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Enhanced Stereoselectivity in Photoelectrocyclization of Tropolone Ethers via Confinement in Chiral Inductor-Modified Lyotropic Liquid Crystals

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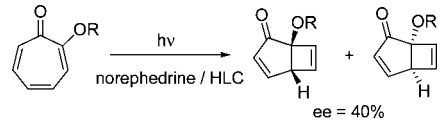
ABSTRACT



Photochemistry of tropolone methyl ether (1) and optically pure (*S*)-tropolone-2-methylbutyl ether (4) has been examined in lyotropic liquid crystals (LCs) in the presence of a chiral inductor. LCs significantly enhance the influence of chiral inductors during the photoelectrocyclization of the tropolone ethers. Chiral inductors that lead to 1:1 mixtures of enantiomers or diastereomers in solution give products in up to 40% enantiomeric excess for 1 and 35% diastereomeric excess for 4 in LCs.

Enantioselectivity in ground-state reactions is commonly achieved by developing appropriate catalytic systems, and great successes have been obtained during the past decades.[1,2] In contrast, there are considerably fewer examples of asymmetric induction in photochemical transformations.[3,4] A successful approach is to make use of chiral inductor(s) and to carry out the photochemical reaction in confined media[5,6] since under such conditions the substrate and inductor molecules are forced to be in close contact which could direct the reaction preferentially toward one of the enantiomers. Of the confined media, the most encouraging results were obtained by the use of the crystalline state and the solid host−guest assemblies,[7,8] and successful examples in fluid solutions are rarely reported.[9,10] In the present work, we use lyotropic liquid crystals (LCs) as reaction media to carry out the photoelectrocyclization of tropolone ethers and found that in the presence of a chiral inductor moderate enantiomeric excesses (ee's) can be obtained.

Lyotropic liquid crystals are long-ordered and thermodynamically stable systems, formed by surfactants in water or oil solutions. Anisotropic lamellar liquid crystals (LLCs) and hexagonal liquid crystals (HLCs) belong to the common LCs

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(Figure 1).[11] These supramolecular assemblies are optically transparent. In particular, due to the large interfaces and

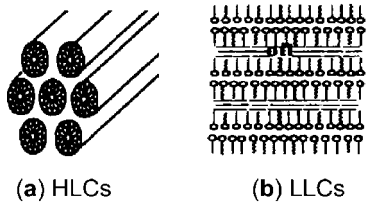
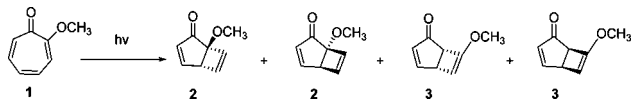


Figure 1. Schematic representations of the structure of the liquid crystals.

various microdomains with different polarities presented in LCs, these ordered aggregates could solubilize many kinds of substrates in high concentrations. Furthermore, LCs have very high viscosity, and the "stiff" structure would influence the arrangement and orientation of substrates. Thus, LCs might act as microreactors to control the selectivity in photochemical reactions.[12–15] In the present study, the samples for the photochemical reaction of the substrates in chiral inductor modified LCs were simply prepared by dissolving the substrate and chiral inductor in *n*-pentanol and subsequent addition of surfactant (sodium dodecyl sulfate, SDS) and water to the solution. After sonicating the mixture at room temperature for 48 h, optically clear samples were obtained. Formation of HLCs or LLCs is dertermined by the composition of the LC components. With the ratio of *n*-pentanol:SDS:H_2O being 1:1.5:1.5 (W/W/W), LLC samples were yielded, while the weight ratio of the three components of 1:6:9 gave HLC samples. The concentration of the substrate in the sample generally was ca. 1 mg/g of sample and that of the inductor ca. 7 mg/g of sample. Prior to irradiation, the samples were degassed by freeze−thaw three times. The experimental details are given in the Supporting Information.

