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Pressure and Temperature Control of Product Chirality in Asymmetric Photochemistry. Enantiodifferentiating Photoisomerization of Cyclooctene Sensitized by Chiral Benzenepolycarboxylates

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Abstract: Pressure effects upon asymmetric photosensitization have been investigated for the first time in the enantiodifferentiating *Z*−*E* photoisomerization of cyclooctene (**1**), sensitized by chiral aromatic esters (**2**−**7**). The product's enantiomeric excess (ee) and *E/Z* ratio were critical functions of the applied pressure, exhibiting an unprecedented switching of the product chirality. Depending upon the chiral sensitizer employed, the differential activation volume ($\Delta\Delta V^{\ddagger}$) varies widely from −3.7 to +5.6 cm^3 mol^{-1}, which is unexpectedly large for an enantiodifferentiation in the excited state. However, the $\Delta\Delta V^{\ddagger}$ values obtained do not correlate with the differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) or entropy ($\Delta\Delta S^{\ddagger}$) obtained from temperature-dependence studies, indicating that pressure and temperature function as independent perturbants for the photoenantiodifferentiation process. Further investigations on the pressure dependence of ee at low temperatures enable us to construct the first three-dimensional diagram that correlates the product's ee with pressure and temperature changes. The combined effects of temperature and pressure provide us with a versatile tool for the multidimensional control of asymmetric photochemical reactions, in which we can switch and/or enhance the product chirality at more readily accessible temperatures and pressures, without using antipodal sensitizers.

Introduction

Asymmetric photosensitization with a catalytic amount of optically active sensitizer, leading to the formation of an excited state complex (exciplex) and ultimately to chiral products, has fascinated (photo)chemists from both a mechanistic and synthetic point of view over the last three decades[1,2] since the first attempt by Hammond and Cole in 1965.[3] Despite the considerable efforts devoted to studies of asymmetric photosensitizations with a variety of substrates and chiral sensitizers, the optical purities (op) or enantiomeric excesses (ee) reported have not exceeded 10% until recently.[2]

The greatest inherent advantage of photochemical asymmetric reactions over their thermal counterparts is the virtually unrestricted temperature range that is available. However, this unique benefit, which is specific to excited-state reactions, had not been positively utilized or even examined in most (asymmetric) photochemical reactions for a long period of time.[2] Only recently we have demonstrated that changing the reaction temperature drastically affects the product's op—as well as the photostationary *E/Z* ratio—obtained in the enantiodifferentiating *Z*−*E* photoisomerization of (*Z*)-cyclooctene (**1Z**) sensitized by optically active (poly)alkyl benzene(poly)carboxylates.[4,5] In several cases, the chirality of the photoproduct (*E*)-cyclooctene (**1E**) can switch simply by changing the irradiation temperature.[4−9] This conflicts with the wide-spread belief that higher op's are generally obtained at lower temperatures. Eyring treatments of the relative rate constants for the production of (*S*)- and (*R*)-**1E** reveal that this unusual temperature switching behavior is entropic in origin. Unequal entropies of activation for the enantiodifferentiating step are responsible for this unusual temperature dependence. Hence, temperature can be used as a convenient, but powerful tool for product chirality control, and both enantiomers can be prepared not by using antipodal sensitizers, but merely by changing the irradiation temperature. These unprecedented results and interpretations open a new concept in the entropic control of asymmetric photochemistry, and we have been prompted to study the effect of pressure as an alternative tool for controlling the weak interactions that discriminate product chirality in the excited state.

The effects of hydrostatic pressure upon chemical and biological reactions and equilibria have been extensively investigated, and considerable amounts of data on the activation and reaction volumes have been compiled.[10−20] Apart from these ground-state reactions and equilibria, several photophysical

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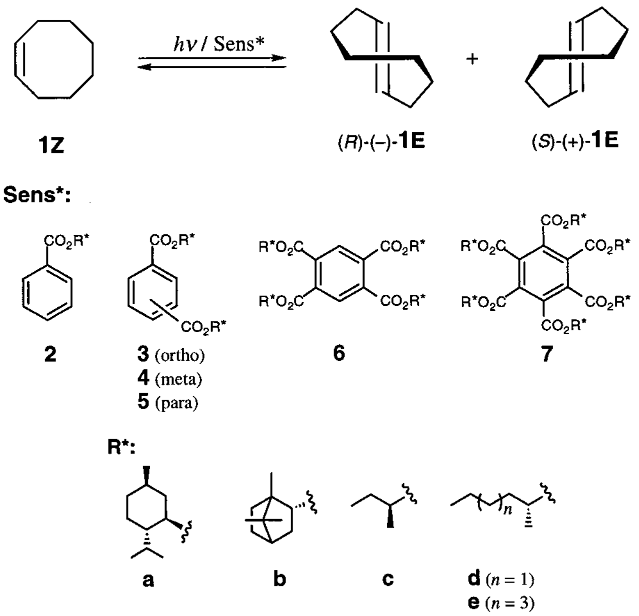
and photochemical processes have recently been subjected to pressure-dependence studies.[10,21−47] Thus, the effects of applied pressure and accompanying viscosity change upon fluorescence,[21−32] excimer/exciplex formation,[33−37] photosubstitution,[10,38] photoisomerization,[34,39−43] and photocycloaddition[44−47] have been studied in considerable detail. In the photocycloaddition reactions,[44−47] the product's regio- or diastereoselectivity has been shown to be more or less dependent upon the applied pressure. However, no such efforts have been devoted to enantiodifferentiating photochemical reactions, partly as a result of the fairly low ee's reported for such asymmetric processes at ambient temperature and pressure.[2]

We now wish to report our results concerning the first pressure-dependence study on the enantiodifferentiating $Z-E$ photoisomerization of cyclooctene, sensitized by optically active benzene(poly)carboxylates at ambient temperature. We have further extended our study to the pressure-dependent behavior of this enantiodifferentiating photoreaction at lower temperatures to construct a three-dimensional $P-T^{-1}-$ee diagram that represents the product's ee as a function of temperature (T) and pressure (P). We have also established a general method for the multidimensional control of asymmetric photochemical reactions by the application of several independent external variables such as T, P, etc.

Scheme 1



Results and Discussion

Under comparable conditions except for the applied pressure, which ranged from 0.1 (atmospheric) to 400 MPa, the enantiodifferentiating photosensitized isomerizations of **1Z** (5 mM) to chiral **1E** were performed in pentane at 25 °C, and subsequently at lower temperatures, using an unfiltered high-pressure mercury arc as the light source (>250 nm). The chiral sensitizers employed were benzene(poly)carboxylic esters **2**−**7** (0.2−1 mM) of optically active alcohols, i.e., (−)-menthol (**a**), (−)-borneol (**b**), (*S*)-(+)-2-butanol (**c**), (*R*)-(−)-2-hexanol (**d**), and (*R*)-(−)-2-octanol (**e**), shown in Scheme 1.

In most of these experiments the course of the photoisomerization process was not monitored, and only data at the initial, intermediate, and final (or photostationary) stages were collected at each pressure and temperature. This is because the ee values obtained in this enantiodifferentiating photoisomerization have been demonstrated to be practically independent of conversion, at least under atmospheric pressure.[5] The *E/Z* ratio, conversion, chemical yield, and ee of **1E** produced are listed in Table 1. The ee values are preceded by the sign of product's optical rotation at 589 nm, thus enabling immediate identification of the enantiomer produced.

