Entropy-Controlled Asymmetric Photochemistry: Switching of Product Chirality by Solvent

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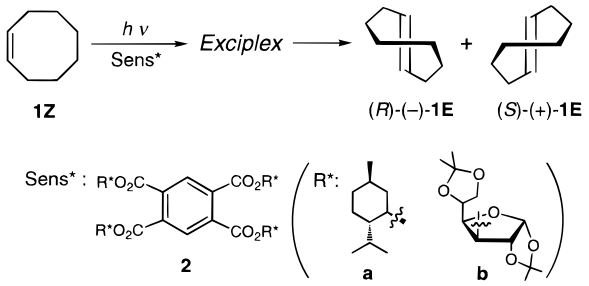
The chirality of molecules is crucial to the action of biological systems, and the development of new or improved methodology to control this property has been an important target of a number of chemical research groups for many years. Thus, considerable efforts have been devoted to thermally driven and enzymatic asymmetric syntheses,[1−5] both of which enable the preferential preparation of one of a pair of mirror-imaged enantiomeric isomers.[6,7] In comparison, the area of photochemical asymmetric synthesis is still relatively new, although it has already been shown to possess several advantages over its thermal and enzymatic counterparts.[8−10] Recently we have shown that the chirality of the product can be inverted at an equipodal point by changing the reaction temperature[11−13] or pressure[14] of the enantiomeric photoisomerization of achiral (*Z*)-cyclooctene (**1Z**) to give chiral (*E*)-cyclooctene (**1E**) which is sensitized by optically active polyalkyl benzenepolycarboxylates (**2**) (Scheme 1). We have now also discovered that even a change of solvent can cause the preferred chirality of the product to invert when a saccharide ester is employed as chiral photosensitizer, thereby demonstrating that the entropy factor lies at the heart of this unusual switching behavior.

Scheme 1. Enantiodifferentiating Photoisomerization of **1E** in the Presence of Chiral Sensitizer (**2a** and **2b**)



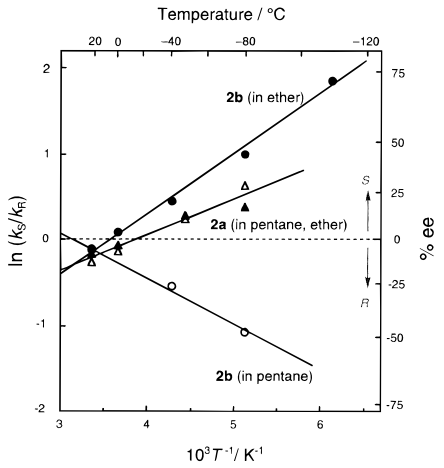


Figure 1. Temperature and solvent effects on the ee of **1E** obtained in the photosensitizations of **1Z** with **2a** in pentane (△) and ether (▲) and with **2b** in pentane (○) and ether (●).

The enantiodifferentiating photoisomerization of **1Z**, sensitized either by the optically active terpenoid or saccharide esters of benzenetetracarboxylic acid (**2a** and **2b**, respectively), was performed in pentane or diethyl ether at several temperatures between −110 to +25 °C. The reaction gave **1E** with varying enantiomeric excess (ee) levels, in good to excellent chemical yields (see refs 12−14 for detailed irradiation and analysis procedures). The temperature dependence profile of the ee value obtained upon photosensitization with **2a** and **2b** in the two solvents is illustrated in Figure 1, where the natural logarithm of the relative rate of formation of (*S*)-(+)- and (*R*)-(−)-**1E**, that is, $\ln(k_S/k_R)$ or $\ln[(100 + \%ee)/(100 - \%ee)]$, is plotted against the reciprocal temperature, giving good straight lines in all four cases. As can be seen from Figure 1, both chiral sensitizers afforded comparable ee values of approximately −5% at 25 °C in both pentane and ether (the negative sign indicates the predominant formation of the (*R*)-(−)-isomer), but gave distinctly different ee's at lower temperatures. When the menthyl ester **2a** was used as a sensitizer, the ee of the product showed very similar temperature dependencies in both pentane and ether. Thus, the major enantiomer produced was switched from (*R*)- to (*S*)-**1E** at the equipodal temperature, $T_0 = -19$ °C, and thereafter the ee continued to increase as the temperature was further reduced. In contrast, the use of the saccharide ester **2b** led to opposite tendencies in the same solvents at lower temperatures. Thus, lowering the reaction temperature enhanced the production of (*R*)-**1E** in pentane, but the enantioselectivity was switched to (*S*)-**1E** in ether, giving an ee of 73% at −110 °C, which is the highest ee ever reported for an enantiodifferentiating photosensitization.[8−10] It is also important to emphasize that, since all of the plots fit to a straight line for each solvent/sensitizer combination over the entire temperature range, the enantiodifferentiation mechanism is expected to remain the same over the studied temperature range. This unprecedented

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Table 1. Enantiodifferentiating Photoisomerization of **1Z** Sensitized by **2b** in Various Solvents

solvent	%ee[a] 25 °C	−40 °C	−78 °C	$\Delta\Delta H^{\ddagger}_{S-R}$ kcal/mol	$\Delta\Delta S^{\ddagger}_{S-R}$[b] cal/mol K
pentane	−5.5	−22.1	−40.4	0.84	2.62
heptane	−3.9	−13.5	−33.4	0.69	2.23
isopentane	−1.8[c]	−20.2	−50.9	1.45	5.26
isooctane	−3.4	−21.4	−49.4	1.13	3.77
methylcyclohexane	−5.7		−57.2	1.08	3.06
ethylcyclohexane	−4.7	−11.7	−34.8	0.77	2.53
diisopropyl ether	3.8	24.3	43.8	−0.97	−3.12
diethyl ether	−5.5	22.4	50.3	−1.41	−5.01
tetrahydrofuran	−0.2	31.8	47.6	−1.15	−3.78
1,2-dimethoxyethane	−5.2	21.3		−1.14	−4.03
acetonitrile	11.3	34.9		−0.94	−2.63
methanol	3.4	16.2	24.3	−0.48	−1.47

[a] Enantiomeric excess determined by chiral gas chromatography (see ref 14). [b] All activation parameters obtained by the Eyring treatment of the enantiomeric excess (see ref 12). [c] Value obtained at 0 °C.

