Entropy Control in Chiral Photochemistry

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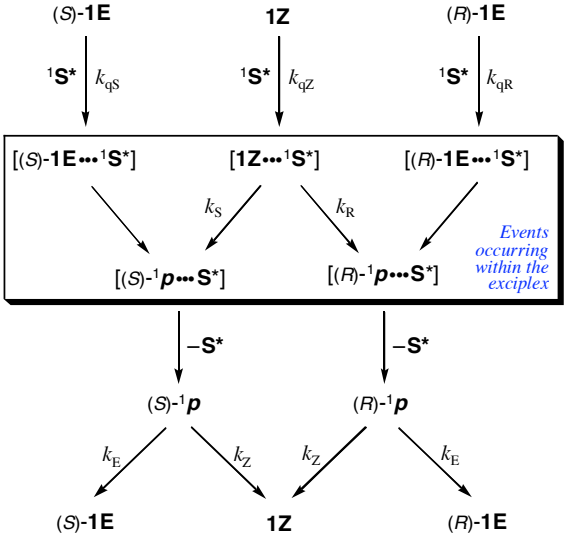
Introduction: Asymmetric synthesis is one of the most important areas in current chemistry. Hence, a considerable amount of effort have been devoted to this area in recent years.[1-9] Thus, enantio- and diastereoselectivity are the principal objective or prerequisite when developing a new asymmetric catalyst or synthetic methodology,[1-3] as well as in synthesizing chiral compounds such as naturally occurring and pharmaceuticals.[4-9] The stereochemical outcome of these asymmetric reactions has been discussed in terms of the empirical rules using the models of Cram,[10] Felkin-Anh[11,12] and others.[4,13] These models are based primarily on the relative steric bulk of the aligned substituents near the reaction centre, which are oriented by steric hindrance, dipole interactions or metal chelation. Obviously, the chiral discrimination mechanism based on these empirical rules can assess only the enthalpic contributions attributable to the steric/stereoelectronic interaction between the substituent and attacking reagent, while the entropic contribution arising from the conformational changes and re-positioning of the solvent molecules during the transition state has not been discussed explicitly for thermal and enzymatic asymmetric syntheses. Nevertheless, these empirical rules, which only take the enthalpy term into account, are generally successful and are frequently employed in interpreting and/or predicting the dominant stereoisomer formed, and also the trend in optical yield obtained in a variety of asymmetric induction and asymmetric catalysis processes. Consequently, the entropic contribution has not been discussed globally, or experimentally examined as a factor in the mechanism of most thermal asymmetric reactions until recently,[14] in spite of some early observations of small to moderate temperature effects on enantio- or diastereoselectivity, *e.g.* in the addition of alcohols or amines to ketenes in the presence of acetylquinine,[15] in the $LiAlH_4$ reduction of acetophenone in the presence of quinine,[16] and in the oxidation of sulfides with optically active peracids.[17] That entropy plays an important role does not seem unreasonable, since the temperature range available is rarely wide enough to thoroughly survey the effect of this variable, and the possible incorporation of different reaction mechanisms or a switch in intermediates resulting from a change in temperature is not rigorously ruled out in many thermal asymmetric reactions.