It is noted that, even at pressures as high as 200 or 400 MPa, the main course of the photosensitization is the geometrical isomerization of **1Z** to highly strained **1E** in good to excellent chemical yields based on consumed **1Z**. Side reactions, such as the cycloaddition of **1** to the sensitizer or the polymerization of **1**, do not accompany this process.

Photoisomerization and Enantiodifferentiation Mechanisms. It has recently been demonstrated that the enantiodifferentiating photoisomerization of **1** sensitized by chiral benzenepolycarboxylates proceeds via a singlet mechanism involving an exciplex intermediate between excited chiral sensitizer and **1**.[4,5] The intervention of an exciplex was confirmed by the efficient quenching of sensitizer fluorescence, accompanied by

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Table 1. Pressure Effects upon Enantiodifferentiating Photoisomerization of Cyclooctene (**1Z**) Sensitized by Chiral (Poly)alkyl Benzene(poly)carboxylates (**2**−**7**) in Pentane at 25 °C[a]

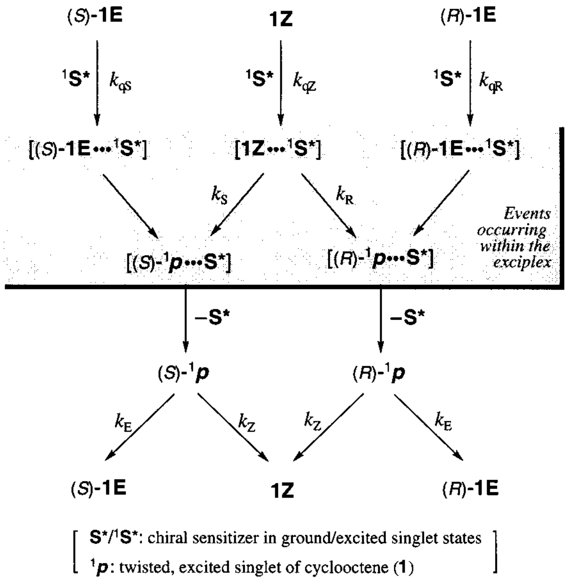
sensitizer	pressure/ MPa	irradiation time/min	**1E**/**1Z**	% conversion	% yield	% ee
2a	0.1	10	0.028	5.8	*b*	*b*
		30	0.082	11	7.3	−2.5
		60	0.12	18	9.7	−2.5
	100	10	0.016	5.8	*b*	−2.3
		30	0.085	10	7.6	−1.8
		60	0.15	17	13	−2.5
	200	10	0.031	*b*	*b*	*b*
		30	0.083	9.2	7.5	−2.4
		60	0.15	19	12	−1.9
2b	0.1	10	0.057	4.7	*b*	+0.1
		30	0.12	11	11	+0.5
		60	0.16	18	13	+0.1
	100	10	0.050	4.9	4.8	−1.1
		30	0.098	13	8.5	−0.6
		60	0.17	18	14	−1.2
	200	10	0.038	2.6	*b*	*b*
		30	0.10	12	9.2	+0.1
		60	0.18	20	14	−0.5
2e	0.1	10	0.051	6.8	4.8	+1.1
		30	0.10	10	9.0	+1.2
		60	0.16	12	14	+0.2
	100	10	0.046	7.2	*b*	+0.5
		30	0.10	9.7	9.3	−0.1
		60	0.17	18	14	−0.5
	200	10	0.033	4.6	*b*	−0.5
		30	0.085	11	7.6	+1.1
		60	0.19	18	16	−0.8
3a	0.1	10	0.028	8.1	*b*	*b*
		30	0.058	11	5.1	+6.3
		60	0.055	17	*b*	+4.9
	100	10	0.018	2.4	*b*	*b*
		30	0.075	3.1	*b*	+4.4
		60	0.080	14	6.8	+3.3
	200	10	0.019	7.3	*b*	*b*
		30	0.10	7.3	9.4	+2.0
		60	0.11	17	9.0	+1.6
3b	0.1	10	0.031	4.9	*b*	+11.0
		30	0.059	6.2	5.5	+11.9
		60	0.079	10	7.1	+10.6
	100	10	0.047	12	4.2	*b*
		30	0.074	17	6.1	+8.2
		60	0.095	22	7.5	+7.2
	200	10	0.043	11	*b*	+5.2
		30	0.099	19	8.1	+5.0
		60	0.10	22	8.0	+4.7
3e	0.1	10	0.028	2.3	*b*	*b*
		30	0.068	7.5	6.3	+2.9
		60	0.068	8.4	6.2	+3.2
	100	10	0.033	3.2	*b*	+3.1
		30	0.071	8.9	6.4	+3.7
		60	0.091	11	8.1	+2.3
		10	0.038	4.5	3.7	+1.9
		30	0.10	9.7	9.1	+1.9
		60	0.13	15	11	+1.6
4a	0.1	10	0.10	7.0	*b*	−3.6
		30	0.24	20	19	−3.9
		60	0.33	30	23	−4.3
	100	10	0.12	6.6	*b*	−3.5
		30	0.29	21	23	−3.8
		60	0.34	32	23	−4.0
		10	0.11	6.8	*b*	−3.5
		30	0.26	14	22	−4.1
		60	0.36	21	28	−4.5
4b	0.1	10	0.11	11	9.5	*b*
		30	0.23	23	18	−0.3
		60	0.33	29	24	−0.4
	100	10	0.11	13	9.6	*b*
		30	0.22	19	18	−0.4
		60	0.31	33	21	+0.4
	200	10	0.06	10	5.7	*b*
		30	0.20	20	16	−0.4
		60	0.32	33	21	−0.4
4e	0.1	10	0.10	7.0	*b*	−1.3
		30	0.23	20	18	−1.1
		60	0.30	27	22	−1.1
	100	10	0.10	9.7	9.1	−1.2
		30	0.24	22	19	−1.0
		60	0.34	29	24	−0.9
	200	10	0.091	9.4	8.2	−1.2
		30	0.24	22	18	−1.2
		60	0.32	29	22	−1.0
5a	0.1	10	0.23	25	17	−6.0
		30	0.32	37	21	−6.6
		60	0.39	36	25	−6.2
	100	10	0.25	33	17	−7.0
		30	0.37	38	23	−7.4
		60	0.40	45	22	−7.0
	200	10	0.24	23	18	−7.5
		30	0.39	43	22	−7.4
		60	0.43	53	20	−7.7
5b	0.1	10	0.18	19	14	−3.9
		30	0.26	29	18	−4.9
		60	0.30	33	20	−4.9
	100	10	0.22	22	17	−5.0
		30	0.39	35	25	−4.9
		60	0.41	40	25	−4.7
	200	10	0.20	19	16	−3.9
		30	0.40	36	26	−5.1
		60	0.47	44	26	−4.9
5e	0.1	10	0.19	17	16	−2.4
		30	0.29	27	21	−3.4
		60	0.31	32	21	−3.1
	100	10	0.22	22	17	−3.0
		30	0.38	34	25	−2.7
		60	0.44	41	26	−2.7
	200	10	0.24	24	19	−2.7
		30	0.44	37	27	−2.9
		60	0.51	45	28	−2.6
6a	0.1	10	0.12	15	10	−9.3
		30	0.19	28	14	−10.7
		60	0.21	38	13	−11.2
	100	10	0.10	20	8.3	−1.9
		30	0.26	34	17	−1.5
		60	0.32	45	18	−3.6
	200	10	0.11	21	8.8	*b*
		30	0.31	40	18	+6.6
		60	0.36	41	21	+5.7
	300	60	0.020	*b*	24	+12.4
	400	60	0.050	*b*	23	+17.9
6b	0.1	10	0.35	32	24	+14.7
		30	0.30	29	22	+16.1
		60	0.31	39	19	+14.2
	100	10	0.19	21	15	+15.0
		30	0.33	35	22	+14.4
		60	0.34	41	20	+14.3
	200	10	0.19	25	14	+13.4
		30	0.36	40	21	+11.9
		60	0.43	46	23	+13.0
6c	0.1	10	0.14	22	11	+2.1
		30	0.20	30	14	+2.3
		60	0.19	35	13	+2.9
	100	10	0.19	25	14	+0.6
		60	0.33	42	19	+0.1
	200	10	0.23	29	16	−0.4
		30	0.39	41	23	−0.3
		60	0.44	48	23	−0.6
6d	0.1	10	0.15	19	12	−2.5
		30	0.20	28	14	−2.5
		60	0.22	35	14	−2.7
	100	10	0.19	19	15	+0.8
		60	0.34	41	20	−1.1
	200	10	0.23	28	16	+1.9
		30	0.34	38	23	+2.3
		60	0.45	49	23	+1.3

