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Paramagnetic Nitroxide Radical Liquid Crystalline Compounds with Methyl di(ethylene glycol) Chain

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We have synthesized a racemic and enantiomerically enriched all-organic paramagnetic nitroxide radical (NR) liquid crystalline (LC) compound, which contains a chiral NR unit in the mesogen core and a methyl di(ethylene glycol) chain as one of their terminal units. This new compound showed remarkable substituent effects of di(ethylene glycol) chain on the phase transition behavior and hydrophilic property in contrast to structural analogs of the previous reported NR-LC compounds containing alkoxy chains.

Keywords: paramagnetic chiral liquid crystals; nitroxide radicals; molecular design; di(ethylene glycol) chain; optical resolution; nematic phase; chiral nematic phase

Introduction

Recently, molecular magnetic materials have attracted a great deal of attention. In contrast to inorganic solid-state materials including transition metals (Fe, Co, Ni, etc.) and/or lanthanides, their magnetic properties are fine-tunable, and some desired functions such as chirality and anisotropy can be added by molecular modification. The spin source of molecular magnetic materials is organic radical species and/or metal complexes. Since organic radicals are chemically unstable for functional materials because of their high reactivity, a protection of the radical moiety by means of bulky substituents is needed to stabilize them. Thus, the bulkiness derived from the steric protection causes low spin density in organic radical materials, and therefore, their intermolecular magnetic interactions are relatively weaker than those in metal complex materials. However, since the organic radical materials are metal-free, they have greater potential as biocompatible magnetic soft materials than the metal complex materials [1], and also, they are more favorable from the point of view of the element strategy [2], [3].

As one of the metal-free magnetic soft materials, nitroxide radical (NR) liquid crystalline (LC) compound **1** containing a five-membered ring NR moiety in the mesogen core has been reported [4], [5]. This compound exhibits some fascinating properties in the externally applied magnetic field [6]. For example, their molecular reorientation occurs in a uniform magnetic field [7], [8] and the motion of magnetic LC droplet occurs in a magnetic-field gradient [9]. In addition, the

increase of magnetic susceptibility at a crystalline (Cr)-to-LC phase transition of compound **1** has been observed (magneto-LC effects) [10]. The magneto-LC effects depend on the molecular structures and the type of LC phases or superstructures; enantiomerically enriched NR-LC compounds show chiral LC phases and stronger magneto-LC effects than the corresponding racemates, a highly ordering chiral smectic A phase shows stronger magneto-LC effects than the chiral nematic phase of the same compound [11], and hydrogen-bonded all-organic NR-LC compounds show twice as strong magneto-LC effects as compound **1** [12]. Moreover, some other desired functions can be added to NR-LC materials easily by molecular modification. As one of the functions, ferroelectricity can be added to enantiomerically enriched NR-LC compounds by introducing long side chains so that they exhibit chiral smectic C phases, and by surface-stabilizing [13].