In contrast, photochemical reactions are driven by the absorption of high-energy photons and proceed through the excited state, which renders them inherently free from temperature restrictions, and they are, therefore, advantageous for investigating the effect of the entropy factor upon stereoselectivity over a wide temperature range without undergoing any essential changes in reaction mechanism or intermediates formed. However, the temperature effect has been rarely and only recently explored in the rather short history of asymmetric photochemistry.[18,19] Thus, in the diastereodifferentiating Paternò-Büchi photocycloaddition of optically active phenylglyoxylic esters with several alkenes,[20] Scharf *et al.* showed that the diastereoselectivity of the oxetane produced not only depends on the irradiation temperature, but also gives a bent Eyring plot as a consequence of the alteration of the rate limiting step that determine the diastereoselectivity. In the enantiodifferentiating *Z-E* photoisomerization of cyclooctene sensitized by optically active sensitizers,[21] we demonstrated that the antipodal (*E*)-cyclooctenes, *i.e.* (*S*)-(–)- and (*R*)-(+)-enantiomers, can be obtained simply by changing the irradiation temperature from -88 to +50 °C, and that the enantiomeric excess (*ee*) of the product increases with increasing temperature, an observation that conflicts with the belief that lowering the temperature will generally enhance the *ee*. This unprecedented temperature dependence and the switching of the major enantiomer produced was revealed to be exclusively entropic in origin through an analysis of the Eyring plot of the enantioselectivity of the reaction. A similar 'unusual' temperature dependence of stereoselectivity, which leads to the switching of product chirality and/or higher selectivity at higher temperature, has been observed in many enantio[22-25] and

diastereodifferentiating photoreactions[26-31] over the last decade. More recently, we have revealed that the product chirality can be controlled, and in some cases, actually switched by changing the pressure from atmospheric to 400 MPa in the photosensitized enantiodifferentiating isomerization of cyclooctene.[32]
In this lecture, I wish to present a global view of recent advances in 'photochirogenesis', particularly in enantiodifferentiating photosensitization reactions. We will also demonstrate how the entropic and enthalpic factors share the roles in manipulating the stereochemical outcome of these enantiodifferentiating photoreactions. Finally, we will show that the combined use of entropy-related factors, such as temperature, pressure and solvent, provides us with a new method for the control of asymmetric photochemistry. Indeed, the basic concepts revealed here by asymmetric photochemistry should also be applicable to thermal and biological asymmetric reactions.

Temperature effect

In the 'Photochirogenesis' project, which aims to devise methods for highly efficient photochemical generation, transfer and multiplication of molecular chirality, we have chosen the enantiodifferentiating geometrical photoisomerization of (*Z*)-cyclooctene (**1Z**) sensitized by optically active aromatic esters as one of the most promising processes for development, simply because this photosensitization was known to give chiral (*E*)-cyclooctene (**1E**) in high chemical and quantum yields and was also found to involve a singlet exciplex between the substrate and sensitizer (S*).[33] The involvement of a structurally well-defined exciplex intermediate, which enables efficient transfer of chiral information in the excited state, is an essential condition for obtaining high optical yield in an enantiodifferentiating photosensitization.
Taking into account the simultaneous formation of the two enantiomers of **1E**, the original sensitization mechanism[33] was modified to include chirality, as shown below.[22a] The photosensitization is initiated by the formation of an encounter complex [**1Z**/**E**•••^{1}**S***] between the excited sensitizer (^{1}**S***) and **1Z** or one of enantiomers of **1E**. Energy transfer within the exciplex intermediate and the subsequent rotation around the C=C bond of **1Z**/**1E** to a dihedral angle of *ca*. 90° afford a relaxed exciplex [^{1}***p***•••**S***], which in turn releases the perpendicular singlet (^{1}***p***), regenerating the ground-state sensitizer (**S***). It should be noted that chirality is induced in ^{1}***p*** during the rotational relaxation step. The subsequent decay of ^{1}***p*** to **1Z** or **1E** concludes the photoisomerization cycle.



