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Color Indicators of Molecular Chirality Based on Doped Liquid Crystals

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With the rapidly increasing role of combinatorial methods in chemistry and (bio)catalysis there is an ever-growing need for fast screening processes for activity and selectivity.^[1] This is particularly evident in the search for high enantioselectivity in asymmetric catalysis, which is often a time-consuming process. Recently reported methods for enantiomeric excess (*ee*) determination employ,^[2] in an elegant way, UV/Vis spectroscopy,^[3] fluorescence,^[4] mass spectrometry,^[5] and IR thermography.^[6] One ingenious assay involves the different fluorescence emission of enantiomers and using a method based on four synthetic steps including a kinetic resolution.^[7] Traditional techniques for chiral chromatographic analysis are currently being miniaturized to allow rapid screening and, although enantiomer separation is still necessary, new methods such as parallel chiral capillary electrophoresis offer promising alternatives.^[8] Direct visualization of molecular

chirality is a fundamental challenge which ultimately could have considerable practical importance for the rapid screening of libraries of nonracemic compounds. Here we report a simple color test for enantiomeric excess (*ee*) based on the chirality-dependent color generation in doped films of liquid crystals. Our design for a color test of chirality is based on the consideration that a change from a nematic to a cholesteric phase in liquid crystalline (LC) materials can be induced upon doping with suitable chiral guest compounds.^[9] For example, we have shown by using chiral molecular switches as dopants that LC materials can function as amplifiers of chirality.^[10, 11]

The chirality of a cholesteric LC material is indicated by the sign and magnitude of the cholesteric pitch. The pitch is dependent on: 1) the concentration (*c* in wt %) of the dopant; 2) the helical twisting power (β) of the dopant, and 3) the enantiomeric excess (*ee*) of the dopant [Eq. (1)].

$$\text{pitch } (p) = (c\beta ee)^{-1} \quad (1)$$

The helical twisting power is an intrinsic property of any chiral dopant which indicates how efficient this molecule is in inducing a chiral orientation in the LC material.

The pitch, for a given chiral substrate doped in an LC matrix at a fixed concentration, is dependent only on the *ee* value of the dopant. This property, therefore, might be used as a measure for the enantiopurity of any chiral compound that can induce a cholesteric phase.

The pitch is generally determined by the Grandjean–Cano technique,^[12] a method which requires an aligned LC sample to be placed between a plane-convex lens and a flat surface. The pitch can then be obtained from the distances between distinct lines seen through a polarizing microscope. It is evident that for screening purposes this technique for the determination of *ee* values can hardly compete with other techniques because of laborious sample preparation. Cholesteric materials, however, show interesting optical properties when the pitch of the liquid crystal lies in the region of the wavelength of visible light. Liquid crystalline samples which are oriented by a linearly rubbed polyimide-covered glass plate show reflection at a specific wavelength (λ) that is dependent on the angle of the incident light (α) relative to the normal of the surface and on the average refractive index of the material (*n*) [Eq. (2)].^[13]

$$\lambda(\alpha) = n p \cos[\sin^{-1}(\sin \alpha / n)] = n(c\beta ee)^{-1} \cos[\sin^{-1}(\sin \alpha / n)] \quad (2)$$

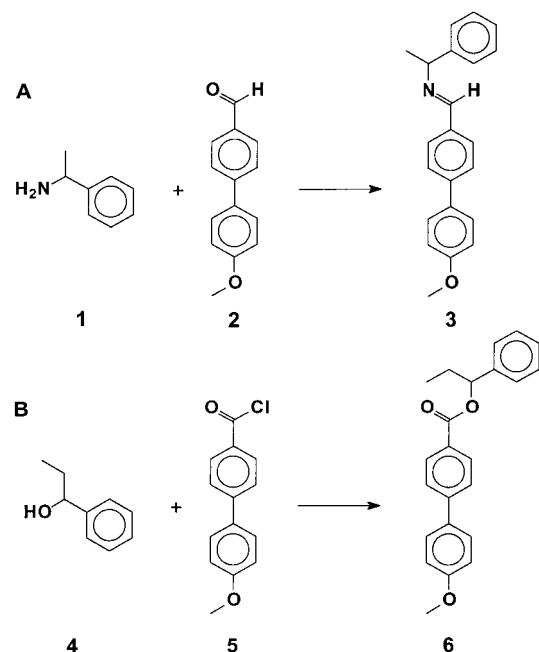
The color, and hence the chiral nature, of such a phase, which is readily prepared, can be instantly assessed by eye. Doped, colored LC materials are therefore promising candidates for color indicators of *ee* values, with potential use in the combinatorial screening of enantioselective catalysts.