Table 1 (Continued)

sensitizer	pressure/ MPa	irradiation time/min	**1E**/**1Z**	% conversion	% yield	% ee	sensitizer	pressure/ MPa	irradiation time/min	**1E**/**1Z**	% conversion	% yield	% ee
6e	0.1	10	0.15	19	13	−3.0	**7b**	0.1	30	0.029	4.9	*b*	+7.1
		30	0.21	26	15	−3.2			60	0.034	7.5	3.2	+5.0
		60	0.22	31	15	−3.8		100	10	0.023	*b*	*b*	+17.3
	100	10	0.19	22	15	0.0			30	0.040	6.2	3.8	+18.5
		30	0.31	31	21	−0.3			60	0.062	13	5.4	+15.8
		60	0.35	37	22	0.0		200	10	0.029	5.3	*b*	+30.0
	200	10	0.23	24	17	+2.1			30	0.057	8.4	5.2	+29.4
		30	0.38	35	25	+2.1			60	0.073	15	6.2	+26.8
		60	0.46	43	26	+2.1	**7e**	0.1	10	0.055	5.2	5.2	+5.0
7a[c]	0.1	30	0.012	*b*	*b*	−14.1		30	0.091	7.7	8.4	+4.3	30
		60	0.026	2.4	*b*	−10.9		60	0.10	11	9.1	+4.2	60
	50	60	0.034	5.1	3.2	−15.0		100	10	0.085	8.0	7.8	*b*
	100	10	*b*	0.1	*b*	−17.0			30	0.15	14	13	+3.4
		60	0.045	5.2	4.2	−17.7			60	0.19	19	15	+3.7
	150	10	0.014	2.6	*b*	−20.9		200	10	0.10	7.3	*b*	+1.4
		60	0.056	9.3	5.1	−21.4			30	0.21	18	17	+1.3
									60	0.26	24	20	+1.9

[a] Irradiation (>280 nm) conducted at 25 °C in a pressurized vessel with a sapphire window, using an unfiltered high-pressure mercury arc; [**1Z**] = 5 mM, [sensitizer] = 1 mM, unless noted otherwise. [b] Value not determined. [c] [Sensitizer] = 0.5 mM.

Scheme 2



the concomitant development of exciplex emission at longer wavelengths. The mechanism of the enantiodifferentiating photosensitized isomerization is illustrated in Scheme 2. The photosensitized geometrical isomerization has been shown to be reversible, affording the same *E/Z* ratio at the photostationary state irrespective of the initial isomer composition employed.[5,48] However, the recycling paths, connecting **1Z**, (*R*)-**1E**, and (*S*)-**1E** on the top and the bottom, are omitted in the scheme for the sake of simplicity. The rate constants k_{qZ}, k_{qR}, and k_{qS} respectively refer to the quenching of excited sensitizer (^{1}**S***) by **1Z**, (*R*)-**1E**, and (*S*)-**1E**, while k_R and k_S refer to the rotational relaxation of **1Z** to twisted singlets (*R*)- and (*S*)-^{1}***p*** within the exciplex, and k_Z and k_E to the subsequent decay of ^{1}***p*** to **1Z** and **1E**.

It has been further revealed that the product's ee's are independent of conversion from the initial stage to the ultimate photostationary state, and an attempted kinetic resolution starting from racemic **1E** gives only negligible ee's during the early stages of photoisomerization.[5] These observations clearly rule out any possible kinetic resolution at the quenching step (i.e., $k_{qS} = k_{qR}$ in Scheme 2) and unequivocally show that the rotational relaxation within the exciplex intermediate is the only enantiodifferentiating process in this photosensitized isomerization (i.e., $k_S \neq k_R$ in Scheme 2), at least at room temperature and atmospheric pressure.

Table 1 shows that the product's ee varies significantly with the electronic and stereochemical structure of sensistizer employed, and also with the applied pressure, but is not appreciably influenced by irradiation period (within experimental error; ±0.5−1.0% ee) at atmospheric as well as at much higher pressures. It is concluded therefore that the photosensitization and enantiodifferentiation mechanisms established at atmospheric pressure can be extended to the photosensitized isomerization at high pressures.

Pressure Effect upon Photoisomerization. According to the reversible photoisomerization mechanism shown in Scheme 2, the *E/Z* ratio at the photostationary state (pss) is given as a product of the excitation ratio, k_{qZ}/k_{qE}, and the decay ratio, k_E/k_Z; i.e., $(E/Z)_{pss} = (k_{qZ}/k_{qE})(k_E/k_Z)$, where $k_{qE} = (k_{qR} + k_{qS})/2$. Since no enantiodifferentiation was observed to occur during the quenching process, the quenching rate constant (k_{qE}) for racemic **1E** is virtually equal to k_{qS} and k_{qR} in the present case; i.e., $k_{qE} = k_{qS} = k_{qR} \neq k_{qZ}$.[5]

To elucidate the effects of pressure upon photosensitized enantiodifferentiation, only three fixed irradiation periods were employed, which are appropriate to check the initial, intermediate, and final stages of the photoisomerization. As can be seen from Table 1, apparent pss's are established in several cases after irradiation for 60 min. We therefore discuss the efficiency of photoisomerization by assuming that these *E/Z* ratios, $(E/Z)_{pss}$, are equal or very close to the real pss values.

From the mechanistic point of view, it should be emphasized that the observed pressure effect on the $(E/Z)_{pss}$ ratio depends critically upon the sensitizer employed, and that the $(E/Z)_{pss}$ ratios obtained are enhanced at high pressures without exception. The first observation clearly rules out the possibility of pressure-dependent decay ratios, indicating that the quenching step must be responsible for the pressure-dependent $(E/Z)_{pss}$ ratios. Since the $(E/Z)_{pss}$ or k_{qZ}/k_{qE} ratios increase with increasing pressure, the activation volume for quenching by **1Z** is inferred to be smaller than that for **1E** in all cases examined, facilitating the quenching by **1Z** and the production of **1E** at high pressures.

Interestingly, the sensitizers used may be classified into two categories on the basis of the magnitude of the pressure effect.

