

Thermotropic liquid-crystalline folic acid derivatives: supramolecular discotic and smectic aggregation†

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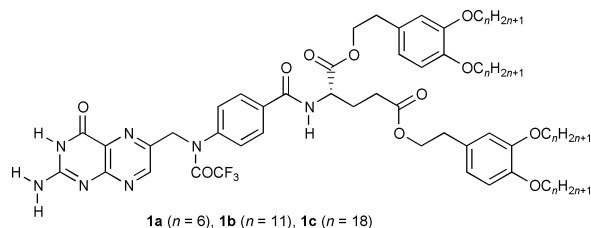
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Thermotropic discotic and smectic liquid crystallinity can be induced for folic acid derivatives having octadecyl and undecyl substituents in wide temperatures ranges, respectively; the addition of sodium triflate to smectic liquid-crystalline folic acid leads to a change of the assembled structures from smectic to columnar phases.

Nanoscale molecular architectures formed by non-covalent interactions have been intensively studied because highly functional molecular materials can be obtained by self-organization processes.^{1–4} For liquid-crystalline (LC) materials, the utilization of the molecular interactions such as hydrogen bonding has been shown to be quite useful.⁴ The control of the patterns and the reversible self-assembling nature of hydrogen-bonded liquid crystals would lead to the preparation of a novel dynamically functional material. Our intention is to use self-organization behavior of biomolecules, which in many cases show lyotropic behavior, for the formation of new thermotropic LC materials.

In the present study, we have focused on the pterin ring of folic acid. Thermotropic LC folic acids have not yet been developed although the lyotropic mesomorphism through discotic tetramer formation of sodium folate in aqueous solution has been reported.⁵ The induction of the thermotropic liquid crystallinity of this molecule may lead to the development of dynamically functional anisotropic systems.

We succeeded in inducing thermotropic liquid crystallinity for folic acid derivatives **1a–c** by incorporating 2-(3,4-dialkyl-



oxyphenyl)ethyl groups into the glutamic acid moiety. Compound **1c** exhibited columnar mesophases, while smectic phases were seen for compounds **1a** and **1b** containing shorter alkyl chains.† The phase transition behavior of **1a–c** is summarized in Table 1.‡

X-Ray diffraction measurements showed that **1c** exhibited ordered and disordered discotic hexagonal columnar (D_{ho} and D_{hd}) phases (D_{ho} phase at 25 °C: $d_{100} = 50.5$, $d_{110} = 29.2$, $d_{200} = 25.3$, and the distance between disks = 4.1 Å; D_{hd} phase at 100 °C: $d_{100} = 50.6$, $d_{110} = 29.2$, and $d_{200} = 25.3$ Å). Only one sharp peak (small angle) and a broad halo were observed for the smectic phases of **1a** and **1b**. The layer spacings for **1a** and **1b** were 37.6 and 41.2 Å at 25 °C, respectively. It is noteworthy that the phase behavior of **1** was greatly dependent on the length of the alkyl chains. The textures observed for these compounds

Table 1 Phase transition temperatures of **1a**

Compound	Phase transition temp./°C						
1a ($n = 6$)			S	238	Iso		
1b ($n = 11$)		Cr	–13	S	240	Iso	
1c ($n = 18$)	D_{ho}	62	D_{hd}	207	M	223	Iso

† Cr: crystalline; S: smectic; D_{ho} : ordered discotic hexagonal columnar; D_{hd} : disordered discotic hexagonal columnar; M: mesomorphic with low viscosity; Iso: isotropic.

supported the difference of the phase structures.⁶ The formation of the smectic and discotic phases can be attributed to the ribbon- and disk-like aggregation of pterin rings of **1**, respectively, as shown in Fig. 1.^{7,8} The IR spectra of **1b** and **1c** also indicated the existence of the two types of the hydrogen-bonded structures.¶ The layer structure for **1a** and **1b** should be induced by the ribbon-like aggregation of the pterin ring (Fig. 1A).⁷ In contrast, the induction of the discotic hexagonal columnar phase of **1c** was based on the disk-like aggregation of the pterin ring of **1c** (Fig. 1B).⁸ For **1c**, the disordered alkyl chains can be closely packed in the discotic arrangement. The difference of these aggregated structures was due to the dynamic nature of the hydrogen bonding.