The major problem to overcome in the development of such a screening technique is that the helical twisting powers of common products of enantioselective catalysis are negligible (and therefore no cholesteric phase can be induced) or they are very small (only pitches in the range of micrometers can be obtained). Color induction is normally only achieved with specially designed dopants.^[9] We reasoned that compounds that structurally resemble the LC material can be expected to

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show high helical twisting powers as well as high compatibility. The present concept is based on the one-step functionalization of chiral compounds with an achiral mesogenic group to obtain derivatives that resemble the LC material and as a consequence possess high helical twisting powers and high compatibility. To prove this principle, 1-phenylethylamine (**1**; Scheme 1) and 1-phenylpropanol (**4**) were selected as representative examples of two classes of chiral products, namely amines and alcohols. Commercially available E7 was chosen as the LC host material. The structural motif of E7 is a *para*-alkoxy-substituted cyanobiphenyl unit, which is frequent in nematic liquid crystalline materials. In order to structurally resemble this material we designed a *para*-methoxy-substituted biphenyl moiety as a mesogenic unit to be affixed to the chiral amine or alcohol to be analyzed.

In the case of 1-phenylethylamine (**1**), such a mesogenic unit was readily introduced through a fast reaction with carbaldehyde **2** to give the corresponding imine **3** (Scheme 1A).



Scheme 1. Derivatization of chiral amine **1** and alcohol **4** with achiral mesogenic units.

Enantiomerically pure (*S*)-imine **3** showed a very high compatibility with E7 (doping up to at least 20 wt % was possible) and, more importantly, cholesteric textures were readily obtained (the imine has a helical twisting power (β) of $-21.4 \pm 0.9 \mu\text{m}^{-1}$), whereas amine **1** itself induces no cholesteric texture. Enantiomerically pure material in the range from 10 to 19 wt % gives LC phases with colors ranging from red (680 nm) to violet (360 nm), thus covering the entire visible spectrum, as predicted by Equations (1) and (2).

The color of the LC film composed of an 18.9 wt % sample of **3** in E7, which is violet for enantiomerically pure imine, should, according to Equations (1) and (2), show a shift to longer wavelengths with decreasing *ee* values of the dopant. Samples of E7 doped with 18.9 wt % of imine **3** derived from

amine **1** with 100, 90, 80, 60, and 50 % *ee* were prepared and the reflected wavelength was measured with an incident light beam at 45° (Figure 1).^[14]

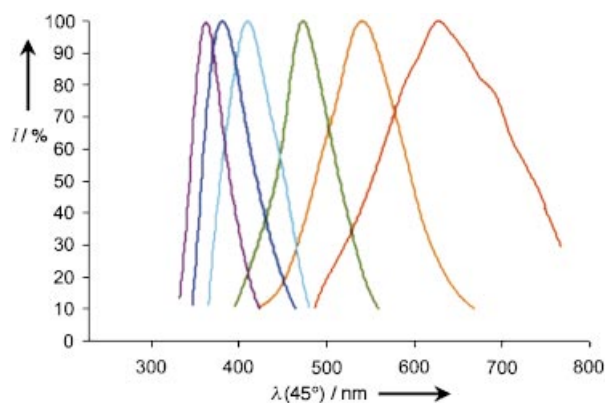


Figure 1. Light intensity versus wavelength of reflected light ($\alpha = 45^\circ$, normalized to 100 %) for E7 doped with imine **3** (18.9 wt %): *ee* values of 100, 90, 80, 70, 60, and 50 % are indicated by the colors purple, dark blue, light blue, green, orange, and red, respectively.

A doped LC matrix is thus seen to function as a visual chirality indicator, with the wavelength of the reflected light increasing as the *ee* values fall. In this way, every LC sample doped with imine **3** with an *ee* value above 50 % can be visualized and those with lower *ee* values remain colorless. From Equation (1) it is evident that the lower limit of the *ee* value that is visually detected can be shifted by varying the concentration of the dopant, if desired.

