Chirality in Liquid Crystals

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A General Method for Measurement of Enantiomeric Excess by Using Electrooptics in Ferroelectric Liquid Crystals**

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Dedicated to Professor Sven T. Lagerwall on the occasion of his 70th birthday

The strongest applications of combinatorial technology to catalyst discovery exploit very large libraries. For example, RNA libraries of approximately 10^{14} distinct members have been screened to produce catalysts for organic reactions such as the Diels–Alder reaction.[1] Application of this technology to asymmetric catalyst development,[2] however, is blocked by lack of an effective high-throughput screen. Although considerable effort aimed at development of high-throughput methods for measurement of enantiomeric excess (*ee*) values is underway worldwide,[3] massively parallel selection such as that demonstrated for RNA catalyst discovery is not available, even conceptually.

Liquid crystals (LCs) have been used for sensitive and convenient detection of *ee* values for some time.[4] Recently, technology for creating ferroelectric liquid crystal (FLC) on silicon video microdisplays comprised of greater than 10^5 individually switched electrooptic (EO) pixels ($\approx$25-fL pixel volume) on small semiconductor substrates has been developed to high-volume commercialization.[5] As this FLC EO depends upon enantioenrichment of at least one of the FLC components,[6] a project has been initiated, aimed at exploring its use as the basis of a method and device for high-throughput measurement of enantiomeric excess, the "*ee*-microdisplay."

This approach involves fabrication of devices similar to video microdisplays, but in which the LC in each pixel is different while the driving signal is the same. This obviates the need for expensive semiconductor substrates, as are required for video microdisplays. The EO signal from each pixel would be relatable to the *ee* value of the LC therein, which would be composed of an achiral LC host doped with a small amount of chiral analyte.

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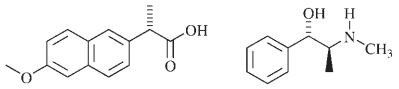
There are many potentially useful chiral signals available with doped smectic LCs. Initial experiments were directed towards use of the EO response time in a smectic C phase (SmC) doped with a chiral analyte, forming a chiral smectic C phase (SmC*) as a measure of the *ee* values.[7,8] It has already been demonstrated that chiral EO in the SmC* is a very sensitive chirality detector.[9] However, it was found that for SmC hosts doped with a chiral analyte, dielectric responses,[10] electric-field-driven deracemization,[11] and alignment issues not directly associated with molecular chirality of the dopant complicate quantitative measurement of *ee* values by using FLC EO.

Therefore, development of a method utilizing the electroclinic effect[12] in chirally doped SmA hosts[13] was undertaken. In the electroclinic effect, application of an electric field parallel to the layers of a SmA* LC induces a tilt in the optic axis in the plane that is normal to the applied field. Enantiomers show equal magnitude but opposite signs for this optic axis rotation, which is linear with the field for small induced tilts. Herein, the basic feasibility of this approach is demonstrated by using the chiral drugs (*S*)-naproxen (**1**) and (*S*,*S*)-pseudoephedrine (**2**) as test analytes. No covalent chemistry is required for the measurement, which should be quite generally applicable to chiral organics.



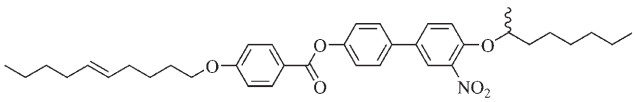
1 **2**

Thus, an achiral SmA host composed of three phenylpyrimidine smectic mesogens was formulated (see the Supporting Information). In these initial experiments, the chiral drug naproxen, commercially available as both the unichiral *S* enantiomer (**1**) and as the racemate, was chosen as a model analyte.

A good, linear calibration curve[14] could, in fact, be obtained by using the phenylpyrimidine SmA host doped with naproxen. However, the expected strong dependence of the electroclinic effect on temperatures close to the SmA*–SmC* transition,[11,13] combined with the fact that the various analyte samples possessed slightly different transition temperatures, precluded use of this method for measurement of *ee* values at a single absolute temperature. This effectively negates the utility of the method for high-throughput screening.

This problem was solved through the use of the racemic de Vries SmA[15] host **3** (phase sequence with transition

temperatures given in °C).[16] Unichiral **3** appears to be quite unique among SmA* materials in that the electroclinic effect, which is quite pronounced, is relatively temperature-independent close to the SmA*–SmC* transition. To our knowledge, no report of the behavior of a racemic de Vries material with chiral doping has been reported, though it is well known that unichiral de Vries materials typically show a large electroclinic effect in the SmA* phase.[14b–f,15b,c,17]



3: SmC — 24 — SmA — 33 — I

To demonstrate the method, three naproxen samples of varying *ee* values (0.25, 0.50, 0.75) were prepared by mixing **1** with racemic naproxen. Each of these materials as well as pure **1** and the pure racemate were then doped at 1% by weight into host **3** by using two serial dilutions. LC cells were fabricated, and the chiral signal from these cells was obtained as follows: Each cell was individually oriented with the rubbing direction (optic axis with no applied field) oriented at 22.5° off the polarizer on the temperature controlled stage of a polarized light microscope, as indicated in Figure 1. In this geometry, the variation in intensity of transmitted light with small changes in optic axis orientation is maximized and linear.