The photochemistry of tropolone ethers in solution and in crystals has been well established.[16–18] Upon excitation, the achiral tropolone methyl ether (**1**, Scheme 1) undergoes a

Scheme 1



four π-electron disrotatory ring closure to yield the chiral bicyclo[3.2.0] product (**2**). Prolonged irradiation leads to **3** via a secondary rearrangement of **2** (Scheme 1).[17] The ratio of **2**:**3** varied with the conversion of **1**. In our experiments, we only focused on the enantioselectivity of **2**, and the samples were irradiated for a short time (5 min). The conversion was kept below 30%, and the ratio of **2**:**3** was ca. 25:1. Irradiation of **1** in chiral inductor modified LCs was performed in a Pyrex reactor with a 500 W high-pressure mercury lamp. After the conversion reached ca. 30%, the sample was extracted with dichloromethane. The extraction was analyzed by GC with a chiral column (Supelco β-Dex 325). The yields of the photoelectrocyclization products **2** and **3** were close to 100% on the basis of the consumption of the starting material. The structure of products **2** and **3** was identified mainly by GC−MS and ^{1}H NMR spectra, which are in close agreement with those reported in the literature.[16] The ratio of the enantiomers for **2** was determined based on their GC trace. Remarkable enantioselectivity was observed. For example, the photochemical reaction of **1** in (1*R*,2*S*)-(−)- or (1*S*,2*R*)-(+)-norephedrine modified HLCs at room temperature gave **2**enriched in one of the enantiomers to the extent of ca. 28%. Figure 2 shows the

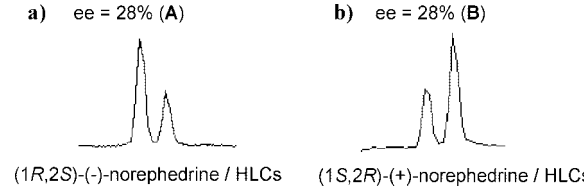


Figure 2. GC traces (Supelco β-Dex 325 column) of product **2** upon irradiation of **1** in norephedrine modified HLCs at room temperature. The first peak on the trace is termed **A**, and the second peak **B**.

GC traces of product **2** upon irradiation of such samples. The first of the two enantiomeric peaks on the GC trace is arbitrarily assigned to be isomer **A** and the second peak isomer **B**. The sample with (1*R*,2*S*)-(−)-norephedrine as inductor enhanced formation of **A**, while that with (1*S*,2*R*)-(+)-norephedrine as inductor enhanced **B** (Figure 2). This result indicates that the system is well behaved in the sense that the optical antipode of the chiral inductor gave the opposite enantiomer of the product. Both chiral inductor and LCs are essential for the enhancement of enantioselectivity, since irradiation of **1** in noninductor HLCs or in methanol solution in the presence of an inductor gave racemic **2**.

Several factors affect the enantioselectivity of the photochemical transformation of **1** in inductor modified LCs. First, the effect of temperature is remarkable (Table 1), which shows that −10 °C is optimum. At this temperature, the ee values are ca. 40%, and above −10 °C, the ee values decrease

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Table 1. Enantioselectivity in Photoelectrocyclization of Tropolone Methyl Ether[a]

chiral inductor	temperature	enantiomeric excess (%) HLCs	LLCs
no inductor	room temperature	0	0
(1*R*,2*S*)-(−)-norephedrine	room temperature	28 (**A**)	8 (**A**)
	0 °C	35 (**A**)	10 (**A**)
	−10 °C	40 (**A**)	10 (**A**)
(1*S*,2*R*)-(+)-norephedrine	room temperature	28 (**B**)	8 (**B**)
	0 °C	35 (**B**)	10 (**B**)
	−10 °C	40 (**B**)	10 (**B**)
L-(−)-menthol	room temperature	5 (**A**)	3 (**A**)
R-(−)-decanol	room temperature	5 (**A**)	3 (**A**)

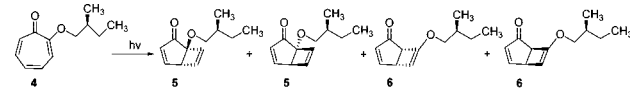
[a] The designations **A** and **B** indicate whether the predominant enantiomer eluted from the chiral GC column is the first peak (**A**) or the second (**B**). The absolute configuration of the photoproducts was not established.

with temperature increase. Second, the enantioselectivity depends on the nature of the chiral inductors. Those that contain only an alcohol functional group (L-(−)-menthol and *R*-(−)-2-decanol, Table 1) give low or negligible chiral induction. Norephedrine that contains both an amine and an alcohol functionality gives good results. Third, the structure of LCs shows significant effects. For example, with norephedrine as an inductor, while remarkable enantioselectivity is observed in HLCs, in LLCs considerably low ee values are obtained.

