Marcel Dekker, New York, 2000; (*c*) T. Kato and J. M. J. Fréchet, *Macromol. Symp.*, 1995, **98**, 311; (*d*) R. P. Sijbesma and E. W. Meijer, *Curr. Opin. Colloid Interface Sci.*, 1999, **4**, 24; (*e*) N. Zimmerman, J. S. Moore and S. C. Zimmerman, *Chem. Ind.*, 1998, 604.

2 J.-H. Fuhrhop and J. Köning, *Membranes and Molecular Assembles: The Synkinetic Approach*, The Royal Society of Chemistry, Cambridge, 1994.

3 G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford, 1997.

4 *Handbook of Liquid Crystals*, eds. D. Demus, J. W. Goodby, G. W. Gray, H.-W. Spiess and V. Vill, Wiley-VCH, Weinheim, 1998.

5 (*a*) T. Kato, *Struct. Bonding*, 2000, **96**, 95; (*b*) T. Kato and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1989, **111**, 8533; (*c*) T. Kato, H. Kihara, U. Kumar, T. Uryu and J. M. J. Fréchet, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1644; (*d*) H. Kihara, T. Kato, T. Uryu and J. M. J. Fréchet, *Chem. Mater.*, 1996, **8**, 961; (*e*) T. Kato, *Handbook of Liquid Crystals*, ed. D. Demus, J. W. Goodby, G. W. Gray, H.-W. Spiess and V. Vill, Wiley-VCH, Weinheim, 1998, Vol. 2B, pp. 969; (*f*) C. M. Paleos and D. Tsiourvas, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1696; (*g*) C. T. Imrie, *Trends Polym. Sci.*, 1995, **3**, 22.

6 (*a*) R. Auzély-Velty, T. Benvegnu, D. Plusquellec, G. Mackenzie, J. A. Haley and J. W. Goodby, *Angew. Chem., Int. Ed.*, 1998, **37**, 2511; (*b*) D. J. Price, K. Willis, T. Richardson, G. Unger and D. W. Bruce, *J. Mater. Chem.*, 1997, **7**, 883; (*c*) F. Hentrich, S. Diele and C. Tschierske, *Liq. Cryst.*, 1994, **17**, 827.

7 (*a*) R. Kleppinger, C. P. Lillya and C. Yang, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1637; (*b*) M. Suárez, J.-M. Lehn, S. C. Zimmerman, A. Skoulios and B. Heinrich, *J. Am. Chem. Soc.*, 1998, **120**, 9526; (*c*) A. Kraft, A. Reichert and R. Kleppinger, *Chem. Commun.*, 2000, 1015; (*d*) D. Goldmann, R. Dietel, D. Janietz, C. Schmidt and J. H. Wendorff, *Liq. Cryst.*, 1998, **24**, 407; (*e*) J.-M. Lehn, *Makromol. Chem., Macromol. Symp.*, 1993, **69**, 1; (*f*) A. R. A. Palmans, J. A. J. M. Vekemans, H. Fischer, R. A. Hikmet and E. W. Meijer, *Chem. Eur. J.*, 1997, **3**, 300.

