## Chirality

Induction of Point Chirality by *E*/*Z* Photoisomerization**

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Point chirality originates from having four different substituents bonded to a central atom to give nonplanar molecules with nonsuperimposable mirror images.[1] The induction of point chirality in molecular systems is of particular interest in connection with the origin of homochirality in nature, as seen in amino acids.[2–4] Our interest is to propose a new concept for the introduction of point chirality and also to understand how small differences in the substituents on the central carbon atom can cause detectable asymmetry in the structure. Previous work has shown that a small difference in the substituents such as position isomerism of pyridyl groups[5] or the presence of different isotopes[6] can cause detectable asymmetry in a molecule. However, chemical bonds need to be broken and made to make even such small differences in the substituents; this observation inspired us to envisage a molecular system in which the asymmetry can be introduced by photoisomerization of the substituents without any bond cleavage.

Herein, a new class of azobenzene-based prochiral molecules and the on/off switching of point chirality is reported. We designed a molecule consisting of a carbon atom having two photoisomerizable azobenzene moieties and a methyl and a benzene group (Scheme 1). The conformational difference caused by the *E*/*Z* photoisomerization of one of the azobenzene moieties was successfully utilized for the generation of point chirality in the molecule. To the best of our knowledge this is the first example of the induction of point chirality in which two of the substituents around an sp^3 carbon atom are geometric isomers.

A solution of **1** in ethyl acetate exhibits a typical absorption spectrum for azobenzene derivatives; this spectrum features an intense π–π* transition band at 327 nm and a weak and broad n–π* transition band at 400–500 nm. Irradiation of the solution at 366 nm caused a gradual decrease in the intensity of the π–π* transition band, with a notable increase in the n–π* transition band owing to photochemical *E*/*Z* isomerization of the azobenzene moieties. The reverse spectral changes were observed upon irradiation at 436 nm. The solutions at the photostationary state (PSS) under 366 and 436 nm light showed about 15 and 80%,
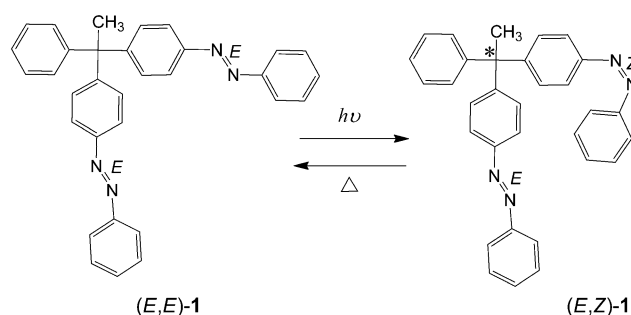
Scheme 1. Schematic representation showing asymmetry induction by *E*/*Z* photoisomerization of an azobenzene derivative.

respectively, of the initial absorbance seen at 327 nm. The isobestic points observed at 279 nm and 387 nm are indicative of almost independent conversion between the three isomers, that is, *EE*, *EZ,* and *ZZ* by *E*/*Z* photoisomerizations of azobenzene moieties (see the Supporting Information for details).

An insight into the chiral nature of molecule **1** was obtained from HPLC studies using a chiral stationary phase.[7] The HPLC chromatogram for compound **1** before irradiation showed a single peak at a retention time $R_t = 13.47$ (Figure 1a). Irradiation of **1** at 366 nm generated three new peaks at $R_t = 23.43$, 26.89, and 46.44 in addition to the initial peak (Figure 1b). The solution that had been irradiated at the 366 nm PSS was then irradiated with light of wavelength 436 nm. This resulted in the first peak increasing in intensity, with a diminished intensity of the fourth peak and increased intensities of the second and third peaks (Figure 1c). The intensities of the second and third peaks changed during irradiation but they remained equal in intensity to each other. Generally, in normal-phase HPLC, including HPLC using a
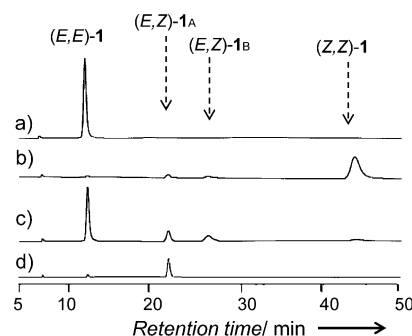
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Figure 1. Chromatogram of (*E,E*)-**1** monitored at 279 nm, the wavelength of an isobestic point: a) before irradiation, b) the PSS after irradiation at 366 nm (*EE/EZ/ZZ* = 2:14:84), c) the PSS after irradiation at 436 nm (*EE/EZ/ZZ* = 62:33:5), and d) (*E,Z*)-**1**$_A$ the first eluted enantiomer obtained by HPLC using a chiral stationary phase with a flow rate at 2 mL min^{-1}.