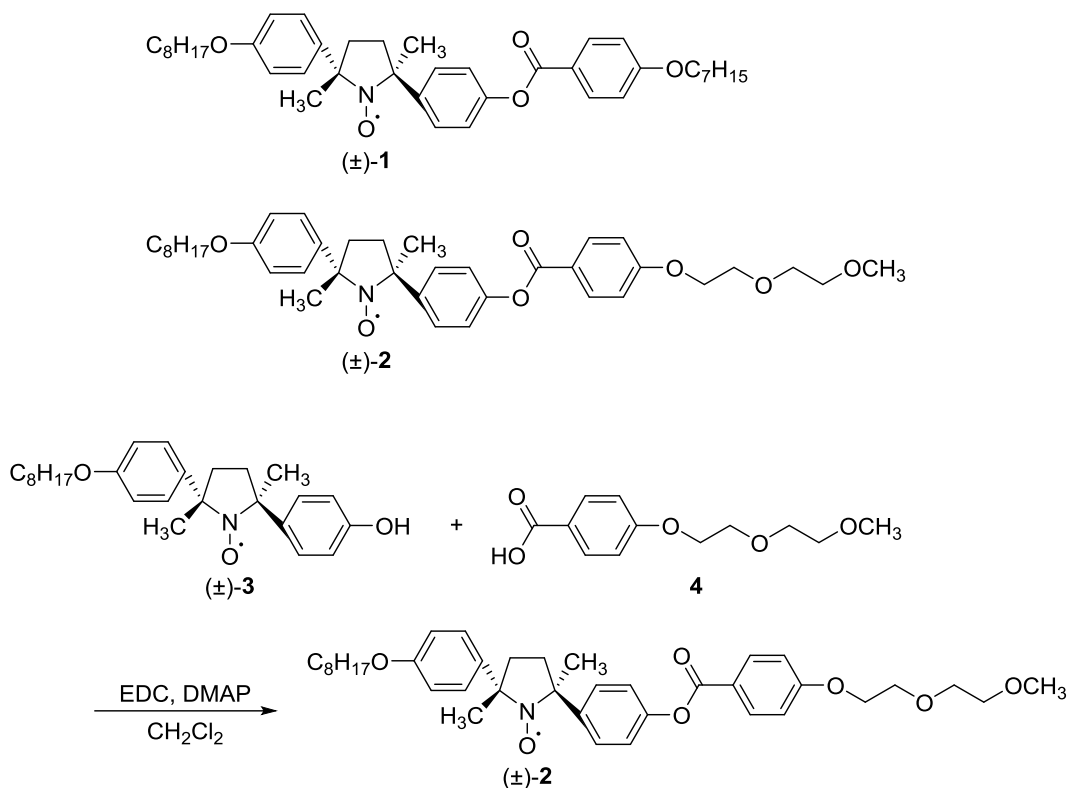
We focused not on the length of the side chains of NR-LC compounds but on the type of side chains to develop new functional NR-LC materials. As new functional side chain for NR-LC compounds, nonionic hydrophilic oligo(ethylene glycol) chain is worthy of remark. The previously reported NR-LC compounds are more or less hydrophobic due to their aromatic rings and alkyl side chains. Thus, a novel amphiphilic NR-LC compounds could be synthesized by replacing an alkyl side chain with an oligo(ethylene glycol) chain. They could be expected to easily form a microphase-separated superstructure because of their amphiphilic molecular

structure, which has many potential applications for functional magnetic soft materials. For example, paramagnetic micelles or vesicles made of amphiphilic NR-LC compounds, which involve specific chemical species, work as material transporters controlled by a magnetic field [14]. Use of amphiphilic NR-LC compounds for electrolytes leads to the possibility of anisotropic lithium ion transporting due to a microphase-separated superstructure usable for magnetic-field-switching batteries because their molecular alignment is controllable by low magnetic field [8], [15], [16]. Moreover, microphase-separated superstructure of amphiphilic NR-LC compounds which could provide ion, electron and/or spin transportable pathways holds great promise for electronics and spintronics [17]–[19].

Here, we report the synthesis of the first example of NR-LC compounds with a methyl di(ethylene glycol) chain. This work focuses in the relationship between the type of side chains and the stability of LC phases. Moreover, optical resolution of the synthesized compound was demonstrated by using high performance liquid chromatography (HPLC) with a chiral column.