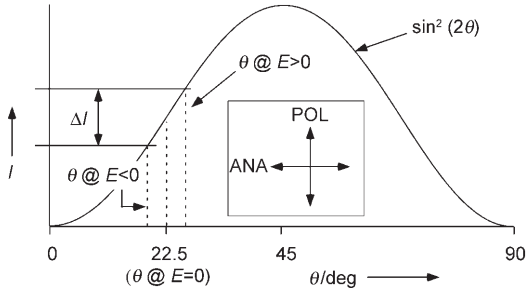


Figure 1. Plot of transmitted light intensity (I) versus optic axis orientation (θ), given as degrees from vertical (deg), when observed between crossed polarizer (POL) and analyzer (ANA) for a uniformly aligned SmA* LC cell.

The chiral signal was obtained by driving the cell with a square wave. The difference in transmitted intensity ΔI of a helium-neon laser probe beam (spot size 400 μm^2) for positive and negative applied fields gives a sensitive measure of the electroclinic tilt as a function of applied field (less than $\pm 0.1°$ in these experiments), which is related to the *ee* value of the chiral dopant. Samples enriched in the *R* isomer would give the same magnitude, but opposite phase of this response. The doped samples were aligned by using rubbed nylon alignment layers on one substrate and unrubbed nylon on the other. The cell gap was 3.1 μm, maintained by spacers added to the perimeter seal glue line. The cells were driven with $V = \pm 10$ V ($E = \pm 3.2$ V μm^{-1}) at 1 kHz.

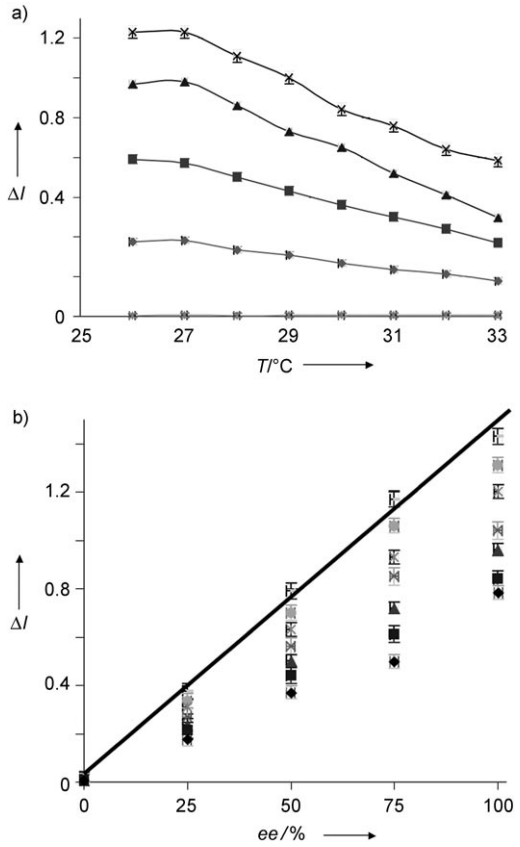


Figure 2. a) Chiral signal ΔI (given as the difference between two voltage readings on a photomultiplier) as a function of temperature for samples of naproxen of various *ee* values in host **3**; from top to bottom: 100% (×), 75% (▲), 50% (■), 25% (◆), 0% (✳). b) Chiral signal ΔI as a function of the *ee* value of naproxen dopant at several temperatures; from top to bottom: 26 °C (—), 28 °C (●), 29 °C (✳), 30 °C (×), 31 °C (▲), 32 °C (■), 33 °C (◆).

As shown in Figure 2, this strategy was remarkably successful. It was found that chirally doped **3** shows a large chiral signal of $\Delta I \approx 1.4$ for the pure enantiomer **1**, or about eight times larger than the maximum signal obtained with **1** in the conventional host. The reading obtained for racemic analyte in both hosts was $\Delta I \approx 0.007$.[18] More importantly, as shown in Figure 2a, the response is relatively temperature-independent. Plots of the chiral signal versus naproxen *ee* values at several absolute temperatures are given in Figure 2b. In this case, linear curves are obtained over a wide temperature range. As expected, the strongest response is obtained at the lowest temperature measured in the SmA* phase.

These experiments prove that the *ee* value of an unknown sample of naproxen can be determined by using the present method to about ±5% *ee*. The amount of analyte in the probe beam in these experiments is approximately 15 pg, and smaller samples sizes are easily envisioned.

To obtain preliminary information regarding the generality of the approach, a calibration curve for the chiral drug (*R**,*R**)-pseudoephedrine was obtained by using **3** as the SmA host. The observed signal from unichiral (*S*,*S*)-pseudo-

ephedrine (**2**) is smaller than that from (*S*)-naproxen (**1**) ($\Delta I \approx 0.6$ with $\pm 5.6\ V\,\mu m^{-1}$ driving field), but again it is possible to measure the *ee* value of pseudoephedrine to $\pm 5\%$ *ee* at one absolute temperature by using this technique (see the Supporting Information).

In conclusion, a new method for measurement of *ee* values, demonstrated for naproxen and pseudoephedrine, is described. By using relatively straightforward modification of known liquid-crystal microdisplay technology, the method is potentially applicable to the determination of very high-throughput *ee* values ($> 10^6$ samples in parallel) at low cost, which is of potential utility for combinatorial asymmetric catalyst development.

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