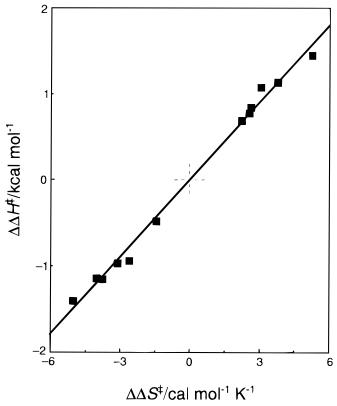

Figure 2. Enthalpy−entropy compensation plot for the enantiodifferentiating photoisomerization of **1Z** sensitized by **2b** in various solvents listed in Table 1.

solvent-controlled enantioselectivity switching behavior found in asymmetric photochemistry is not only of academic and mechanistic interest but also has synthetic and industrial potential, since it is often difficult to obtain antipodal products in conventional thermally driven or enzymatic asymmetric syntheses which employ the sole enantiomer of catalyst or enzyme that is available from the natural chiral pool.

To elucidate the nature of this important solvent effect, we performed enantiodifferentiating photosensitizations with **2b** in several solvents, allowing us to investigate a range of different polarities. From the ee of the product and the activation parameters obtained (Table 1), the solvents can be placed into one of two categories. Thus, all of the straight-chain, branched, or cyclic hydrocarbon solvents examined gave negative slopes ($\Delta\Delta H^{\ddagger}_{S-R} > 0$) and positive intercepts ($\Delta\Delta S^{\ddagger}_{S-R} > 0$) of comparable magnitudes, whereas polar solvents such as ethers, acetonitrile, and methanol showed the opposite behavior, affording positive slopes ($\Delta\Delta H^{\ddagger}_{S-R} < 0$) and negative intercepts ($\Delta\Delta S^{\ddagger}_{S-R} < 0$). Interestingly, the enthalpy−entropy compensation plot for the

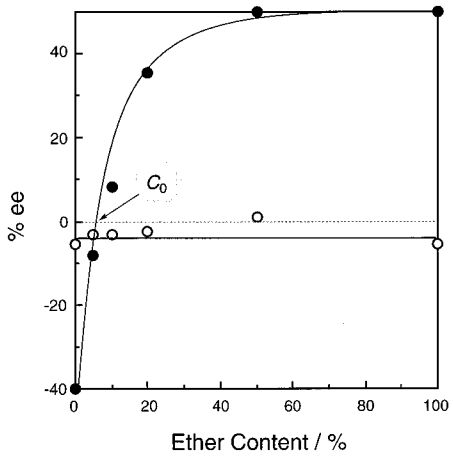

Figure 3. Effect of ether content upon enantiodifferentiating photoisomerization of **1Z** sensitized by **2b** at 25 °C (○) and −78 °C (●) in pentane−ether mixture.

differential activation parameters gives an excellent straight line passing through the origin, as shown in Figure 2, confirming that the enantiodifferentiation mechanism is not altered by a change in the solvent. The slope of this line gives an isokinetic, or isoenantiodifferentiating, temperature[15] of 26 °C, at which all of the solvents afford essentially the same ee.

This unusual solvent effect was further examined using a pentane-ether mixed solvent system of various compositions. At −78 °C, the change in the ee of the product was not directly proportional to the ether content but increased sharply with increasing ether content, changing from −40% ee in neat pentane to 0% ee when the ether content reached 8%, ultimately reaching a plateau of +50% ee in 50% ether (see Figure 3). No significant effect was observed for the same solvent changes at 25 °C. These results suggest that the ether solvent selectively solvates the ether moieties of the protected saccharide in **2b**, especially at low temperatures, resulting in the switching of product chirality.

Historically, the enthalpy factor has been believed to govern most chemical reactions which accompany the formation and/or cleavage of strong covalent or ionic bonds. However, in chemical and biological molecular recognition processes, where weak interactions such as hydrogen bonding, van der Waals forces, and $\pi-\pi$ interactions are known to play crucial roles, the entropy factor is thought to become more important in determining the outcome of the process.[15] Although this theory sounds quite reasonable, it has not been unequivocally demonstrated by experimental data, since thermal and biological reactions do not allow us to carry out experiments over a wide range of temperatures while maintaining the same reaction mechanism. However, photochemistry does not require thermal energy to promote reaction and has the inherent advantage of allowing us to examine the contribution of the entropy factor. In this and recent work,[11−14] we have shown that the weak interactions that occur in the exciplex intermediate can be controlled not only by enthalpy but also by entropy-related factors, such as temperature, pressure, and solvent. It is likely that the combined use of these factors will open up a new channel in the multidimensional control of the rate of reaction and the equilibrium position in both ground and excited states under more readily accessible conditions. Finally we should note that entropy control should not be restricted to photochemical processes, but should be a key concept when discussing chemical and biological supramolecular interactions, where weak interactions are dominant.[16−19]

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