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The increments in $(E/Z)_{pss}$ induced by increasing the pressure from 0.1 to 200 MPa are less than 20% of the original values in the majority of cases which employ benzoates **2**, isophthalates **4**, and terephthalates **5** as sensitizers. On the other hand, the $(E/Z)_{pss}$ ratio is enhanced 100% or more at 200 MPa in the photosensitizations with phthalates **3**, 1,2,4,5-benzenetetracarboxylates **6**, and benzenehexacarboxylates **7**. Thus, $(E/Z)_{pss}$ ratios as high as 0.4−0.5, which are difficult to attain at ambient temperatures as a result of the high strain energy of **1E**,[48−51] are quite easily obtained at high pressure. Incidentally, the same categorization of sensitizer has been proposed on the basis of the large temperature dependence of the product's ee obtained in the enantiodifferentiating photosensitizations by the ortho esters **3**, **6**, and **7**.[4,5] It is likely that each of the pressure and temperature effects observed are entropy-related, and originate from the conformational flexibility of mutually interacting ortho substituents in **3**, **6**, and **7**. In this context, it is interesting to note that the pressure effect upon $(E/Z)_{pss}$ appears to be particularly exaggerated when more substituted sensitizers with less bulky ester groups such as **6c**−**e** and **7e** are used, probably as a result of their greater compressibility arising from their conformational flexibility. This rationalization may be justified by the much higher compressibility of hexane (17.09×10^{-10} $m^2\ N^{-1}$)[52] than that of cyclohexane (11.40×10^{-10} $m^2\ N^{-1}$)[53] determined at 25 °C and 0.1 MPa.

Pressure Effect upon Enantiodifferentiation. From the pressure dependence of product's ee, a more rigorous distinction between the chiral sensitizers can be made between ortho and nonortho benzene(poly)carboxylates. As shown in Table 1, negligible pressure effects are found in the ee's obtained upon photosensitizations with all benzoates **2**, isophthalates **4**, and terephthalates **5**. In contrast, the use of ortho benzenepolycarboxylates (**3**, **6**, and **7**) as chiral sensitizers under comparable conditions leads to drastically pressure-dependent ee's, although the outcome can either be positive or negative.

Interestingly, *the product chirality is switched at the equipodal pressure (P_0) simply by changing the pressure applied* upon sensitization with benzeneteteracarboxylates (**6a**,**c**,**d**). In an extreme case, the chiral sensitizer **6a** gave (*R*)-**1E**, with an 11% ee at atmospheric pressure, but the antipodal (*S*)-**1E** with an 18% ee at 400 MPa.

Although the effects of pressure upon enantiodifferentiating photochemical reactions have not yet been explored and, as a result, no such observations are found in the literature, an unusual temperature switching of the product's chirality has been reported to occur in the same enantiodifferentiating photosensitization system.[4,5] The temperature-switching phenomenon, also observed only with the ortho benzenepolycarboxylate sensitizers, has been attributed to a significant contribution by the entropy factor, arising from global conformational changes of the mutually interacting ortho ester moieties, which are believed to synchronize with the enantiodifferentiating rotational relaxation of the double bond of **1** within the exciplex intermediate.[5] Judging from the similar tendencies shared by the temperature and pressure effects, it is obvious that the mutually interacting ortho ester groups play a crucial role in determining the product's ee.

The unprecedented pressure dependence of the product's ee cannot be attributed to increased viscosity at high pressure, since the solvent viscosity does not appreciably affect the product's ee, at least at atmospheric pressure.[5] For instance, in the photosensitizations of **1Z** with **2a** and **5a**, practically identical op's of **1E** are given in pentane (η 0.225 mPa s)[54] and in cyclohexane (η 0.898)[54] at 25 °C. Similarly, upon sensitizations with **6a**, the op values of **1E** produced at 25 °C are −9.4, −8.8, and −8.7% in pentane (η 0.225),[54] heptane (η 0.397),[54] and decane (η 0.861),[54] respectively, and those obtained at −87 °C are −28.9 and −30.7% in pentane (η 0.645)[55] and heptane (η 1.22),[55] respectively. We may conclude that the product's ee is governed not by the viscosity change caused by increasing pressure, but through the direct effect of pressure upon the enantiodifferentiating process in the photoisomerization sensitized by chiral benzenepolycarboxylates.

Activation Volume. To discuss the pressure effect upon the product's ee more quantitatively, it is necessary to calculate the differential volume of activation for the enantiodifferentiating photosensitized isomerization.

Rate constants are known to depend on temperature and pressure. At a given temperature (*T*), the effect of pressure (*P*) upon rate constant (*k*) is described by eq 1:

$$(\partial \ln k/\partial P)_T = -\Delta V^{\ddagger}/RT \qquad (1)$$

where $\Delta V^{\ddagger}$ stands for the activation volume and *R* the gas constant (8.314 $cm^3\ MPa\ K^{-1}\ mol^{-1}$). Applying this general equation to each enantiomeric photoisomerization process, which affords (*S*)- and (*R*)-**1E** in the present case, we obtain:

$$(\partial \ln k_S/\partial P)_T = -\Delta V^{\ddagger}{}_S/RT \qquad (2)$$

$$(\partial \ln k_R/\partial P)_T = -\Delta V^{\ddagger}{}_R/RT \qquad (3)$$

Following on, the relationship between the relative rate constant k_S/k_R and pressure is expressed by eq 4.

$$[\partial \ln(k_S/k_R)/\partial P]_T = -\Delta\Delta V^{\ddagger}{}_{S-R}/RT \qquad (4)$$

Assuming a constant activation volume over the entire pressure range employed, the relative rate constant is expressed as a linear function of pressure (eq 5), in which the differential activation volume $\Delta\Delta V^{\ddagger}{}_{S-R}$ is calculated from the proportionality coefficient.

$$\ln(k_S/k_R) = -(\Delta\Delta V^{\ddagger}{}_{S-R}/RT)P + C \qquad (5)$$

In eq 5, the integration constant *C* is equal to $\ln(k_S/k_R)$ at $P = 0$.

Using eq 5, we plotted the logarithm of the relative rate constant obtained experimentally from the ee value (i.e. $k_S/k_R = (100 + \%\ ee)/(100 - \%\ ee)$) as a function of the applied pressure. In all cases, good straight lines were obtained over the pressure range examined, as exemplified in Figure 1. The differential activation volumes ($\Delta\Delta V^{\ddagger}{}_{S-R}$) obtained from the plots are listed in Table 2, along with the differential enthalpy ($\Delta\Delta H^{\ddagger}{}_{S-R}$) and entropy ($\Delta\Delta S^{\ddagger}{}_{S-R}$) of activation calculated from the data obtained in the temperature-dependence studies previously reported.[5]

From the linear *P* vs ln *k* plots obtained, it may be concluded that the hydrostatic pressure causes no alterations to the enantiodifferentiation mechanism, or to the activation volumes

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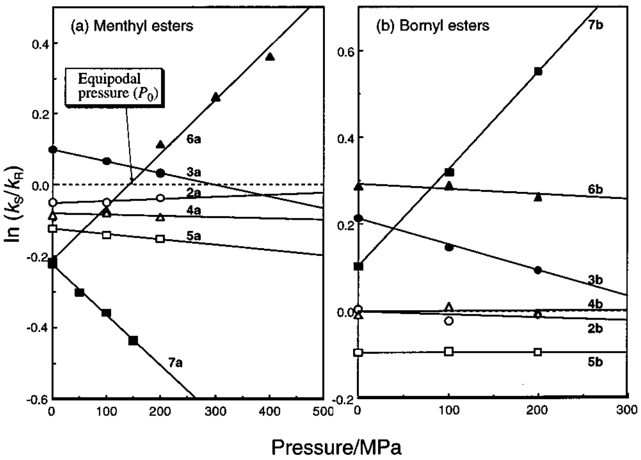

Figure 1. Pressure dependence of the relative rate constant k_S/k_R in the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene **1Z** sensitized by (−)-menthyl (a) and (−)-bornyl (b) benzoates **2a**,**b** (○), phthalates **3a**,**b** (●), isophthalate **4a**,**b** (△), terephthalate **5a**,**b** (□), benzenetetracarboxylates **6a**,**b** (▲), and benzenehexacarboxylates **7a**,**b** (■) in pentane at 25 °C.

