# Photoinversion of Sulfoxides as a Source of Diversity in Dynamic Combinatorial Chemistry
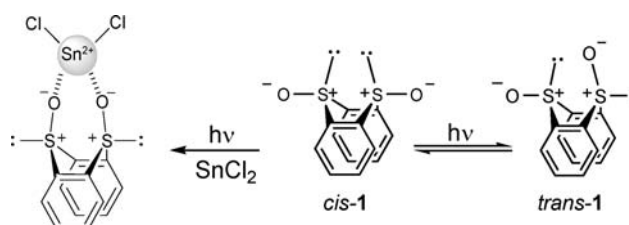
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**ABSTRACT**



Photochemical interconversion of the two diastereoisomers *cis-* and *trans-*thianthrene dioxide (1) can be considered an example of photodynamic combinatorial chemistry (PDCC) in which the interconversion among diastereomeric equilibrating species is brought about by electromagnetic irradiation. Photoequilibrium can be shifted by irradiation at different wavelengths or by addition of $SnCl_2$ that binds *cis-*1 more efficiently than *trans-*1.

The investigation of reactions carried out under thermodynamic control has received considerable attention in recent years, mainly because of the increasing interest in dynamic combinatorial chemistry (DCC).[1] The related prospects of "proof reading and editing" via repeated bond dissociation–recombination processes and of amplification of a desired component of the equilibrated mixture via specific interaction with a complexing entity (template) make DCC particularly appealing. Several reversible reactions leading to covalent bonds have been employed in DCC such as olefin metathesis,[2] imine[3] and hydrazone[4] formation, transesterification,[5]

thiol–disulfide interchange,[6] transacetalation,[7] and so on. All of the above reactions are carried out in the absence of any interaction between electromagnetic field and matter. In this paper, we report an example of photodynamic combinatorial

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chemistry (PDCC), herein defined as the DCC, in which the interconversion among equilibrating species is brought about by electromagnetic irradiation instead of thermal bond-breaking and bond-forming processes.[8]

Sulfoxides are attracting continuous attention for their importance as bioactive compounds and drugs, as valuable intermediates in organic synthesis, and as ligands for asymmetric transformations.[9] An attractive characteristic of sulfoxides is their well-known stereochemical stability. Consequently, experimental conditions leading to stereomutation of sulfoxides and in particular photochemically induced (direct or sensitized) racemization of enantiopure sulfoxides are the object of intensive investigation.[10,11] Stereomutation of the sulfur center causes racemization in the absence of other stereogenic centers, but diastereomeric interconversions can occur in the presence of other chiral centers as found in the photochemical studies of (S,R) sulfoxides of penicillin derivatives.[12] Very recently, axial to equatorial change in 1,9-dithiaalkane-bridged thianthrene 10-oxides was accomplished by photoinduced S—O configuration change.[13]

When two or more sulfinyl groups are present in the same molecule, inversion of one of them leads to interconversion among diastereomers. Accordingly, we felt it worthwhile to analyze the photochemical interconversion of the two diastereoisomeric *cis*- and *trans*-thianthrene dioxides (**1**) (Scheme 1). While the *trans*-**1** isomer exists in two identical *endo-exo* conformers, the *cis*-**1** isomer exists in two conformers of different stability, namely *endo-endo* and *exo-exo*. The latter is less stable than the former by 11 kcal/mol and, therefore, not appreciably populated at room temperature.[14]

To the best of our knowledge, inversion of configuration of a tetrahedral stereogenic center, although potentially useful to interconvert molecules with different properties, was never used as a diversity source in DCC.

**Scheme 1.** Photochemical Interconversion of the Two Diastereoisomers *cis*- and *trans*-Thianthrene Dioxide (**1**)

Upon UV irradiation ($\lambda = 280$ nm) of a 3.0 mM solution of *trans*-**1** in $C_6D_6$, a partial isomerization to *cis*-**1** was observed by ^{1}H NMR analysis (Figure 1a and Figure S1 in

**Figure 1.** Photoisomerization of thianthrene dioxide **1** (irradiation at $\lambda = 280$ nm) in $C_6D_6$ at 25 °C (a) starting from *trans*-**1** and (b) starting from *cis*-**1**.

the Supporting Information). The process occurs with the absence of side products at short times, but after prolonged irradiation (>120 min), partial deoxygenation[15] of **1** to give thianthrene oxide was observed (see the experimental details in the Supporting Information). The photoisomerization follows first-order kinetics with a rate constant ($k_{trans} + k_{cis}$) of $5.4 \times 10^{-4}$ s$^{-1}$. The reverse process (*cis*-**1** → *trans*-**1**) is also observed upon irradiation at 280 nm in $C_6D_6$ and shows a very similar first-order rate constant (Figure 1b). The same final photostationary ratio of diastereoisomers ([*cis*-**1**]/[*trans*-**1**] = 2.4) is obtained in both experiments.