Experimental

Unless otherwise noted, solvents and reagents were reagent grade and used without further purification. Tetrahydrofuran (THF) that was used for electron paramagnetic resonance (EPR) spectroscopy and Grignard reactions was distilled from sodium/benzophenone ketyl under nitrogen. Phase transition behaviors were determined by differential scanning calorimetry (DSC) (SHIMADZU DSC-60) and polarized optical microscopy (Olympus BX51). A hot stage (Japan High Tech, 10083) was used as the temperature control unit for the microscopy. Enantiomeric excess (ee) were determined by HPLC analysis using a chiral stationary phase column (DAICEL CHIRALCEL OD-H, 4.6 mm × 250 mm, particle size 5 μm), a mixture of hexane and 2-propanol (9:1) as the mobile phase at a flow rate of 1 mL/min, and a UV detector (254 nm). IR spectra were recorded with SHIMADZU IRAffinity-1. EPR spectra were recorded with a JEOL JES-FA200. Magnetization was recorded with QUANTUN DESIGN MPMS-3. For variable temperature X-ray diffraction measurement, the data collections were performed on a Philips X'Pert-MPD diffractometer using Cu-K α radiation with 1.5418 Å. Circular dichroism (CD) spectra were measured with a JASCO J-820.

General Synthetic Procedure of Compounds (±)-2 (Scheme 1)**Scheme 1** Molecular structures of (±)-1 and (±)-2, and synthesis of (±)-2.

Compound (±)-3 was prepared according to the previously reported procedure [20]. Dichloromethane (50 mL) was charged with the phenol **3** (0.3 mmol), the benzoic acid **4** [21] (0.33 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl, 0.33 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.09 mmol). After the mixture was stirred for 12 h at room temperature, reaction solution was added saturated aqueous NaHCO₃ (50 mL), and extracted with diethyl ether (50 mL × 2). The extract was dried over MgSO₄ and evaporated. The residue was purified by flash column chromatography (silica gel, dichloromethane/ether = 9/1) and recrystallization (hexane/ethanol) to afford the ester (±)-2 as yellow crystals (yield 60% from

3).

(±)-**2**: EPR (THF): $g = 2.0059$, $a_N = 1.34$ mT; IR (KBr) ν 2929, 1730, 1607, 1510, 1458, 1171, 1050, 764 cm^{-1} ; HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{38}\text{H}_{50}\text{NO}_7$, 632.3587; found, 632.3588; analysis (calcd., found for $\text{C}_{38}\text{H}_{50}\text{NO}_7$): C (72.12, 72.43), H (7.96, 8.30), N (2.21, 2.18).

Optical Resolution of Compound 2

The racemate of **2** is separated by using HPLC with a chiral column (DAICEL CHIRALCEL OD-H, 20 mm \times 250 mm, particle size 5 μm) and hexane/2-propanol (8:2) as a mobile phase. The separated eluent was evaporated to obtain (2*S*,5*S*) and (2*R*,5*R*) enantiomers as 98.9% ee and 98.3% ee, respectively. The absolute configuration of each enantiomer was determined by circular dichroism (CD) spectra.

Results and Discussion

The magnetic properties of compound **2** are summarized in **Table 1**. Their g values and hyperfine coupling constants (a_N) were determined by electron paramagnetic resonance (EPR) spectra, which were measured as THF solutions at a field of 0.33 T at room temperature, displaying an intense 1:1:1 triplet specific to NR compounds. The magnetic susceptibility was measured on a SQUID magnetometer at a field of 0.5 T in the temperature range 1.8–300 K. (\pm)-**2** shows weak antiferromagnetic intermolecular interactions ($\theta < 0$), whereas (2*S*,5*S*)-**2** shows very weak ferromagnetic intermolecular interactions ($\theta > 0$).

Table 1 Magnetic properties of compound **2**.

Compound	EPR ^[a]		SQUID	
	g	a_N [mT]	C ^[b] [emu K mol ⁻¹]	θ ^[c] [K]
(\pm)- 2	2.0059	1.34	0.38	-0.39
(2 <i>S</i> ,5 <i>S</i>)- 2			0.36	0.02

^[a]Measured as THF solutions at room temperature. ^[b]Curie constant. ^[c]Weiss temperature.