There are two steps in this mechanism that are potentially enantiodifferentiating: (i) the quenching of ^{1}**S*** by enantiomeric **1E** and (ii) rotational relaxation within the exciplex [**1Z**•••^{1}**S***]. Thus, the rate constants for quenching (k_{qS}, k_{qR}) and/or rotation (k_S, k_R) may be different from one another. Experimentally, no appreciable optical rotation was detected in **1E** recovered during the initial stages of the enantiodifferentiating photosensitization of racemic **1E**, and the *ee* of product **1E** did not show any conversion dependency in the enantiodifferentiating photosensitization of **1Z**,[22b] both of which rule out the

possibility of enantiodifferentiation in the quenching process, and thus $k_{qS} = k_{qR}$. Hence, the rotational relaxation of **1Z** to $^1\boldsymbol{p}$ within the exciplex intermediate can be the only enantiodifferentiating step in this asymmetric photosensitization, and the *ee* of **1E** is determined exclusively by the relative rate, k_S/k_R. This seems quite reasonable, since intimate interaction, which leads to efficient chiral recognition, is more likely to occur in the long-lived exciplex intermediate that possesses a more defined structure than during the collisional quenching stage.

In order to discuss quantitatively the temperature dependence of the *ee*'s observed for this asymmetric photosensitization, the rate constants k_S and k_R were analyzed according to the Arrhenius, or Eyring equation. The relative rate constant, k_S/k_R, can then be expressed by the following equations:

$$\ln(k_S/k_R) = -\Delta E_{S\text{-}R}/RT + \ln(A_S/A_R) \quad (1a)$$

$$= -\Delta\Delta H^{\ddagger}_{S\text{-}R}/RT + \Delta\Delta S^{\ddagger}_{S\text{-}R}/R \quad (1b)$$

where $\Delta E_{S\text{-}R}$ represents the differential energy of activation, A_S/A_R is the relative frequency factor, and $\Delta\Delta H^{\ddagger}_{S\text{-}R}$ and $\Delta\Delta S^{\ddagger}_{S\text{-}R}$ denote the differential enthalpy and entropy of activation, respectively.

The enantiodifferentiating photosensitizations of **1Z** were performed in several solvents at temperatures ranging from +50 to -90 °C, using a variety of optically pure (poly)alkyl benzene(poly)carboxylates as chiral sensitizers.[22] Interestingly, the product chirality switched at a specific, or equipodal temperature, T_0, upon sensitization with most *ortho*-substituted benzenepolycarboxylates, whereas no chirality inversion was observed for non-*ortho* sensitizers; typical examples are shown in Fig. 1. This is the first observation of an enantiodifferentiating reaction where the *ee* of the product is not only inverted by temperature, but also raised with increasing temperature above T_0. It is also important that both enantiomers can be prepared simply by changing the temperature without using antipodal sensitizer.

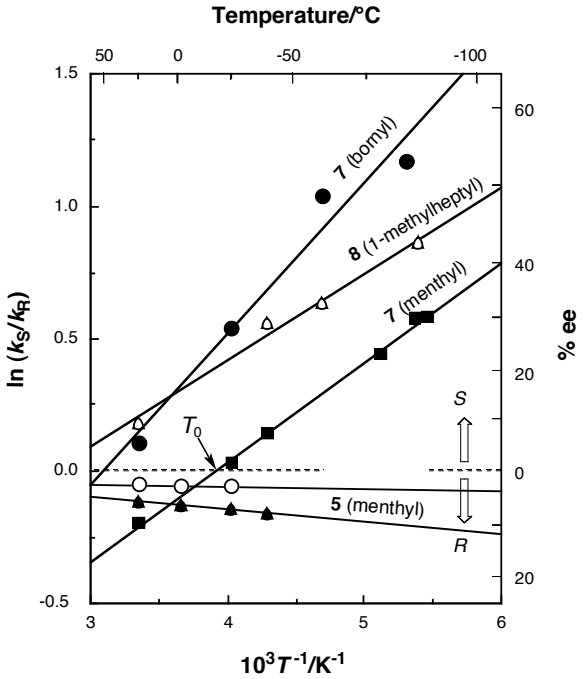


Fig. 1 Temperature dependence of the *ee* of the product in enantiodifferentiating photoisomerization of cyclooctene (**1Z**) sensitized by (–)-menthyl benzoate **2** (○) and terephthalate **5** (●), (–)-menthyl and (–)-bornyl 1,2,4,5-benzenetetracarboxylate **7** (■ and △), and (–)-1-methylheptyl benzenehexacarboxylate **8** (●) in pentane. The chirality of product **1E** is switched at the equipodal temperature, T_0.

