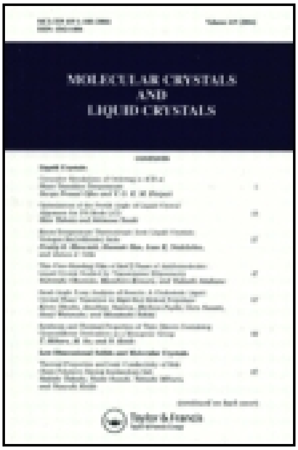

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A Study of Photochromic Azobenzene Liquid Crystals as Controlled Release Drug Delivery Systems

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A Study of Photochromic Azobenzene Liquid Crystals as Controlled Release Drug Delivery Systems

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Photochemically induced liquid crystal phase transitions are considered in the context of photo-induced controlled drug release. The model materials examined are the homologous series of 4-n-butyl-4'-n-alkoxyazobenzenes (BAABs). Radiation from a low power argon ion laser is used to induce the photochromic trans-cis isomerisation of the materials, resulting in an isothermal phase transition from the nematic to the isotropic phase. The response times are examined with respect to temperature, cell thickness and homologue. The data are discussed in the context of such systems' usefulness and ultimate applicability in photo-responsive drug delivery devices.

Keywords: liquid crystal; azobenzene; photochromic; drug release

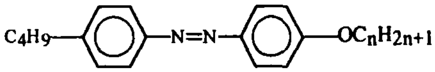
INTRODUCTION

There is much interest in using advanced, functional materials for the controlled release of drugs. *In vitro* experiments have demonstrated that the diffusion coefficient of a drug through a liquid crystal embedded membrane may be varied by the application of external stimuli (e.g. thermal and electric fields), and photochromic liquid crystals (LCs) are interesting new candidates for controlled drug release applications. Recent advances in drug delivery have focused on systems that show long term zero order or first order release. However, for many drugs, a more responsive manner of delivery is appropriate, and can lead to improved therapy, reduced side effects and minimised drug tolerance(1).

The ultimate aim of this work is to determine if pulsatile delivery of a drug from a reservoir can be achieved by controlling the phase of a photochromic liquid crystal embedded in a porous membrane.(2) The less geometrically anisotropic, non mesogenic *cis* isomer of certain photochromic LCs is formed on irradiation with light of a suitable wavelength. Its presence reduces the order in the system and can cause an isothermal transition to the isotropic phase. The reaction back to the *trans* isomer occurs thermally or via irradiation with a different wavelength of light[3]. For controlled drug release applications, the most interesting materials are those with relatively long lived *cis* isomers, and the homologous series of 4-n-butyl-4'-n-alkoxyazobenzenes are such compounds. This study investigates the response and relaxation times of these materials as a function of cell thickness and temperature.

EXPERIMENTAL

The photochromic properties of eight homologues of 4-n-butyl-4'-n-alkoxyazobenzene (BAAB) were investigated. Figure 1 shows the structures and phase transition temperatures of the materials. The materials were contained in glass devices of well defined thickness and treated for planar alignment.



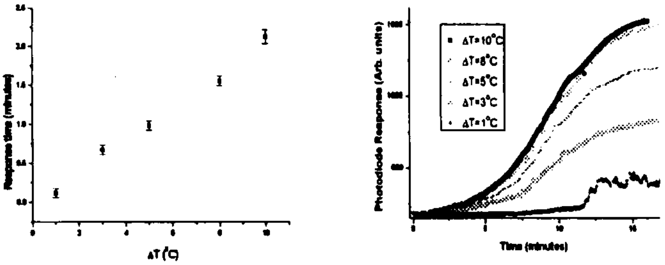
n=2	K 48 N 83 I
n=3	K 67 N 68 I
n=4	K 65 N 75 I
n=6	K 44 S_A (41) N 74 I
n=7	K 56 S_A (55) N 72 I
n=8	K 57 S_A (58) N 77 I
n=9	K 63 S_A (64) N 74 I
n=10	K 55 S_A 71 N 77 I

FIGURE 1 Chemical structure and phase transition temperatures of the homologous series 4-n-butyl-4'-n-alkoxyazobenzene (BAAB). Monotropic phase transitions are in parentheses.

The method used to investigate the photochromic response and thermal relaxation of the LCs is described in detail elsewhere.⁽⁴⁾ Briefly, the device was held on a hot stage and irradiated by an Ar^+ laser (λ=488nm, power=2mW, spot size≈2mm) with the polarisation of the beam coincident with the liquid crystal director. 488nm light induces the *trans-cis* isomerisation of the photoresponsive molecule which may in turn cause an *in situ* isothermal transition from the liquid crystal phase to the isotropic liquid. The time taken for the isothermal phase transitions to occur were studied by monitoring the change in the transmittance of a probe He-Ne laser (λ=633nm, power=1.8mW, spot size≈2mm) with the device between crossed polarisers and the orientation axis at 45° to the polariser/analyser directions. The relaxation times were determined similarly in the absence of 488nm light.

RESULTS AND DISCUSSION

Figure 2a shows the variation of the 488nm driven response times for the n=2 homologue at a cell width of 4μm. The response is shown as a function of reduced temperature, $\Delta T = T_{NI} - T$ (T_{NI} is the nematic to isotropic transition temperature). It can be seen that the response time of the LC to isotropic phase transition decreases approximately linearly with ΔT.



(a) (b)

FIGURE 2 (a) The time taken for the transmitted intensity to change between 90% and 10% of its original value and (b) relaxation times as a function of ΔT, for the 2nd homologue of BAAB.