Table 2. Activation Parameters at 25 °C Determined from Temperature and Pressure Dependence of Enantiomeric Excess in Enantiodifferentiating Photoisomerization of Cyclooctene (**1Z**) Sensitized by Chiral Benzenepolycarboxylates (**2**−**7**) in Pentane

sensitizer	$\Delta\Delta H^{\ddagger}_{S-R}$[a]/ kcal mol^{-1}	$\Delta\Delta S^{\ddagger}_{S-R}$[a]/ cal mol^{-1} K^{-1}	$\Delta\Delta V^{\ddagger}_{S-R}$/ cm^3 mol^{-1}
2a	0.014	−0.039	−0.13
2b	*b*	*b*	+0.16
2e	*b*	*b*	+0.27
3a	−0.19	−0.51	+0.83
3b	−0.50	−1.38	+1.48
3e	*b*	*b*	+0.39
4a	+0.1	+0.1	+0.07
4b	*b*	*b*	−0.03
4e	*b*	*b*	−0.02
5a	+0.092	+0.077	+0.36
5b	*b*	*b*	+0.01
5e	*b*	*b*	−0.12
6a	−0.77	−3.00	−3.71
6b	−0.61	−1.55	+0.29
6c	+0.29	+1.01	+0.87
6d	−0.54	−1.89	−0.99
6e	−0.54	−1.93	−1.44
7a	−0.96	−3.85	+3.50
7b	−0.86	−2.60	−5.56
7e	−1.13	−3.48	+0.56

[a] Reference 5. [b] Value not available.

Table 3. Temperature and Pressure Effects upon Enantiodifferentiating Photoisomerization of Cyclooctene (**1Z**) Sensitized by (−)-Menthyl, (−)-Bornyl, and/or (*R*)-1-Methylheptyl Pyromellitate (**6a**) and Mellitates (**7a**,**b**,**e**) in Pentane[a]

sensitizer	temp/ °C	pressure/ MPa	irradiation time/min	**1E**/ **1Z**	% conversion	% yield	% ee
6a	7	0.1	10	0.16	18	13	−3.8
			30	0.28	29	20	−4.4
			60	0.35	36	22	−6.1
		100	60	0.47	42	27	+7.7
		200	10	0.17	18	14	+16.7
			30	0.35	32	24	+16.8
			60	0.55	46	30	+16.5
	−9	0.1	10	0.14	15	12	+1.9
			30	0.30	29	21	+2.7
			60	0.42	40	25	+1.6
		25	60	0.44	39	27	+6.1
		50	60	0.44	38	27	+9.4
7a	5	0.1	10	*b*	0.7	*b*	−14.4
			30	*b*	3.6	*b*	−13.4
			60	0.018	2.0	*b*	−12.3
		50	10	*b*	1.8	*b*	−17.9
			60	0.023	3.8	*b*	−12.9
		100	10	*b*	2.5	*b*	−16.7
			30	0.020	3.8	*b*	−17.1
			60	0.032	2.8	3.1	−15.3
	−6	0.1	30	*b*	1.0	*b*	−11.9
			60	0.014	*b*	*b*	−12.7
		25	10	*b*	*b*	*b*	−12.4
			60	0.014	1.6	*b*	−10.4
		50	10	*b*	*b*	*b*	−12.8
			30	*b*	*b*	*b*	−12.1
			60	0.016	*b*	*b*	*b*
7b	5	0.1	10	0.008	0.7	*b*	+16.2
			30	0.026	3.2	*b*	+16.5
			60	0.048	5.2	4.5	+14.0
		50	10	0.008	*b*	*b*	+24.2
			60	0.043	6.8	4.0	+18.3
		100	10	0.009	0.4	*b*	+27.6
			30	0.026	1.6	*b*	+27.3
			60	0.049	5.6	4.6	+24.0
	−9	0.1	10	*b*	1.5	*b*	+24.5
			30	0.015	1.4	*b*	+21.3
			60	0.030	2.4	3.0	+20.8
		25	10	*b*	1.2	*b*	+25.7
			60	0.026	5.2	2.4	+23.1
		50	10	*b*	2.2	*b*	+28.7
			30	0.017	1.7	*b*	+27.8
			60	0.029	3.6	2.8	+25.3
7e	4	0.1	10	0.034	5.1	*b*	+15.6
			30	0.091	10.6	8.2	+14.4
			60	0.139	15.7	11.7	+16.5
		50	10	0.032	5.2	*b*	+16.0
			60	0.153	17.6	12.6	+14.4
		100	10	0.033	5.7	*b*	*b*
			30	0.100	12.8	8.7	+12.4
			60	0.173	19.4	13.9	+12.0
	−10	0.1	10	0.022	6.2	*b*	+20.8
			30	0.066	9.8	5.9	+21.7
			60	0.116	15.6	9.8	+18.2
		25	10	0.017	3.5	*b*	+16.1
			60	0.111	12.3	9.8	+17.9
		50	10	0.023	6.0	*b*	*b*
			30	0.068	11.2	6.0	+16.9
			60	0.132	16.0	11.1	+15.9

[a] Irradiation (>280 nm) conducted in a thermostated pressurized cell with a sapphire window, using an unfiltered high-pressure mercury arc; [**1Z**] = 5 mM, [sensitizer] = 1 mM. [b] Value not determined.

for these sensitizers over the pressure range employed, since any change in mechanism caused by pressure would lead to nonlinearity.[10] Naturally, the magnitude of $\Delta\Delta V^{\ddagger}$ is strongly dependent upon the sensitizer employed. As listed in Table 2, the nonortho sensitizers **2**, **4**, and **5** afford only small or negligible $|\Delta\Delta V^{\ddagger}|$ values ($\ll$1.0 cm^3 mol^{-1}), whereas much greater $|\Delta\Delta V^{\ddagger}|$ values ($\leq$1.5, 3.4, and 5.5 cm^3 mol^{-1}) are obtained with the ortho sensitizers (**3**, **6**, and **7**, respectively).

Although we could not find any appropriate data for comparison in the literature, *differential* activation volumes of up to 5.5 cm^3 mol^{-1} obtained in the present study are unexpectedly large for the *Z*−*E* photoisomerization of such a simple cycloalkene in view of the small *actual* $\Delta V^{\ddagger}$ values of −0.6 to +9.3 cm^3 mol^{-1} which are reported for thermal *Z*−*E* isomerizations of more bulky indigo derivatives.[56] A very small $\Delta\Delta V^{\ddagger}$ of −0.8 cm^3 mol^{-1} was reported for the Lewis acid-catalyzed enantiodifferentiating Wagner−Meerwein rearrangement of 1,1-diphenyl-2-methyl-2-anisyloxirane in the presence of (−)-menthol.[10b,57] The pressure effects upon regio- or diastereoselectivity have also been examined in some thermal and photochemical reactions. Thus, both the thermal Diels−