chiral stationary phase, the polar (*Z*)-azobenzene derivative elutes slower than the corresponding *E* isomer. Since the *E* isomer of the azobenzene derivative is thermodynamically stable, the compound should exist as the *E,E* isomer before irradiation. From the above information and the obtained results the second and third HPLC peaks can be assigned as enantiomers of the (*E,Z*)-**1** isomer. To fully assign the HPLC peaks we isolated the second and third fractions of the HPLC chromatogram, preparatively (Figure 1 d) and obtained their CD and NMR spectra. The CD spectrum of the second eluted fraction shows one positive (282 nm) and two negative bands (at 330 nm and 430 nm), and the mirror image of this spectrum was observed in the case of the third fraction (Figure 2). The NMR spectra for the second and third fractions were identical, and contained peaks corresponding
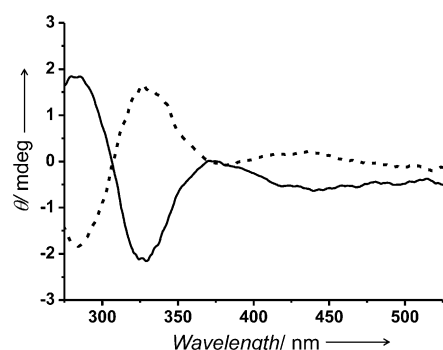

Figure 2. CD spectra of enantiomers of (*E,Z*)-**1** in ethyl acetate: first eluted enantiomer (*E,Z*)-**1$_A$** (solid line) and second eluted enantiomer (*E,Z*)-**1$_B$** (dotted line). The concentration of the solution was 3.75×10^{-4} mol L^{-1}.

to both (*E*)- and (*Z*)-azobenzene moieties at $\delta = 7.90$, 7.85 and at $\delta = 6.85$, 6.76, respectively (see the Supporting Information). From these results, we could unambiguously assign the first peak in the HPLC as (*E,E*)-**1**, where both the azobenzene units are in the *trans* form, and the second and third peaks as (*E,Z*)-**1$_A$** and (*E,Z*)-**1$_B$**, respectively. (*E,Z*)-**1$_A$** and (*E,Z*)-**1$_B$** both have one azobenzene unit in the *trans* form and the other in the *cis* form but they have opposite stereostructures. The fourth peak in the HPLC chromatogram can be assigned as (*Z,Z*)-**1**, in which both the azobenzene units are in the *cis* form. Hence, it is clear that the geometric difference in the substituents caused by the *E/Z* photo-isomerization of one of the azobenzene moieties generated asymmetry in the structure, and this asymmetry results in separable enantiomers with detectable differences in the CD spectra.

The racemization behavior of the (*E,Z*)-**1** enantiomers was investigated by HPLC and CD experiments. The HPLC chromatograms obtained after irradiation with 436 nm of the isolated second ((*E,Z*)-**1$_A$**) or third ((*E,Z*)-**1$_B$**) fraction were completely the same as the chromatogram shown in Figure 1 c obtained for the 436 nm PSS from (*E,E*)-**1** (see the Supporting Information). This suggests the photochemical racemiza-

tion generates equal amounts of (*E,Z*)-**1$_A$** and (*E,Z*)-**1$_B$** from (*E,Z*)-**1$_A$** or (*E,Z*)-**1$_B$** via (*E,E*)-**1** or (*Z,Z*)-**1**. The thermal back isomerization from (*E,Z*)-**1$_A$** to (*E,E*)-**1** was found to occur (rate constant 3.8×10^{-6} s^{-1} at 30 °C), as observed by the change in the HPLC profile (see the Supporting Information). The intensity of the CD band of (*E,Z*)-**1$_A$** gradually decreased over one week in the dark with a rate constant of 4×10^{-6} s^{-1} at 30 °C. The rate constants obtained from UV absorption (3.88×10^{-6} s^{-1} at 30 °C as a sum of $ZZ \rightarrow EZ$ and $EZ \rightarrow EE$), HPLC, and CD studies on the thermal back reaction were all in reasonable agreement within the experimental error. These results suggest that the *Z–E* isomerization directly removes the asymmetry in the molecule.

In conclusion we have introduced a novel prochiral molecule in which two azobenzene moieties were connected to a common carbon atom having methyl and benzene units. On irradiation at a suitable wavelength, *E/Z* photoisomerization of one of the azobenzene moieties ocurred to generate a change in the substituents around the central carbon atom and thus asymmetry was induced in compound **1**. Moreover, *Z/E* thermal isomerization regenerated the initial achiral molecule and this on/off switching of the induced asymmetry was repeatedly accomplished by light and heat respectively.[8]

It is expected that this method could be used for the asymmetric synthesis or the enrichment of one of the enantiomers of **1** or related compounds in the presence of a physical or chemical chiral source in addition to the action of light.[9] Such a photoisomerization favoring one of the enantiomers as a product at PSS is under investigation.

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