Compound (\pm)-**2** was successfully separated into each of enantiomers by using HPLC with a analytical chiral column. Compound **2** has longer retention time than compound **1** (**Figure 1**). It is likely that methyl di(ethylene glycol) chain strongly interacts with the chiral stationary phase. Moreover, the methyl di(ethylene glycol) chain improved the peak resolution of each enantiomer, which enables us to carry out the optical resolution by using a semipreparative chiral column (See Experimental). After optical resolution, we determined absolute configuration of each enantiomer

Chiral NRLC with hydrophilic group

by circular dichroism (CD) spectra measured as acetonitrile solutions at room temperature. One of them showed a CD peak at 231 nm with the same sign as previously reported compound (2*S*,5*S*)-**1**, whereas the other showed a CD peak at the same wavelength with the opposite sign. We identified the former as (2*S*,5*S*) enantiomer and the latter as (2*R*,5*R*) enantiomer. The hydrophilic groups such as oligo(ethylene glycol), hydroxy and carboxy groups hold great promise for key moiety to separate the racemic mixture of analogs of NR-LC compounds by means of a preparative chiral column [22], [23]. The synthesis of enantiomerically enriched NR-LC compounds have been performed by asymmetric synthesis and/or partial resolution using diastereomeric salt formation method of key intermediates, whereas optical resolution with a chiral column is greatly expected to provide an alternative.

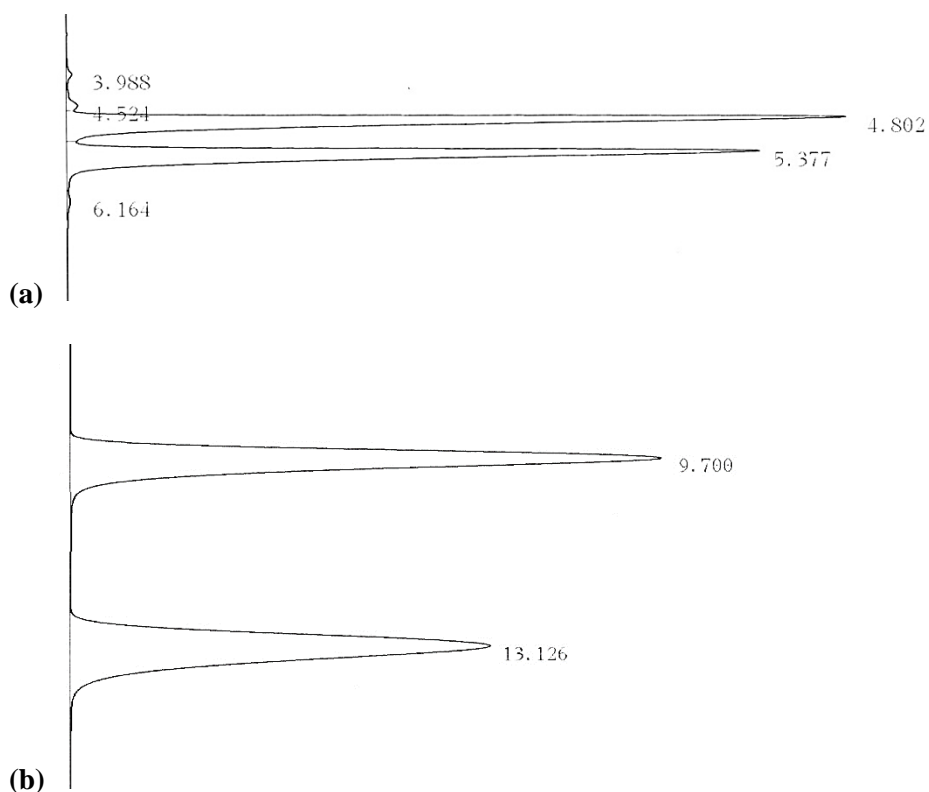


Figure 1 Chiral chromatograms of (a) (±)-**1** and (b) (±)-**2** on DAICEL OD-H, 4.6 mm × 250 mm, a mixture of hexane and 2-propanol (9:1) as the mobile phase and flow rate of 1 mL/min.