A slight change in the mesogenic unit is necessary if the same concept is to be used for chiral alcohols. Acid chloride **5** was tested for the visual determination of the *ee* value of **4** (Scheme 1B). 1-Phenylpropanol is an important compound in terms of combinatorial catalysis since it is the product of the extensively studied enantioselective catalytic addition of diethylzinc to benzaldehyde.^[15] A simple esterification reaction of alcohol **4** with acid chloride **5** results in carboxylate **6**.

The enantiomerically pure (*S*)-ester **6** shows very high compatibility with E7, and dopant concentrations of at least 23 wt % could be obtained. The helical twisting power of this ester ($\beta = -28.8 \pm 0.7 \mu\text{m}^{-1}$) is significantly higher than that of imine **3**. The doping of E7 with 14.8 wt % of ester **6** leads to colored LC phases that range from violet for 100 % *ee* to red for 50 % *ee*, with reflection spectra of **6** similar to those of imine **3** (Figure 2). The measurement of the wavelength of maximum reflection by absorption spectroscopy allows quantitative determination of the *ee* values, where a change in the *ee* value of only 1 % results in a readily detectable shift of at least 3.6 nm in the wavelength of the maximum reflection. The results for both compounds are summarized in Figure 2.^[16]

Again, all the colors can also be observed instantaneously by eye. Figure 3 shows the colors of the doped LC phases with different *ee* values of the dopant. Samples with *ee* values lower than 50 % do not show any color. In this way, potential enantioselective catalysts can be screened rapidly and the enantiomeric excess of the products can then be further quantified by measurement of the wavelength of reflection as discussed above.

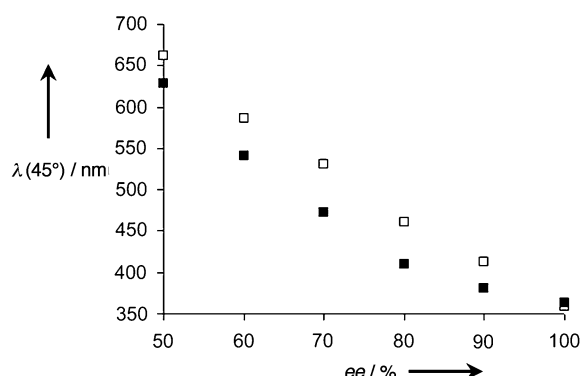


Figure 2. Wavelength of the maximum reflection ($\lambda(45^\circ)$) versus the enantiomeric excess for both imine **3** (■, 18.9 wt %) and ester **6** (□, 14.8 wt %) in E7 (the wavelengths of reflection are independent of whether the *S* or the *R* enantiomer is used in excess).

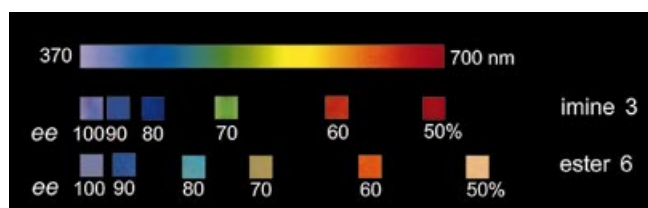


Figure 3. Color of the reflection ($\lambda(0^\circ)$) of doped LC samples with different enantiomeric excesses for both imine **3** and ester **6**. The colors shown are photographs of the aligned LC films taken perpendicular to the surface.

The main criterion for substrates to be amenable to analysis by this method is that the combination of the helical twisting power and maximum dopant concentration of the derivative in an LC phase results in pitches in the visible range. A change in the helical twisting power going from one substrate to another, structurally related, substrate can be readily balanced by changing the dopant concentration. If the current method is used for the direct screening of the *ee* values of products of enantioselective catalysis, for example, in a combinatorial fashion, one should realize that the color of the obtained liquid crystal is not solely dependent on the *ee* value of the product (or the enantioselectivity of the catalyst) but is also dependent on the concentration of the product (for example, the conversion of the catalytic reaction and thus the activity of the catalyst). The dependency of the generated color on the conversion and *ee* value is particularly useful for the initial screening of chiral catalysts where a set lower limit of both conversion and enantioselectivity is to be detected.^[17]

The presented method requires no chiral auxiliaries, only microgram quantities of chiral products, and has excellent prospects for automation in view of recent advances in liquid crystal technology.^[18] Since a variety of mesogenic units bearing suitable functional groups for coupling to the analyte can be readily prepared and a large number of nematic LC materials are available it should be possible to “custom design” these color indicators for numerous chiral products.

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