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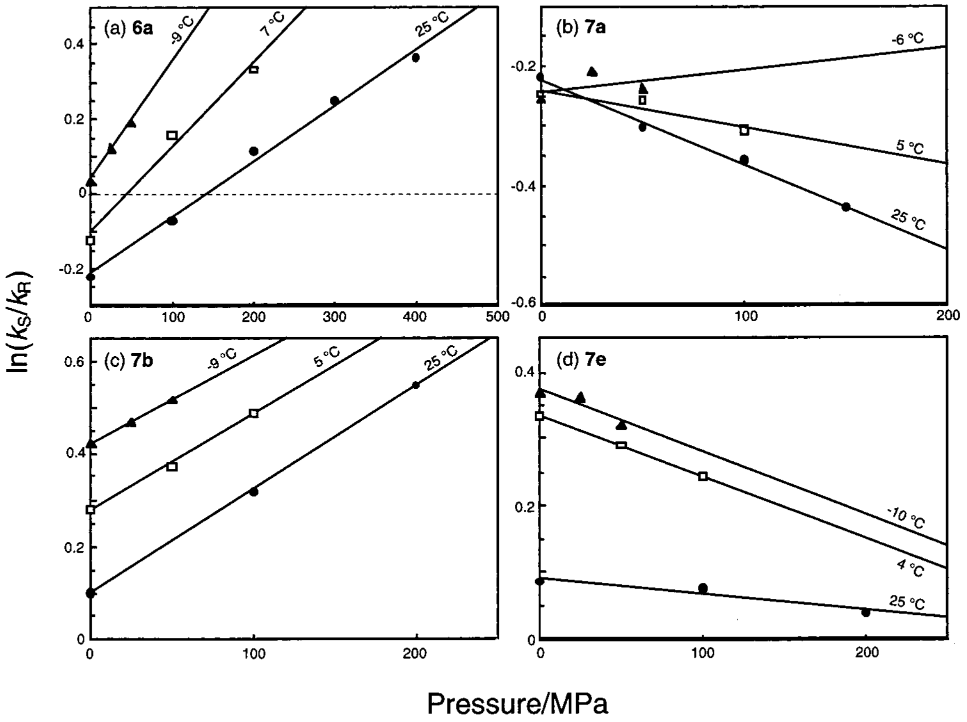

Figure 2. Temperature and pressure dependencies of the relative rate constant k_S/k_R in the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene **1Z** sensitized by (−)-menthyl benzeneteteracarboxylates **6a** (a) and (−)-menthyl (b), (−)-bornyl (c), and (*S*)-1-methylpropyl (d) benzenehexacarboxylates **7a**,**b**,**e** in pentane.

Alder reactions of various dienes and alkenes[10b] and the photochemical [2+2] cycloadditions of cyclopentenones with alkenes[45] also give relatively small $\Delta\Delta V^\ddagger$ values of 0.5−4.5 and 0−2.0 cm^3 mol^{-1}, respectively. In the [4+2] photocyclodimerization of 1,3-cyclohexadiene, the $\Delta\Delta V^\ddagger$ value for endo/exo selectivity depends substantially upon the solvent and the substrate concentration employed, affording small values of 1.2−2.4 cm^3 mol^{-1} in acetonitrile, but unusually large values of 9−12 cm^3 mol^{-1} in benzene as a result of the involvement of different types of solvated ion pairs in the two solvents.[47] It is therefore inferred that, in the absence of any active participation of solvent molecules in pentane solution in the present study, the large absolute $\Delta\Delta V^\ddagger_{S-R}$ values which are obtained only for ortho sensitizers reflect possible differences in the degree of conformational changes upon enantiodifferentiating rotational relaxation of **1Z** to (*S*)- ^{1}***p*** or (*R*)-^{1}***p*** within the exciplex intermediate, as shown in Scheme 2.

It is difficult to anticipate the sign and magnitude of the $\Delta\Delta V^\ddagger$ value, as is the case for the $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ values.[5,6] Nonetheless, the sensitizers possessing more bulky substituents generally afford greater $\Delta\Delta V^\ddagger$ values, as demonstrated by the series of sensitizers **6c**−**e** with increasing chain length. Similar general trends have been observed in the $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ values reported for the same enantiodifferentiating photoisomerization at varying temperatures.[5] In this context, it would be interesting to examine the general validity of the proposed linear relationship between $\Delta S^\ddagger$ and $\Delta V^\ddagger$, which was originally claimed for some thermal inorganic reactions[58−60] and solvent−solute interactions.[61,62] However, it should be emphasized that, in our case, the sign and magnitude of $\Delta\Delta V^\ddagger$ obtained with individual sensitizer do not necessarily correspond with those of $\Delta\Delta S^\ddagger$, even in a qualitative sense. This can be seen if a comparison of the data for **3b**, **6a**, and **7a**,**b**,**e** is made. The inconsistent tendencies of $\Delta\Delta S^\ddagger$ and $\Delta\Delta V^\ddagger$ unequivocally show that the temperature and pressure effects cannot be directly correlated with one another, but instead behave as independent perturbing factors on the enantiodifferentiation process.

Table 4. Differential Activation Volume ($\Delta\Delta V^\ddagger_{S-R}$)[a] for Enantiodifferentiating Photoisomerization of Cyclooctene Sensitized by Chiral Aromatic Esters in Pentane

	temperature/°C						
sensitizer	25	7	4	5	−6	−9	−10
6a	−3.4	−5.2				−6.8	
7a	+1.9			+1.1	−2.6		
7b	−5.5			−4.8		−4.1	
7e	+0.6		+2.1				+2.1

[a] In cm^3 mol^{-1}.

We therefore attempted the determination of $\Delta\Delta V^\ddagger$ values at lower temperatures. Only a limited temperature range (down to −10 °C) is available in the high-pressure experiments as a result of pressure leakage caused by the inevitable contraction of the pressure vessel. However, the high-pressure irradiations at varying temperature not only reveal details and correlation between the temperature and pressure effects upon this enantiodifferentiating photosensitization, but also provide us with a powerful, versatile tool for the multidimensional control of enantioselectivity in photochemical reactions.

Temperature Dependence of Activation Volume. The enantiodifferentiating photoisomerizations of **1Z** sensitized by a representative group of ortho esters **6a** and **7a**,**b**,**e** were performed in pentane at two temperatures lower than 10 °C under pressures ranging from 0.1 to 200 MPa. The results are listed in Table 3. To facilitate a quantitative discussion, the effects of pressure at varying temperatures, the ln(k_S/k_R) values obtained at each temperature are plotted against the pressure, affording straight lines for all sensitizers employed (see Figure