From eqns. 1a and 1b and the experimental plots exemplified in Fig. 1, the activation parameters were determined for these enantiodifferentiating photoisomerizations using various chiral benzenecarboxylate sensitizers. ; the relevant activation parameters and equipodal temperatures obtained for several sensitizers are listed in Table 1

Table 1 Activation parameters at 25 °C, determined from the temperature and pressure dependence of the *ee* of **1E** obtained in enantiodifferentiating photoisomerization of cyclooctene (**1Z**), sensitized by chiral benzenepolycarboxylates **2**-**5**, **7** and **8** in pentane

Sensitizer		$\Delta\Delta H^{\ddagger}_{S\text{-}R}$ [a]	$T\Delta\Delta S^{\ddagger}_{S\text{-}R}$ [a]			$\Delta\Delta V^{\ddagger}_{S\text{-}R}$ [b]
Compound	R*	/kcal mol^{-1}	/kcal mol^{-1}	A_S/A_R	T_0/°C	/kcal mol^{-1}
2	(–)-Menthyl	+0.014	-0.039	0.99	*c*	-0.13
3	(–)-Menthyl	-0.19	-0.51	0.90	100	+0.83
	(–)-Bornyl	-0.50	-1.38	0.74	91	+1.48
4	(–)-Menthyl	+0.08	+0.15	1.16	530	+0.07
5	(–)-Menthyl	+0.09	+0.08	1.02	940	+0.36
7	(–)-Menthyl	-0.77	-3.00	0.52	-15	-3.71
	(–)-Bornyl	-0.61	-1.55	0.71	123	+0.29
	(–)-1-Methylheptyl	-0.54	-1.93	0.67	8	-1.44
8	(–)-Menthyl	-0.96	-3.85	0.43	-23	+3.50
	(–)-Bornyl	-0.86	-2.60	0.56	60	-5.56
	(–)-1-Methylheptyl	-1.13	-3.48	0.47	51	+0.56

[a] Reference 22b. [b] Reference 32. [c] T_0 does not exist.

By examining eqn. 1, it is apparent that this temperature switching behavior of product chirality is attributable to the non-zero differential entropy of activation ($\Delta\Delta S^{\ddagger}_{S\text{-}R} \neq 0$) or the unequal frequency factor ($A_S \neq A_R$). Thus, the entropy factor is shown to play a decisive role in the enantiodifferentiation process. It should be emphasized that the *ortho*-substituted benzenepolycarboxylates, such as phthalate, benzenetetracarboxylate and benzenehexacarboxylate, afford very large deviations from unity for the ratio A_S/A_R, while benzoate and terephthalate show almost equal frequency factors for the (*R*)- and (*S*)-isomers, as can be seen in Table 1. This tendency is not incidental, but implies that the rotational motion of the double bond of **1** in the exciplex causes simultaneous global conformational changes of the closely situated *ortho*-alkoxycarbonyl groups of the sensitizer. Such dynamic changes during rotational relaxation in the exciplex inevitably produce large differences in the activation entropy of enantiodifferentiation.

Although we have hitherto concentrated on the enantiodifferentiating photoisomerization of **1**, similar chirality inversion phenomena have been observed in the enantiodifferentiating photosensitizations of 1-methylcyclooctene[22f] and 1,3-cyclooctadiene,[24] as well as in the enantiodifferentiating *anti*-Markovnikov photoaddition of methanol to 1,1-diphenylpropene (**9**).[25b] Of these, the diphenylpropene case is particularly interesting, since this is the first bimolecular enantiodifferentiating photoreaction that affords the *anti*-Markovnikov adduct (**12**) upon sensitization with chiral 1,4-naphthalenedicarboxylates (**17**), with moderate *ee*'s of up to 33% observed. In this photosensitized polar addition, the use of *ortho* aromatic esters is no longer required to cause the inversion of product chirality by altering the temperature, probably because the termolecular interaction of the attacking methanol with the initially formed sensitizer-substrate exciplex exaggerates the influence of the conformational differences on the enantiodifferentiating process.