The detailed mechanism for the enhanced enantioselectivity in this work has not been fully understood. We tentatively proposed that the substrate and the inductor are located in the hydrophobic domain of LCs, thus their local concentration is high. The carbonyl and methoxy groups of tropolone methyl ether might form hydrogen bonds with the hydroxyl and amino groups of norephedrine to yield a substrate−inductor chelate complex. The organized semirigid environment of LCs will prevent the dissociation of such a complex. The tight complexation between the reactant and the chiral inductor molecules is expected to favor one of the two modes of disrotatory cyclization ("in" and "out" in Scheme 1) of **1**. The fact that chiral inductors containing only an alcohol group fail to yield significant enantioselectivity supports the above proposal because in this case the inductor and reactant cannot form a chelate complex. The temperature and LC structure dependencies of the enantioselectivity are also consistent with the above proposal. It has been established[11] that the viscosity within HLCs is greater than that in LLCs, and the viscosity of LCs increases with temperature decrease. The more rigid environment provided by HLCs at low temperature would more effectively inhibit the substrate−inductor chelate complex from dissociation. As shown in Table 1, even in the best case, i.e., norephedrine as the chiral inductor and HLCs as reaction media, only moderate enantioselectivity was observed. One reason for this fact is that not every reactant molecule is placed next to a chiral inductor molecule to form a chelate complex.

The above proposal that the enantioselectivity is originated from a substrate−inductor chelate complex is further strengthened by the photochemical transformation of (*S*)-tropolone-2-methylbutyl ether (**4**, Scheme 2). As in the case of **1**,

Scheme 2



irradiation of **4** results in the ring closure product **5** and the secondary rearrangement product **6**. We kept the conversion below 30%, and the ratio of **5** to **6** was greater than 25:1. In **4**, an inductor group ((*S*)-2-methylbutyl) is covalently linked to the reaction moiety. Although every reaction moiety is placed next to a chiral inductor, they cannot form a substrate−inductor chelate complex. Thus, one can expect that no significant chiral induction is observed. Indeed, irradiation of optically pure **4** included in HLCs at room temperature gave **5** only with ca. 5% diastereomeric excess (de). The product was analyzed by GC with a chiral column. The first eluted isomer (termed **A**) is diastereomerically enriched. Interestingly, irradiation of **4** in methanol solution gave **5** also with ca. 5% de. Evidently, for a covalently linked substrate−inductor system, a rigid environment is not needed to prevent the separation of the substrate and inductor.

To improve the diastereoselectivity, we also carried out the photochemical reaction of **4** in LCs in the presence of an additional chiral inductor. As shown in Figure 3 and Table

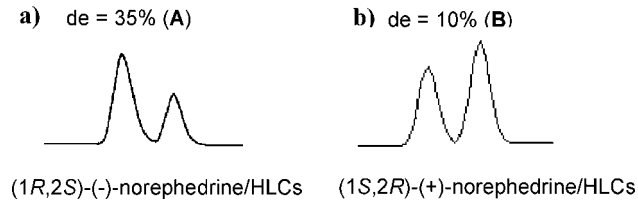


Figure 3. GC traces (Supelco β-Dex 325 column) of product **5** upon irradiation of **4** in norephedrine-modified HLCs at room temperature. The first peak on the trace is termed **A**, and the second **B**.