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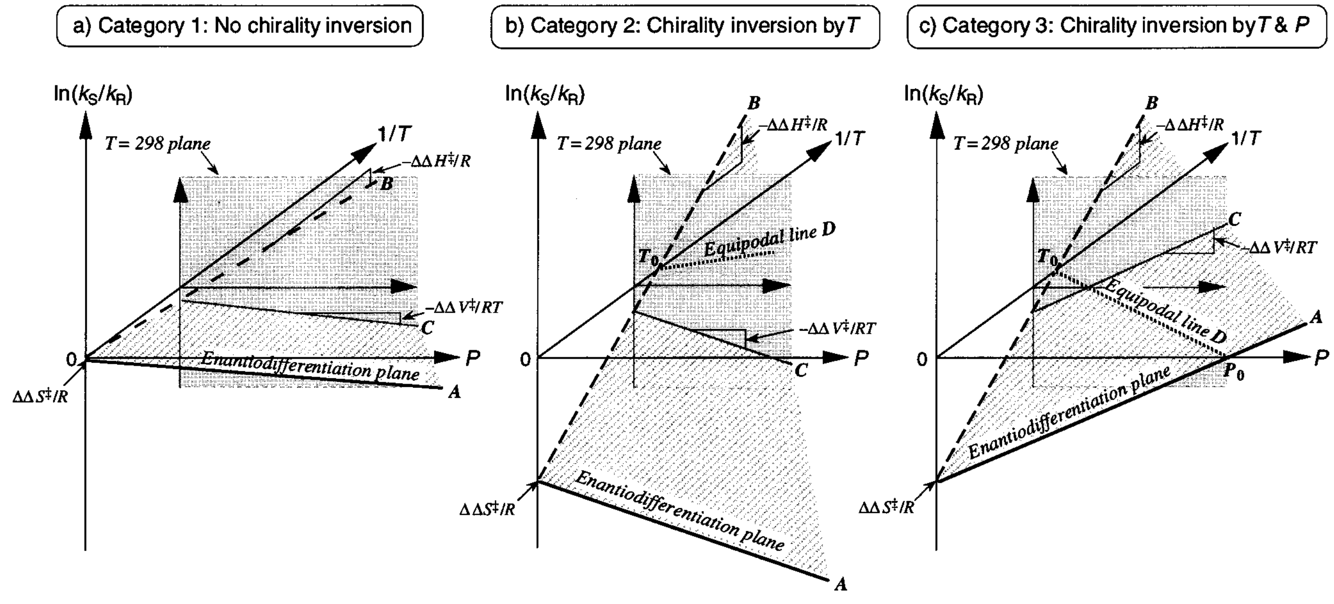

Figure 3. Representative P vs T^{-1} vs ln(k_S/k_R) diagrams. Schematic drawings of the ln(k_S/k_R) value as a function of pressure and temperature: no inversion of product chirality occurs in category 1; the product chirality is inverted either by temperature, affording an equipodal temperature (T_0), or by pressure (not shown, but essentially the same diagram can be drawn just by switching the axes) in category 2; the chirality is switched by both pressure and temperature at the equipodal points P_0 and T_0 in category 3. In each category, all results should fall on the enantiodifferentiation plane (hatched), which intersects the P vs ln(k_S/k_R) and T^{-1} vs ln(k_S/k_R) planes at lines ***A*** and ***B***, while the vertical plane (gray) illustrates a typical pressure-dependence plot obtained at 25 °C, affording the $-\Delta\Delta V^{\ddagger}/R$ value as a slope of the intersecting line ***C***.

2). From these plots and eq 5, we can calculate the $\Delta\Delta V^{\ddagger}$ at each temperature for these sensitizers, the values of which are listed in Table 4.

As can be seen from Figure 2 and Table 4, the $\Delta\Delta V^{\ddagger}$ values obtained are highly dependent upon temperature, even over a relatively narrow range. The temperature dependence of $\Delta\Delta V^{\ddagger}$ is also a critical function of the sensitizer structure. Whereas sensitizers **6a** and **7e** give greater absolute $\Delta\Delta V^{\ddagger}$ values at lower temperatures, **7b** shows the opposite behavior, and interestingly the sign of $\Delta\Delta V^{\ddagger}$ for **7a** is switched within this narrow temperature range. The apparently puzzling dependency of ee upon both pressure (as measured by $\Delta\Delta V^{\ddagger}$) and temperature (as measured by $\Delta\Delta H^{\ddagger}$ or $\Delta\Delta S^{\ddagger}$) can be graphically represented and globally understood by a three-dimensional diagram depicting the relationships between ee, T, and P.

The *P* vs T^{-1} vs ee Diagram: Correlated Temperature and Pressure Effects upon ee. The ln(k_S/k_R) values have been demonstrated experimentally to be proportional to the pressure (P) at a constant temperature, and also to the inverse temperature (T^{-1}) at a constant pressure. This allows us to construct a three-dimensional P vs T^{-1} vs ee diagram shown in Figure 3. The observed behavior of ee as a function of pressure and temperature, although apparently complicated and quite specific to each sensitizer, can be classified into three categories based on the presence/absence of an intrinsic equipodal temperature (T_0) or equipodal pressure (P_0). In Figure 3, the ln(k_S/k_R) value is expressed as a function of pressure (P) and inverse temperature (T^{-1}) giving the lightly shaded plane which crosses the P vs ln(k_S/k_R) plane at intersection ***A*** (solid line) in the foreground and the T^{-1} vs ln(k_S/k_R) plane at intersection ***B*** (dashed line) in the background. *All enantiodifferentiating events in the photosensitizations in this study should occur on this enantiodifferentiation plane.* Our experiments, which considered the pressure dependence of ee at, for example, 25 °C, are performed on the vertical plane (dark shadow) in Figure 3. These give the $-\Delta\Delta V^{\ddagger}/RT$ value as the slope of line ***C*** which intersects the lightly shaded *enantiodifferentiation plane*. The dependence of ee upon temperature at 0 MPa gives the intersection ***B***, of slope $-\Delta\Delta H^{\ddagger}/R$, and intercept $\Delta\Delta S^{\ddagger}/R$ on the T^{-1} vs ln(k_S/k_R) plane.

Category 1 is illustrated in Figure 3a. The solid and dashed bold lines (***A*** and ***B***), at which the *enantiodifferentiation plane* intersects the P vs ln(k_S/k_R) and T^{-1} vs ln(k_S/k_R) planes, respectively, afford very small slopes and intercepts which have the same sign, and no inversion of product chirality is seen, or is predicted at any pressure or temperature. Most benzoate, isophthalate, and terephthalate sensitizers (**2**, **4**, and **5**), which give very small $\Delta\Delta V^{\ddagger}$, $\Delta\Delta H^{\ddagger}$, and $\Delta\Delta S^{\ddagger}$, fall in this category. Thus, upon sensitization with these chiral benzene(di)carboxylates, the product's ee is not significantly improved by increasing pressure or by decreasing temperature.

More interestingly, photosensitizations with ortho esters **3**, **6**, and **7** belong to one of the latter two categories. In category 2 examples, the slope and intercept of line ***A*** possess the same sign. However, the slope and intercept of line ***B*** have opposite signs, affording the equipodal line ***D*** at the intersection of the *enantiodifferentiation plane* with the P vs T^{-1} plane. Switching of the axes P and T^{-1} in category 2 leads to an apparently different diagram, which might be classified as an independent category 2′ since the product's chirality is inverted by pressure, not by temperature.

Unfortunately the temperature and pressure effects do not work cooperatively to enhance the product's ee in category 2 (or 2′). As can be seen from Figure 3b, the applied pressure reduces the temperature dependence of ee or $\Delta\Delta H^{\ddagger}$ and 100% ee could be attained when either P or T^{-1} is infinite. The occurrence of the equipodal line ***D*** with a positive slope in the P vs T^{-1} plane simply means that the ee value will never become zero at temperatures higher than T_0.