The roles of entropy and enthalpy

The contributions of the enthalpy and entropy factors to the enantiodifferentiating process can be discussed in terms of eqn. 1b, or using the Gibbs-Helmholtz equation for the differential activation free energy:

$$\Delta\Delta G^{\ddagger}_{S\text{-}R} = \Delta\Delta H^{\ddagger}_{S\text{-}R} - T\Delta\Delta S^{\ddagger}_{S\text{-}R} \qquad (2)$$

As can be seen from eqn. 2, T_0 is the critical point, at which the enthalpic and entropic contributions balance with each other ($\Delta\Delta H^{\ddagger}_{S\text{-}R} = T_0\Delta\Delta S^{\ddagger}_{S\text{-}R}$), affording no enantiodifferentiation. Below T_0, the enthalpy difference, $\Delta\Delta H^{\ddagger}_{S\text{-}R}$, controls the enantiodifferentiating process, while the entropic term, $T\Delta\Delta S^{\ddagger}_{S\text{-}R}$, is dominant at temperatures higher than T_0. If both $\Delta\Delta H^{\ddagger}_{S\text{-}R}$ and $\Delta\Delta S^{\ddagger}_{S\text{-}R}$ possess the same sign, switching of the dominant term in the enantiodifferentiation process leads to the inversion of product chirality, as exemplified above. In the enthalpy-controlled temperature region below T_0, the difference in the conformational freedom of the enantiodifferentiating transition states does not seriously affect the stereochemical consequence of the photoreaction, which is determined by the steric and stacking interactions in the exciplex intermediate. Since the p-p stacking interaction in the exciplex does not vary a great deal by changing the chiral auxiliary attached to the sensitizer, the majority of the enthalpy difference ($\Delta\Delta H^{\ddagger}_{S\text{-}R}$) may be attributed to different levels of steric interaction. In this context, it is reasonable to assume that the absolute configuration of the chiral sensitizer can be related directly and exclusively to that of photoproduct. In the following section, we first examine the appropriateness of this simple theory and then explore its scope and limitations, using the enantiodifferentiating photoisomerization of cyclooctene as a representative system which can provide extensive information concerning the effects of temperature and chiral auxiliary on the *ee* of the product.

Stereochemical correlation

The chiral photosensitizers employed in the enantiodifferentiating photoisomerization of cyclooctene can be classified into two categories,[22] according to the temperature dependency of the *ee* of **1E** obtained. As shown in Fig. 1, non-*ortho* benzene(poly)carboxylate sensitizers give only small *ee* values and low gradient slopes in the Eyring plots, where the T_0 does not exist at all, or appears only at an extreme temperature. In contrast, *ortho*-benzenepolycarboxylates, such as **3**, **7** and **8**, give much higher *ee*'s and steep slopes, and the product chirality is often switched at a readily accessible temperature. Since this contrasting behavior originates from the entropy term alone, it is probable that different enantiodifferentiation mechanism operates for the *ortho* and non-*ortho* sensitizers, from the conformational point of view.