Photoisomerization of *trans*-**1** to *cis*-**1** was also carried out in different solvents ($CD_2Cl_2$, $CD_3CN$, and $CD_3OD$) under continuous irradiation at 280 nm. In all cases, isomerization follows a first-order process leading to a solvent-dependent [*cis*-**1**]/[*trans*-**1**] ratio. Rate constants $k_{trans}$ and $k_{cis}$ and the pertinent [*cis*-**1**]/[*trans*-**1**] photoequilibrium ratios are listed in Table 1.

Since the UV spectra of *cis*-**1** and *trans*-**1** differ markedly in the position and shape of the absorption bands (Figure S2, Supporting Information),[16] we analyzed the effect of

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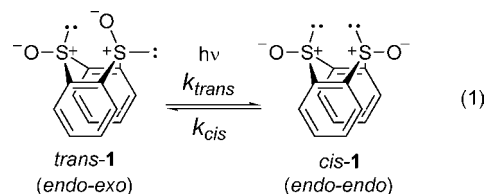
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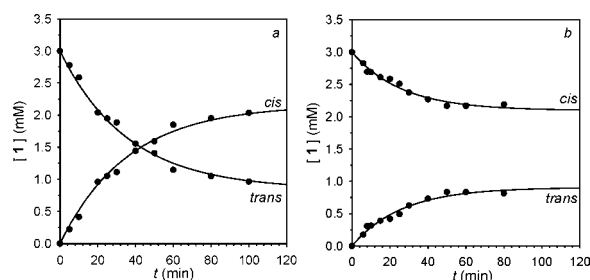
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**Table 1.** Rate Constants for the Photoisomerization of *trans*-**1** to *cis*-**1** ($k_{trans}$)[a] and of *cis*-**1** to *trans*-**1** ($k_{cis}$)[a] and [*cis*-**1**]/[*trans*-**1**] Photoequilibrium Ratios Determined under Irradiation of 3.0 mM Solutions of Thianthrene Dioxide at 25 °C

| solvent | $\lambda$ (nm) | $k_{trans}$ ($10^{-4}$ s$^{-1}$)[b] | $k_{cis}$ ($10^{-4}$ s$^{-1}$)[b] | [*cis* - **1**]/(*trans* - **1**) |
|---------|------|----------|----------|----------|
| $C_6D_6$ | 280 | 3.83 | 1.61 | 2.4 |
| $CD_2Cl_2$ | 280 | 3.33 | 0.53 | 6.3 |
| $CD_3OD$ | 280 | 2.50 | 0.67 | 3.8 |
| $CD_3CN$ | 280 | 3.61 | 0.69 | 5.2 |
|  | 250 | 0.83 | 1.33 | 0.63 |
|  | 259 | 1.25 | 1.36 | 0.92 |
|  | 315 | 1.83 | n.d. | >100[c] |

[a] Calculated from $k_{obs}$ ($k_{trans}+k_{cis}$) and final photostationary [*cis*-**1**]/[*trans*-**1**] ratios ($k_{trans}/k_{cis}$). [b] Error ±10%. [c] No traces of *trans*-**1** have been detected.

wavelength variations on the photoisomerization process. Thus, kinetic measurements were carried out by irradiating 3.0 mM solutions of *trans*-**1** in CD$_3$CN[17] at 280, 259, and 250 nm where the molar absorptivity of *trans*-**1** is higher, equal, and lower, respectively, than that of *cis*-**1**. Photoirradiation was also carried out at 315 nm where only *trans*-**1** has a significant absorption. In Table 1 are reported the photoisomerization rate constants $k_{trans}$ and $k_{cis}$ determined at the four wavelengths and the corresponding [*cis*-**1**]/[*trans*-**1**] photoequilibrium ratios.