The difference between categories 2 and 3 lies only in the signs of slope and intercept, but the consequences of these differences are crucial to obtain very high ee's at reasonable

Table 5. Enantiomeric Excesses (%ee) Observed or Extrapolated at Several Pressures and Temperatures in the Photosensitization of Cyclooctene (**1Z**) with (−)-Tetramenthyl 1,2,4,5-Benzenetetracarboxylate (**6a**)

	pressure/MPa								
temp/°C	0.1	25	50	100	200	300	400	1000	1500
25	−11.2			−3.6	+5.7	+12.4	+17.9	(+56.6)[a]	(+76.8)[a]
7	−6.1			+7.7	+16.5		(+38.1)[a]	(+79.5)[a]	(+92.9)[a]
−9	+1.6	+6.1	+9.4			(+45.5)[a]	(+57.1)[a]	(+92.1)[a]	(+98.3)[a]

[a] Extrapolated value.

temperatures and pressures. In category 3, the slope and intercept of lines ***A*** and ***B*** possess opposite signs, affording the equipodal line ***D*** with a negative slope. The equipodal line connecting T_0 and P_0 not only indicates that the ee value never becomes zero at temperatures lower than T_0 and at pressures greater than P_0, but also demonstrates that temperature and pressure work cooperatively to significantly enhance the product's ee. Despite the limited number of chiral sensitizers examined, such a fortuitous situation is realized in photosensitizations with (−)-menthyl benzenetetracarboxylate **6a** as the sensitizer. As can be seen from Table 4, **6a** affords fairly large $|\Delta\Delta V^{\ddagger}|$ values that are enhanced from 3.4 to 6.8 cm^3 mol^{-1} simply as a result of lowering the temperature from 25 to −9 °C. Thus, the product's ee is anticipated to increase dramatically in particular at low temperatures, ultimately giving almost completely pure (*S*)-(+)-**1E** at −9 °C under 1500 MPa, as shown in Table 5. These conditions are realistically attainable and experiments along this line are currently planned, not only to obtain the very high ee's, but also to examine the linearity of the *P* vs ln(k_S/k_R) plot, i.e., the pressure dependence of $\Delta\Delta V^{\ddagger}$ at much higher pressures.

Conclusions

The present studies clearly indicate that, in addition to temperature, external pressure can be used as a practical tool for controling product's ee in asymmetric photochemical reactions. The combined effects of temperature and pressure provide us with a versatile and powerful multidimensional control that allows us to switch the product's chirality more easily than by the manipulation of either these factors on their own. Although further examinations of a wide variety of asymmetric (photo)reaction systems may be needed to generalize these unprecedented chirality-switching phenomena caused by changing temperature and/or pressure, it is evident that the product chirality in photochemical, and probably thermal, asymmetric syntheses is governed not only by the enthalpic factor, symbolically represented by steric hindrance, but also by the entropic factor, typically illustrated by structural freedom in the transition state. Finally, we wish to emphasize that the most crucial role is played by the entropy factor in photochemical and thermal processes that are governed by weak interactions such as electrostatic, hydrogen-bonding, van der Waals, and/or $\pi-\pi$ stacking interactions.[63] In such systems, the reaction itself is mostly enthalpy-driven, while the selectivity is entropy-controlled. It is under these conditions that external perturbants such as temperature and pressure become effective tools to control the weakly interacting crucial processes.

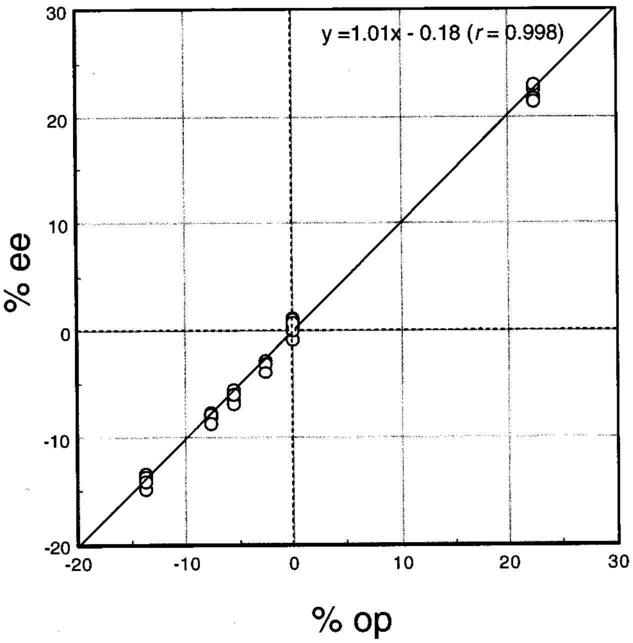

Figure 4. Calibration plot of the enantiomeric excess (% ee) determined by chiral gas chromatography against the optical purity (% op) determined by polarimeter using the same samples of (+)-rich, (−)-rich, and racemic **1E**, exhibiting an excellent correlation, with unit slope and negligible intercept.

Experimental Section

Instruments. Specific rotations were determined on a Perkin-Elmer model 243B polarimeter with a temperature-controlled 10 cm cell. Gas chromatographic (GC) analyses of photolyzed samples were performed on a Shimadzu GC6A or GC14B instrument with a packed or chiral capillary column. The temperature of the injection port was kept below 150 °C to avoid the thermal *E*−*Z* isomerization of (*E*)-cyclooctene **1E** in the irradiated solutions.

Materials. The pentane solvent was shaken repeatedly with concentrated sulfuric acid until the acid layer no longer turned yellow, then washed with water, neutralized with sodium carbonate powder, and fractionally distilled. (*Z*)-Cyclooctene **1Z** (Nakarai Tesque) was purified by treatment with 20% aqueous silver nitrate solution, followed by fractional distillation. The purified sample of **1Z** contained 3−4% cyclooctane as the sole detectable impurity, but was completely free of the (*E*)-isomer and 1,3- and 1,5-cyclooctadienes.

Optically active alkyl benzoates **2**, phthalates **3**, isophthalates **4**, terephthalates **5**, 1,2,4,5-benzenetetracarboxylates **6**, and benzenehexacarboxylates **7** were prepared by mixing the corresponding acid chlorides and optically active alcohols in pyridine, and purified by fractional distillation or repeated recrystallization from ethanol, according to the method reported previously.[5]

Photolysis. All irradiations were conducted in a pressure vessel HKP-921208 designed and manufactured by Hikari Koatsu Co., which was equipped with a sapphire window (5 mm i.d.) for external irradiation, and also with a coolant circulation system in the body of the reactor. A solution (11 cm^3) of (*Z*)-cyclooctene (5 mM), containing optically active sensitizer (0.2−1.0 mM) and cycloheptane added as an internal standard, was placed in the vessel, and pressurized up to 400 MPa with a high-pressure pump KP5B, thermostated at a constant temperature (±0.1 °C) between +25 and −10 °C by circulating water or water−methanol coolant through the reactor body. The solution was then irradiated for a given period of time with a 250-W high-pressure mercury arc (Ushio UI-501C). The collimated incident beam

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from the lamp housing was focused with a quartz lens (*f* 16.5 cm) which was placed in front of the sapphire window, allowing an efficient irradiation.

The conversion, chemical yield, and *E/Z* ratio of photolyzed samples were determined by GC on a 3-m packed column of 25% β,β'-oxydipropionitrile at 65 °C. (*E*)-Isomer **1E** produced was selectively extracted from the irradiated solution with a 2 cm^3 portion of 20% aqueous silver nitrate at <5 °C.[5,62] The aqueous extract was washed with two 1 cm^3 portions of pentane and then added to concentrated ammonium hydroxide (1 cm^3) at 0 °C to liberate a chemically pure sample of **1E** ($>99\%$), which was in turn extracted with a small portion (0.1−0.5 cm^3) of pentane. The product's ee in the pentane extract was determined by chiral capillary GC over a Supelco β-DEX 120 column (30 m × 0.25 mm i.d.) at 60 °C, which gave a satisfactory enantiomeric separation of (*R*)- and (*S*)-**1E**. In separate experiments, it was demonstrated that the ee values determined by chiral GC were highly reproducible within ±0.5% ee and in excellent agreement with the optical purities calculated from the specific rotations of the same samples, as long as the integrated area of each peak falls within a certain range (20 000−200 000 μV s) on a Shimadzu C-R6A integrator, as shown in Figure 4.

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