In order to elucidate whether or not the absolute configuration of product **1E** can be correlated directly and globally to that of the stereogenic centre of the relevant chiral sensitizer, the data reported for the enantiodifferentiating photoisomerization of **1Z** sensitized by chiral benzene(poly)carboxylates in different solvents at ambient and low temperatures were determined.[22b,c] The sensitizers that carry phenyl group(s) in the chiral auxiliary are not included in this Table, nor in the following discussion, since they are known to form an intramolecular exciplex, to which the substrate **1Z** approaches from the phenyl side.[22c]

Firstly, we will consider the stereochemical consequence observed upon sensitization with the non-*ortho* sensitizers (**2**, **4**, **5** and **7**). As demonstrated by several representative examples, these sensitizers do not exhibit chirality inversion behaviour caused by a change in temperature. It is reasonable, therefore, to discuss the relationship between the absolute configuration of **1E** obtained at any temperature with that of the stereogenic centre of the sensitizer. In examining this correlation, we will take into account only the stereogenic centre directly connected to the ester oxygen of the relevant sensitizer when the chiral auxiliary has many such centres. This approach may be justified, since the configuration around the stereogenic centre nearest to the benzenecarboxylate chromophore is expected, in general, to dominate the steric interactions in the exciplex intermediate. After examining the data for 23 different non-*ortho* sensitizers in a variety of solvents, we found a perfect stereochemical correlation between the stereogenic centres of the relevant sensitizer and product, in spite of the low *ee*'s obtained. Thus, non-*ortho* sensitizers with *R*-configuration at the nearest stereogenic centre afford (*R*)-(–)-**1E** without exception, and the opposite is true of *S*-configuration sensitizers.

Encouraged by the above result, we made further attempts to understand the seemingly complex stereochemical outcome observed for *ortho* sensitizers (*i.e.* **3**, **7** and **8**). *Ortho* sensitizers are known to cause the chirality inversion of product through a change in the reaction temperature as a consequence of the significant contribution of the entropy term. However, the entropic contribution is minimized or made negligible at temperatures below T_0. Under these conditions, the absolute configuration of the chiral sensitizer correlates to that of **1E**. Examining the results for the *ortho* sensitizers presented in Table 1, a highly consistent stereochemical correlation was observed again. Apart from those sensitizers that possess highly congested secondary and tertiary chiral auxiliaries, *e.g.* the *endo,endo*- and exo,*exo*-3-

cyclohexylmethyl-2-bornyl, cedryl, 2-dicyclohexylmethyl-5-methylcyclohexyl and isopinocampheyl auxiliaries, the other 21 *ortho* sensitizers completely obey a rule which is opposite to that observed for the non-*ortho* sensitizers, *i.e. ortho* sensitizers with *R*-configuration afford (*S*)-(–)-**1E**.

These two mutually opposing stereochemical correlations, which are separately applicable to non-*ortho* and *ortho* sensitizers, urged us to derive plausible models which are compatible with them. A similar attempt to derive an exciplex model for a non-*ortho* sensitizer has already been carried out for (–)-menthyl benzoate, where an interaction of the ester carbonyl of excited benzoate with the C=C bond of **1Z** was proposed.[22b] This model is based on the fact that the *ee* values obtained upon sensitization with (–)-menthyl methyl terephthalate are exactly half of the values obtained with the (–)-dimenthyl analogue at all temperatures examined, and that a semiempirical MNDO calculation for methyl benzoate indicates a good match between the MO lobes of the ester carbonyl and the C=C bond of **1Z**.[22b] In the present study, we carried out the MO recalculations on methyl benzoate and phthalate in the excited singlet state, using the PM3 program (MOPAC). The results are mostly consistent with the previous ones,[22b] except for the highly developed antibonding lobes on the carbonyl and the different pattern of the aromatic lobes in HSOMO. However, steric interactions in (–)-menthyl benzoate and phthalate are better evaluated by MM2 calculations to give the optimized conformations shown in Fig. 3. As can be seen from the front view (Fig. 3a, bottom), the lower side of menthyl benzoate is covered by the menthyl isopropyl group preventing the approach of cyclooctene molecule to the ester carbonyl. If the top view is considered, it appears that the interaction of **1Z** with the C=O bond from the front side and the subsequent rotation of the C=C bond to the open side in the exciplex affords (*R*)-**1E**, in accord with the experimentally observed configuration. In the dimenthyl phthalate case (Fig. 3b), the optimized conformation is substantially different from that of the benzoate due to steric hindrance between the adjacent menthoxycarbonyl groups. Thus, the two ester groups are non-equivalent, with one carbonyl orientated inside and the other outside. It is assumed that the less hindered C=O group, which is directed outwards, can interact with cyclooctene molecule from the open face, forming the exciplex. The subsequent rotation in the exciplex towards the open side of the menthyl group results in the formation of (*S*)-**1E**, as observed experimentally at temperatures lower than T_0.