2, in the (1*R*,2*S*)-(−)-norephedrine modified HLCs at room temperature, irradiation of **4** gave **5** with a de value of ca. 35% (**A** was enriched), a 30% increase compared with the case in the absence of norephedrine. This stereoselectivity is also greater than the case of **1** in (1*R*,2*S*)-(−)-norephedrine modified HLCs (28% ee, Table 1). Evidently, in the double chiral induction,[19] the inductions of the (*S*)-2-methylbutyl group in **4** and the added inductor ((1*R*,2*S*)-(−)-norephedrine) are matched, both favor the formation of isomer **A**, and the

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Table 2. Diastereoselectivity in the Photoelectrocyclization of (*S*)-Tropolone-2-methylbutyl Ether[a]

	diastereomeric excess (%)	
chiral inductor	HLCs	LLCs
no inductor	5 (**A**)	5 (**A**)
(1*R*,2*S*)-(−)-norephedrine	35 (**A**)	6 (**A**)
D-(−)-prolinol	35 (**A**)	6 (**A**)
(1*S*,2*R*)-(+)-norephedrine	10 (**B**)	5 (**B**)
L-(−)-menthol	5 (**A**)	5 (**A**)
R-(−)-2-decanol	5 (**A**)	5 (**A**)

[a] The designations **A** and **B** indicate whether the predominant diastereomer eluted from the chiral GC column is the first peak (**A**) or the second (**B**). The absolute configuration of the photoproducts was not established.

35% de is a result of the cooperation of the two chiral inductors. In contrast, in the (1*S*,2*R*)-(+)-norephedrine modified HLCs at room temperature, the de value for the photochemical reaction of **4** was decreased to 10% with **B** enriched (Figure 3, Table 2). As mentioned above, (1*S*,2*R*)-(+)-norephedrine favored the formation of isomer **B** (Figure 2), while the (*S*)-2-methylbutyl group enhanced the formation of isomer **A**. Their inductions are mismatched.[19] As a result, the de value is relatively low. Inspection of Table 2 reveals that as in the case of **1** the inductors containing an amine and an alcohol group (norephedrine and prolinol) can induce high diastereoselectivity, while those that only possess an alcohol functionality give negligible chiral induction. Again, the chiral induction also depends on the structure of LCs. With the same chiral inductor, the de values in HLCs are much greater than those in LLCs.

Ramamurthy, Scheffer, and their co-workers have investigated the photoelectrocyclization of tropolone ethylphenyl ether in zeolites modified with chiral inductors.[20–22] They obtained ee values of up to 78% of the photoelectrocyclization products in NaY zeolite with optically pure norephedrine as the chiral inductor. They postulated that there exist hydrogen bonding interactions between the reactant molecule and the chiral inductor and electrostatic interaction between the cations present in the zeolite interior and the chiral inductor. The reaction cavity of the zeolite has fixed volume and shape and very "hard" walls and perhaps is not fully occupied by the reactant and inductor molecules. However, the cations help to anchor the chiral inductor to the zeolite interior surface, and the chiral inductor helps to adsorb tropolone ether preferentially from one enantiotropic face. Thus, one of the two modes of the disrotatory cyclization is favored. By contrast, in the case of LCs as reaction media, the "walls" of the reaction cavity are relatively "soft" and collapse around the substrate−inductor complex in orientations that maximize van der Waals contacts. Thus, the dissociation of the substrate−inductor chelate complex is prevented, and the chiral inductor allows one of the two modes of the disrotatory cyclization to be favored. Evidently, LCs complement zeolites. Each medium has its relative merits. Now it is possible to select the one that is more compatible with a particular reactant and a particular photochemical reaction.

In summary, we have found that chiral inductor modified LCs may act as microreactors to enhance the stereoselectivity in the photoelectrocyclization of tropolone ethers. To gain high stereoselectivity, the chiral inductor should contain at least two functional groups that form hydrogen bonds with tropolone ether. The semirigid environment of LCs prevents the dissociation of the substrate−inductor complex, thus enhancing the stereoselectivity of the photochemical products.

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Supporting Information Available: Syntheses of **1** and **4**, experimental data of the photochemical reactions of **1** and **4** in chiral inductor-modified lyotropic liquid crystals, and ^{1}H NMR of **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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