The time taken for the sample to relax to its original LC state after irradiation has been completed is shown in figure 2b. The plateau values for each ΔT value differ in accordance with the temperature dependant birefringence of the LCs. The relaxation times are much longer than the times taken to induce the isothermal phase transition, indicating that the thermal back reaction is much slower than the light induced *trans-cis* isomerisation. There is also evidence of a small increase in relaxation time with increasing temperature which becomes marked very close to the phase transition (ΔT=1°C). It is thought that the relaxation process is somewhat hindered at higher temperatures due to the abrupt decrease in the order parameter near the nematic to isotropic transition, together with the increased thermal diffusion of molecules from the isotropic area into the mesophasic region. These effects result in a reluctance of the system to revert to the equilibrium liquid crystal phase for that temperature. These phenomena were also observed for the other BAAB homologues (data not shown).

The photoinduced switching time from the mesomorphic to the isotropic state, for selected homologues is shown in figure 3. All data are for samples of thickness of 5μm, at ΔT=5°C. The graph indicates that there is an alkyl chain length for which the photoinduced switching is least efficient. This can be understood as the *trans-cis* isomerisation of molecules with longer alkyl chains causes more disruption of the liquid crystalline packing. However, the shorter homologues in general have lower viscosity, resulting in faster switching times.

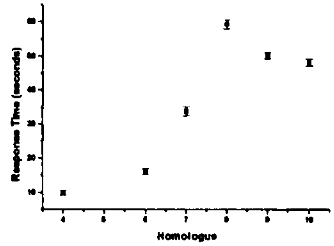
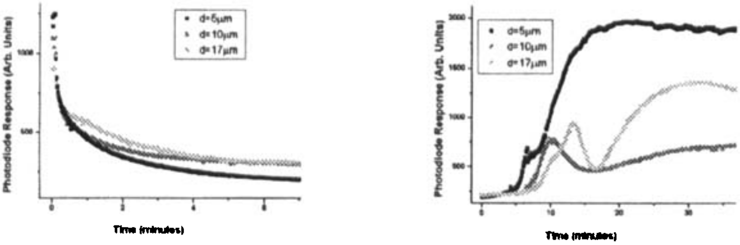


FIGURE 3 Photoinduced switching times for selected members of the BAAB homologous series, where d=5μm and ΔT=5°C.

Figure 4 shows the relationship between switching times and cell thickness for the homologue n=8 at ΔT=10°C. The initial and final intensities are all different, corresponding to the different retardances of the three samples due to the different thicknesses. It might be expected that since each device studied has a retardance of greater than λ (Δn=0.19(5)), structure should be observed in the driven photochromic responses as the device passes through one or more full and half wave conditions, corresponding to minima and maxima respectively. In fact, no such structure is observed in the response plots. This is almost certainly due to the Gaussian profile of the irradiating Ar^+ laser. The central area of the irradiated region of the sample experiences a far higher intensity than the edges and the photochromic isomerisation of the system will occur correspondingly faster. However, the probe beam samples the complete irradiated area and the photodiode measures the complete transmitted intensity, effectively averaging over the different responses of the illuminated area. The relaxation curves, figure 4b, do, however, show some structure, indicating that the relaxation process occurs far more uniformly over the irradiated area. Nonetheless, the minima that can be observed in the data of figure 4b for all three of the devices do not approach zero, an indication that the relaxation processes are not completely uniform.



(a) (b)

FIGURE 4 (a) Response and (b) relaxation times of the n= 8 homologue for different cell thicknesses, d, at ΔT=10°C.

Comparing the response times of the devices of different thickness, it was found that the speed of response increased slightly with increasing cell thickness, and that at lower temperatures and at the larger cell thicknesses, it became increasingly more difficult to induce complete switching of the LC phase. The differences in relaxation time are more marked, figure 4b clearly showing that the 5μm, 10μm and 17μm samples relax into the liquid crystal state after approximately 5, 7 and 8.5 minutes respectively. This difference in relaxation times is significant and is likely to be due to the surfaces of the device influencing the rate of back reaction. The phenomenon is currently under further investigation.

To put these results into the context of drug delivery, it is necessary to consider the requirements of a responsive drug delivery system. The device will need to respond rapidly to the applied stimuli, but also show a significant relaxation time. These requirements are best fulfilled by the materials that are closer to their isotropic phase transition temperatures. However, this effect must be counter-balanced by the fact that it is also necessary to avoid unintentional switching of the liquid crystal device by increases in ambient temperature driving the device into the isotropic phase. The membranes that are currently used in conjunction with the LC have a pore size of approximately 0.5 μm. Assuming that materials included in such membranes will act in a fashion most closely resembling that of the thinnest cells, both the response and relaxation times can be expected to be relatively fast. With these stipulations in mind, it seems that the ideal photochromic material for controlled drug release applications will be one in which T_{NI} is several degrees above body temperature, and which has a relatively short chain length such that the driven response is rapid. Since the relaxation time appears to be dominated by the geometry of the device, membranes with larger pore sizes are likely to be more useful.

CONCLUSIONS

Some general trends are evident in the isothermal nematic to isotropic isothermal phase transition studied for this system of materials. On approaching T_{NI} the response times for the nematic to isotropic transition decrease, whilst the relaxation times increase. Increasing the cell thickness increases the switching time for LC to isotropic transition only slightly, while significantly increasing the time of the relaxation process. The response time of the homologues varies as a function of chain length, with the slowest response observed for a chain length of n=8. The dependence of response time on chain length was attributed to a balance of two factors; the geometry of the molecules ensures that the higher homologues can cause more disruption of the phase on isomerisation, but this is weighed up against their increased viscosity, which will slow the photochromic response.

Investigations are currently underway on cellulose nitrate membranes embedded with a variety of liquid crystals materials. Preliminary results suggest that it is possible to achieve pulsatile release of drugs through these membranes, and these results will be reported shortly.

Acknowledgements

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