In view of the low ee's obtained, especially for non-*ortho* sensitizers, other rationales cannot be ruled out absolutely. However, we could not find any other model which was compatible with all of the experimental and MO calculation data.

The effect of pressure

In the preceding sections, we have demonstrated that weak interactions in the exciplex intermediate can be controlled by temperature as a result of the contribution of the entropy term. In this context, it is interesting to study the way in which pressure can be used as an alternative tool for controlling the weak interactions that determine the stereochemical outcome in the excited state. Although pressure effects upon thermochemical and photochemical reactions have been studied in considerable detail,[34] very little effort has been extended to enantiodifferentiating photochemical reactions until recently, probably as a result of the low *ee*'s reported for such processes. However, we have recently discovered that the enantiodifferentiating photoisomerization of **1Z** (shown in Scheme 1) is significantly affected by pressure, resulting in the inversion of product chirality.[32]

The pressure effect on the relative rate constant, k_S/k_R (Scheme 2), can be expressed as a linear function of pressure (P) at a constant temperature, [32]

$$\ln (k_S/k_R) = -(\Delta\Delta V^{\ddagger}_{S\text{-}R}/RT)P + C \qquad (3)$$

where $\Delta\Delta V^{\ddagger}_{S\text{-}R}$ represents the difference in activation volume and C is equal to ln (k_S/k_R) at P = 0. The effect of hydrostatic pressure of up to 400 MPa was investigated in the enantiodifferentiating photoisomerization of **1Z** sensitized by chiral benzene(poly)carboxylates.[32] According to eqn. 4, the ln (k_S/k_R) values obtained were plotted against pressure.

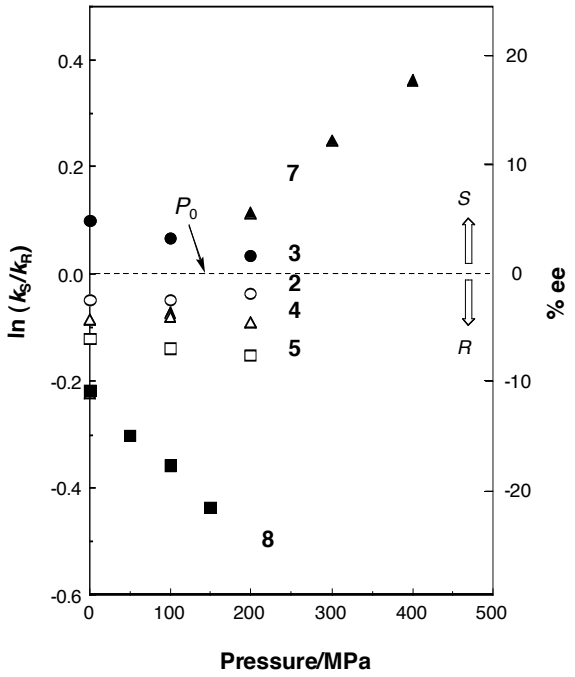


Fig. 4 Pressure dependence of the *ee* of the product in enantiodifferentiating photoisomerization of cyclooctene (**1Z**) sensitized by (–)-menthyl benzoate **2** (○), phthalate **3** (●), isophthalate **4** (⌂), terephthalate **5** (□), 1,2,4,5-benzenetetracarboxylate **7** (▲), and benzenehexacarboxylate **8** (■) in pentane at 25 °C; the chirality of product **1E** was switched at the equipodal pressure (P_0).