The formation of columnar molecular assemblies has been a recent topic for the development of functional materials.^{9,10} We were able to change the LC phase of **1b** from smectic to columnar by the addition of sodium triflate (NaOTf). The isotropization temperatures and the mesomorphic temperature

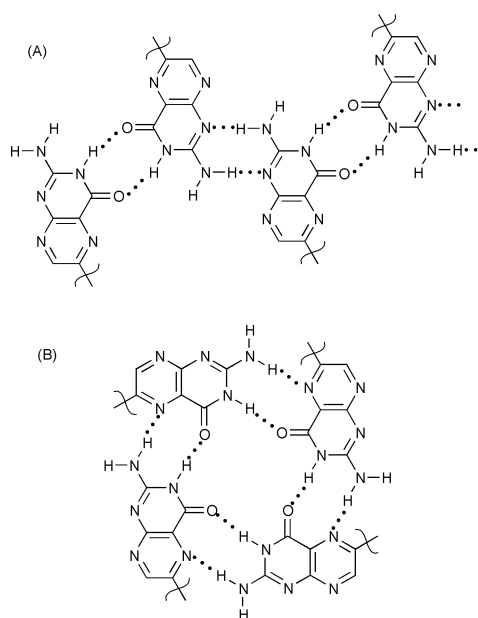


Fig. 1 Hydrogen-bonded self-assembled structures of the pterin rings of folic acid. (A) Linear ribbon-like aggregation style, (B) cyclic disk-like aggregation style.

† Electronic supplementary information (ESI) available: synthesis details and IR data. See <http://www.rsc.org/suppdata/cc/b0/b0048151/>

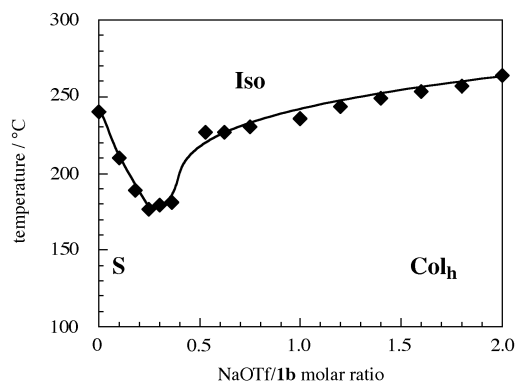


Fig. 2 Isotropization temperatures of the complexes of NaOTf and **1b**.

ranges of the resulting mixtures of **1b** and NaOTf on heating are summarized in Fig. 2.

The temperatures decrease drastically with the increase of the molar ratio of NaOTf to **1b** from 0 to 0.3. Further addition of NaOTf results in the increase of the clearing points. Fan-like textures characteristic of a hexagonal columnar phase (Col_h) were observed for the mixtures in the ratio of NaOTf to **1b** from 0.5 to 2.0. The addition of more than 2.5 mol of NaOTf led to the phase separation of the sodium salt from the mixture. The X-ray diffraction pattern of an equimolar complex of NaOTf and **1b** at 200 °C showed a sharp inner peak at 45.2 Å (d_{100}), small peaks at 26.0 and 22.6 Å (d_{110} and d_{200} , respectively), and a diffuse halo at 4.1 Å, which confirmed the formation of a disordered Col_h phase.

This phase transition behavior of the complexes can be explained as follows. The initial decrease of the temperatures was caused by the co-existence of hydrogen-bonded forms A and B (Fig. 1) in the smectic order. Further addition of NaOTf resulted in the formation of discotic aggregates leading to the induction of a hexagonal columnar order by ion–dipole interaction through sodium salts and the carbonyl oxygen of the pterin rings. These aggregates were further stabilized by the increase of the ion–dipole interactions. The formation of columnar phases by the complexation of covalently bonded cyclic molecules with metal salts has been reported.¹¹ However, to our knowledge, there has been no example of liquid crystals changing from smectic to columnar phases due to the change of hydrogen-bonding patterns by the effect of metals.

In summary, we have prepared, for the first time, thermotropic LC folic acid derivatives. In particular, for compound **1b**, the smectic phase can be changed to hexagonal columnar phases by the ion–dipole interactions. We are further exploring nanostructures formed by hydrogen-bonded aggregation of folic acid derivatives.

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Notes and references

‡ Compound **1b** was prepared by amidation¹² of *N*¹⁰-trifluoroacetylpteronic acid with bis[2-(3,4-diundecyloxyphenyl)ethyl] L-glutamate (**2b**) resulting

in a yield of 40% as a pale yellow waxy oil. $R_f = 0.40$ (CH_2Cl_2 /ethanol/benzene = 13/1/1); ¹H NMR (400 MHz, $CDCl_3$) 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); Maldi-TOF MAS (matrix, IAA): m/z 1427.65. Experimental details for the preparation of **2b** as well as **1b** are summarized in the ESI.†

§ A differential scanning calorimetric apparatus (Mettler DSC 30) and a polarizing microscope (Olympus BH2) equipped with a Mettler FP82HT hot stage were used for characterization of **1**. X-Ray diffraction measurements were carried out on a Rigaku X-ray Rad 2B system with a heating stage using Ni-filtered $Cu-K\alpha$ radiation. IR spectra were recorded on a JASCO FT/IR-8900 μ at room temperature using a thin pellet of KBr as the substrate.

¶ Similar patterns were observed for the N–H stretching band of **1a** and **1b** in IR spectra (3351 and 3341 cm^{-1} , respectively), whereas the peaks were split to 3304 and 3251 cm^{-1} for **1c**. See ESI† for the IR spectra.

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