The phase transition behaviors of **2** are characterized by DSC analysis and polarized optical microscopy (**Table 2** and

Figure 2). Compounds (±)-**2** and (2*S*,5*S*)-**2** showed a Schlieren texture typical of the nematic (N) phase and an oily streak texture typical of the chiral nematic (N*) phase, respectively, in cooling process by hot-stage polarized optical microscopy (**Figure 3**) [24].

These N or N* phases were monotropic and observed over a wide temperature range during

the cooling process. Variable temperature X-ray diffraction analyses of (\pm)-**2** and (2*S*,5*S*)-**2** showed only a halo. Thus, the LC phases are likely to be N and N* phases.

Table 2 Optical data and phase transition behaviors of compounds **1** and **2**.

Compound	ee ^[d] [%]	Phase transition behavior ^[e] [°C]
(\pm)- 1 ^[5]	0	Cr 78.8 N 106.1 Iso
(2 <i>S</i> ,5 <i>S</i>)- 1 ^[5]	92.7	Cr 62.5 N* 104.7 Iso
(\pm)- 2	0	Cr 89.6 (N 72.0) Iso
(2 <i>S</i> ,5 <i>S</i>)- 2	98.9	Cr 72.1 (N* 71.8) Iso

^[d]Determined by HPLC analysis on a chiral stationary phase column (DAICEL OD-H, 4.6 mm \times 250 mm) and a mixture of hexane and 2-propanol (9:1) as the mobile phase. ^[e]Determined by DSC analysis upon heating and cooling processes. Standard notation gives the transition temperatures between the crystalline (Cr), nematic (N), chiral nematic (N*) and isotropic (Iso) phases.

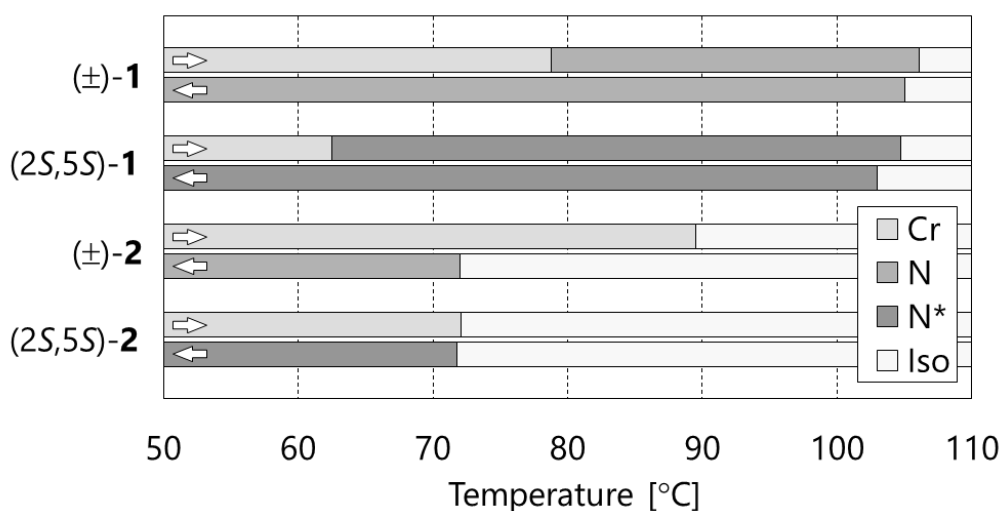
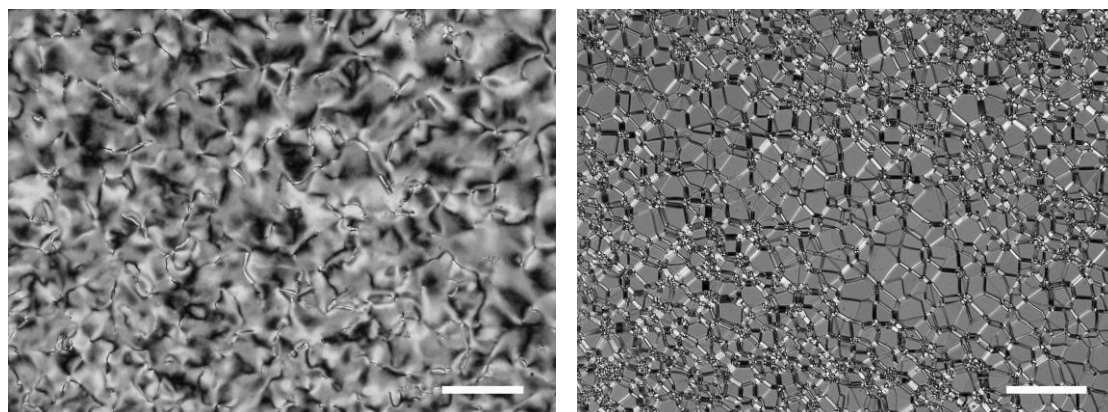