As can be seen from Fig. 4, variations in the reaction pressure significantly affect the *ee* of **1E**, and often the product chirality is switched at the equipodal pressure (P_0) upon sensitization with *ortho* benzenepolycarboxylates (**3**, **7**, **8**). However, *ee*'s obtained for non-*ortho* sensitizers (**2**, **4**, **5**) were generally small and insensitive to pressure changes. This contrasting behaviour of the *ortho* and non-*ortho* sensitizers is similar to that observed for the temperature dependency of *ee*, again indicating a significant contribution of the entropy factor in the enantiodifferentiating process. However, the differential activation parameters obtained from the temperature- and pressure-dependence experiments,[22b,32] which are listed in Table 1, behave quite differently. Indeed, inconsistencies become evident particularly in the parameters obtained for *ortho* esters, as sensitizers that give large $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values do not always show a strong pressure dependency, and no consistent relationship is found for the signs of $\Delta\Delta H^{\ddagger}$ or $\Delta\Delta S^{\ddagger}$ and $\Delta\Delta V^{\ddagger}$.

Multidimensional control of product chirality

The above discrepancy observed for temperature and pressure is not surprising, since both can be regarded as inherently independent variables. In order to verify this experimentally, and also to reveal the relationship between the *ee* of the product and these variables, we further investigated the effect of pressure on the enantiodifferentiating photoisomerization at several different temperatures, and found that the $\Delta\Delta V^{\ddagger}$ value depends critically on the reaction temperature.[32] From the data obtained, novel three-dimensional diagrams that correlate the *ee* with temperature and pressure were constructed for all possible cases. Two representative cases show inversion of the product chirality by temperature and/or pressure. In both cases, the enantiodifferentiating event occurs exclusively on one of the two intersecting planes that correspond to the antipodal sensitizers, and these two enantiodifferentiation planes are symmetrical to each other with respect to the T^{-1}–P plane. The temperature and pressure drive the product's *ee* in opposite

directions in Fig. 5a, where they act as independent factors. In spite of the limited number of sensitizers examined, a (–)-menthyl benzenetetracarboxylate sensitizer provides us with fortuitous example, in which the *ee* of **1E** increases with decreasing temperature and increasing pressure, ultimately affording an extrapolated *ee* as high as 98.3% under conditions which are practically accessible, *i.e.* -9 °C and 1500 MPa.[32]

Conclusions

From the extensive experiments and comprehensive analyses of a variety of enantio- and diastereodifferentiating photochemical reactions,[20-32] it has been revealed that the entropy term plays unexpectedly vital role in the stereodifferentiating processes where weak interactions determine rates and equilibria. However, it is important to emphasize that at temperatures below T_0, the stereoselectivity is dominated by the enthalpy difference arising mostly from steric and electrostatic interactions, while the dynamic behaviour of stereoselectivity over the whole temperature range, including the chirality switching phenomenon, is exclusively attributable to the entropy difference.

Experimental verification that temperature and pressure can function indeed as independent, yet cooperative, factors governing the product chirality in the enantiodifferentiating photosensitization gives us the new and versatile methodology of 'multidimensional control of asymmetric photochemistry'.[32] This strategy employs several entropy-related factors, such as temperature,[35] pressure, solvent,[36] concentration[37] and substituent flexibility, as tools for controlling the stereochemistry and stereoselectivity of photoproducts more conveniently and effectively through the manipulation of the steric and electronic weak interactions involved in the exciplex intermediates. Further, the concept of multidimensional control is not necessarily restricted to the asymmetric photochemical reactions described in this paper, but may be applied in general to any thermal and biochemical reaction or equilibria where weak interactions are the principal driving force or determining factor, and therefore, where the entropy factor plays a major role.[38]

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