8 (*a*) K. G. Rothberg, Y. Ying, J. F. Kolhouse, B. A. Kamen and

R. G. W. Anderson, *J. Cell Biol.*, 1990, **110**, 637; (*b*) C. P. Leamon, I. Pastan and P. S. Low, *J. Biol. Chem.*, 1993, **268**, 24847.
9 F. Ciuchi, G. D. Nicola, H. Franz, G. Gottarelli, P. Mariani, M. G. P. Bossi and G. P. Spada, *J. Am. Chem. Soc.*, 1994, **116**, 7064.
10 Hydrogen-bonded ribbon-like aggregations of guanine bases are reported, see: (*a*) G. Gottarelli, S. Masiero, E. Mezzina, S. Pieraccini, J. P. Rabe, P. Samorí and G. P. Spada, *Chem. Eur. J.*, 2000, **6**, 3242; (*b*) K. Araki, M. Abe, A. Ishizaki and T. Ohya, *Chem. Lett.*, 1995, 359; (*c*) G. Gottarelli, S. Masiero, E. Mezzina, G. P. Spada, P. Mariani and M. Recanatini, *Helv. Chim. Acta*, 1998, **81**, 2078; (*d*) G. Gottarelli, S. Masiero, E. Mezzina, S. Pieraccini, G. P. Spada and P. Mariani, *Liq. Cryst.*, 1999, **26**, 965.
11 For disk-like aggregation, see: J. L. Sessler, M. Sathiosatham, K. Doerr, V. Lynch and K. A. Abboud, *Angew. Chem., Int. Ed.*, 2000, **39**, 1300.
12 Preliminary communication: K. Kanie, T. Yasuda, S. Ujiie and T. Kato, *Chem. Commun.*, 2000, 1899.
13 S. Wang, R. J. Lee, C. J. Mathias, M. A. Green and P. S. Low, *Bioconjugate Chem.*, 1996, **7**, 56.
14 A. Rosowsky and C.-S. Yu, *Pteridines*, 1998, **1**, 143.
15 (*a*) H. A. Godwin, I. H. Rosenberg, C. R. Ferenz, P. M. Jacobs and J. Meienhofer, *J. Biol. Chem.*, 1972, **247**, 2266; (*b*) J. Luo, M. D. Smith, D. A. Lantrip, S. Wang and P. L. Fuchs, *J. Am. Chem. Soc.*, 1997, **119**, 10004; (*c*) M. Nomura, S. Shuto and A. Matsuda, *J. Org. Chem.*, 2000, **65**, 5016; (*d*) G. Steinberg and R. F. Borch, *J. Med. Chem.*, 2001, **44**, 69.
16 L. T. Plante, E. J. Crawford and M. Friedkin, *J. Biol. Chem.*, 1967, **242**, 1466.
17 B. ElAmin, G. M. Anantharamaiah, G. P. Royer and G. E. Means, *J. Org. Chem.*, 1979, **44**, 3442.
18 G. W. Gray and J. W. Goodby, *Smectic Liquid Crystals*, Leonard Hill, Glasgow, 1984.
19 (*a*) B. P. Hoag and D. L. Gin, *Adv. Mater.*, 1998, **10**, 1546; (*b*) A. R. A. Palmans, J. A. J. M. Vekemans, R. A. Hikmet, H. Fischer and E. W. Meijer, *Adv. Mater.*, 1998, **10**, 873; (*c*) H. Ringsdorf, R. Wüstefeld, E. Zerta, M. Ebert and J. H. Wendorff, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 914.
20 (*a*) G. Johannson, V. Percec, G. Ungar and J. P. Zhou, *Macromolecules*, 1996, **29**, 646; (*b*) M. A. Reppy, D. H. Gray, B. A. Pindzola, J. L. Smithers and D. L. Gin, *J. Am. Chem. Soc.*, 2001, **123**, 363.
21 (*a*) H.-A. Klok, K. A. Jolliffe, C. L. Schauer, L. J. Prins, J. P. Spatz, M. Möller, P. Timmerman and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1999, **121**, 7154; (*b*) M. Sano, A. Kamino and S. Shinkai, *Langmuir*, 1999, **15**, 13; (*c*) T. Shimizu, S. Ohnishi and M. Kogiso, *Angew. Chem., Int. Ed.*, 1998, **37**, 3260.
22 (*a*) H. Fischer, T. Plesnivy, H. Ringsdorf and M. Seitz, *J. Mater. Chem.*, 1998, **8**, 343; (*b*) A. Liebmann, C. Mertesdorf, T. Plesnvy, H. Ringsdorf and J. H. Wendorff, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1375; (*c*) V. Percec, G. Johansson, G. Ungar and J. Zhou, *J. Am. Chem. Soc.*, 1996, **118**, 9855; (*d*) V. Percec, D. Tomazos, J. Heck, H. Blackwell and G. Ungar, *J. Chem. Soc., Perkin Trans. 2*, 1994, 31; (*e*) M. Lee and N.-K. Oh, *J. Mater. Chem.*, 1996, **6**, 1079; (*f*) M. Lee, N.-K. Oh, H. K. Lee and W.-C. Zin, *Macromolecules*, 1996, **29**, 5567; (*g*) C. Tschierske, *J. Mater. Chem.*, 1998, **8**, 1485; (*h*) J. A. Schröter, C. Tschierske, M. Wittenberg and J. H. Wendorff, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1119; (*i*) J. W. Goodby, G. H. Mehl, I. M. Saez, R. P. Tuffin, G. Mackenzie, R. Auzély-Velty, T. Benvegnu and D. Plusquellec, *Chem. Commun.*, 1998, 2057.
23 (*a*) G. Gottarelli, S. Masiero and G. P. Spada, *J. Chem. Soc., Chem. Commun.*, 1995, 2555; (*b*) S. C. Forman, J. C. Fettinger, S. Pieraccini, G. Gottarelli and J. T. Davis, *J. Am. Chem. Soc.*, 2000, **122**, 4060; (*c*) S. Tirumala and J. T. Davis, *J. Am. Chem. Soc.*, 1997, **119**, 2769; (*d*) V. Andrisano, G. Gottarelli, S. Masiero, E. H. Heijne, S. Pieraccini and G. P. Spada, *Angew. Chem., Int. Ed.*, 1999, **38**, 2386.
24 F. W. Kotch, J. C. Fettinger and J. T. Davis, *Org. Lett.*, 2000, **2**, 3277.