Figure 2 Comparison of LC phase behaviors of compounds **1** and **2**. Transition temperatures determined by DSC analysis at a scanning rate of 5°C/min upon the heating and cooling processes. During the cooling process, **2** showed the supercooled Iso-to-LC transition and LC phases were kept stable to around room temperature.



(a)

(b)

Figure 3 Polarized optical micrographs showing **(a)** a Schlieren texture for (\pm) -**2** and **(b)** an oily streak texture for $(2S,5S)$ -**2** at 70°C in the cooling run. The scale bars are 100 μm .

The methyl di(ethylene glycol) chain destabilized LC phases. Due to the exchange of a heptyloxy chain with a methyl di(ethylene glycol) chain, clearing point drops by about 30°C regardless of chirality. As a result, LC phase of compound **2** containing a methyl di(ethylene glycol) chain became monotropic. The difference between compounds **1** and **2** is only whether side chain bound to phenyl benzoate group is heptyloxy or methyl di(ethylene glycol) chain; in more detail, linking group between sp^3 -carbons is methylene or ether. This could make di(ethylene glycol) chain more flexible than heptyloxy chain because the absence of two hydrogen atoms in ether decrease the barrier of bond rotation. We can assume that the excess of flexibility derived from ether destabilized LC phases due to a loss of balance of flexibility and rigidity that is important factor for the stability of LC phases.

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Enantiomerically enriched substances have lower melting points than the corresponding racemates; (2*S*,5*S*)-**1** and (2*S*,5*S*)-**2** show lower melting point than (±)-**1** and (±)-**2**, respectively.

The optical resolution caused the depression of melting points by about 15°C regardless of the type of the side chains. The lack of one of the enantiomers is likely to disturb molecular packing in the crystalline state. We can conclude that the breaking of mirror symmetry destabilizes crystalline phases. Meanwhile, note that in contrast to melting points, the clearing points were not influenced by mirror symmetry breaking, but the LC phases are changed from N phases to N* phases. We should consider that the molecular mirror symmetry affects the stability not of LC phases but of crystalline phases.

Conclusion

We have synthesized the racemic and enantiomerically enriched NR-LC compound **2**, which contains a chiral NR unit in the mesogen core and a methyl di(ethylene glycol) chain as one of the terminal units. Compounds (\pm)-**2** and (2*S*,5*S*)-**2** show N and N* phases over a wide temperature range during the cooling process. Compound (2*S*,5*S*)-**2** shows lower melting point due to the disturbance of molecular packing caused by the mirror symmetry breaking. On the one hand, the methyl di(ethylene glycol) chain destabilizes LC phases due to the excess of flexibility compared to the heptyloxy chain. On the other hand, it enhances hydrophilic property, which enables us to separate enantiomers by HPLC with a chiral column. We believe that LC phase could be stabilized by introducing even more rigid substructure such as benzene rings, so that the lack of molecular rigidity induced by flexible side chain is covered.

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