The [*cis*-**1**]/[*trans*-**1**] ratio varies significantly by changing the irradiation wavelength. As expected, irradiation of **1** at 280 and 250 nm shifted the equilibrium (1) toward the *cis*-**1** and *trans*-**1** isomers, respectively. Irradiation at 259 nm, where the two isomers have the same molar absorptivity, led to comparable amounts of *cis*-**1** and *trans*-**1**. Finally, irradiation at 315 nm, where *cis*-**1** has no significant absorption, leads to an almost complete isomerization of *trans*-**1** to *cis*-**1**.[18] On the basis of these results it is possible to rationalize the effect of changing the nature of the solvent on the photostationary equilibrium observed by irradiation at 280 nm (Table 1). The different [*cis*-**1**]/[*trans*-**1**] ratios observed depend on the differences of the molar absorptivity of the two isomers in the four solvents investigated, in that the [*cis*-**1**]/[*trans*-**1**] ratio increases on increasing the $\varepsilon_{trans\text{-}\mathbf{1}}/\varepsilon_{cis\text{-}\mathbf{1}}$ at 280 nm in the four solvents (Figure S3, Supporting Information).

We have also determined the quantum yield ($\Phi_{iso}$) for the photoisomerization of *trans*-**1** to *cis*-**1** in acetonitrile at 280 nm using the photolysis of azoxybenzene to form 2-hydroxyazobenzene as actinometer.[19] A high value of $\Phi_{iso}$ (0.61) was obtained which is not surprising since values even higher than 0.8 were found for the quantum yields of the loss of optical rotation in enantiopure aryl sulfoxides.[20] The

high photoisomerization quantum yield clearly indicates that a significant nonradiative decay of the excited state occurs by stereomutation at the sulfinyl group. It is interesting to note that the photoisomerization process is not influenced by the presence of oxygen; photoisomerization of *trans*-**1** to *cis*-**1** occurred with the same rate ($k_{trans} = 3.6 \times 10^{-4}$ s$^{-1}$) in N$_2$- and O$_2$-saturated CD$_3$CN solutions. Moreover, we found that photoisomerization of *trans*-**1** to *cis*-**1** occurred to a very small extent by irradiating at 280 nm a 3.0 mM solution of *trans*-**1** in acetone.[21] The lack of photo-stereomutation with triplet sensitization suggests that a nonradiative decay of a singlet excited state of **1** occurs as found for the photoinduced racemization of aryl methyl sulfoxides.[22]

The photoequilibration properties related to *trans*-**1** and *cis*-**1** can be exploited to generate a minimal dynamic library consisting of two interconverting compounds. This is a small dynamic system in which the interconversion among species is guaranteed by irradiation. An important characteristic of a dynamic system is its ability to modify the product distribution by changing the factors that rule the equilibrium. Actually, changes in the *cis*−*trans* distribution of **1** at photoequilibrium were observed at different irradiation wavelengths. Moreover the addition of a complexing species able to tightly and selectively bind one of the photoequilibrating diastereomers should shift the photoequilibrium toward the complexed species.

With the aim of finding a suitable complexing species, we studied the effect of the presence of several metal cations in acetonitrile solution of *trans*-**1** and *cis*-**1**. We discovered that SnCl$_2$ binds to both *trans*-**1** and *cis*-**1**. When a 10-fold excess of SnCl$_2$ is added to an equimolar solution (1.5 mM) of *trans*-**1** and *cis*-**1** in CD$_3$CN, $^1$H NMR aromatic signals of both *trans*-**1** and *cis*-**1** show a significant downfield shift which is higher for *trans*-**1** (0.15 ppm) than for *cis*-**1** (0.05 ppm) (see Figure S4, Supporting Information). When photoirradiation ($\lambda = 280$ nm) of a 3.0 mM solution of *trans*-**1** in CD$_3$CN is carried out in the presence of SnCl$_2$ (1.5 mM, 0.5 equiv), $^1$H NMR analysis of the reaction mixture shows that the photostationary equilibrium is significantly shifted toward the *cis* isomer.[23] This effect is stronger at increasing SnCl$_2$ concentration (Table 2).

On addition of 1 or 2 equiv of SnCl$_2$, no traces of *trans*-**1** were detected in the $^1$H NMR spectra of the photoequilibrated

(17) Acetonitrile was chosen because of its transparency in the UV spectral region investigated.

(18) The photoinduced axial to equatorial S−O configuration change in 1,9-dithiaalkane-bridged thianthrene 10-oxides was accounted for in terms of the weak UV absorption of the axial isomer and the negligible absorption of the equatorial isomer (ref 13).

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(21) Acetone triplet energy ($E_T = 82$ kcal/mol) should be higher than that of **1** since for a large number of aryl and diaryl sulfoxides $E_T < 81$ kcal/mol. Jenks, W. S.; Lee, W.; Shutters, D. *J. Phys. Chem.* **1994**, *98*, 2282–2289.

(22) The evidence in favor of the existence of such mechanisms for photochemical isomerization that does not produce homolytic α-cleavage but involves a nonradiative decay from an exited state was discussed in detail by Jenks and co-workers (ref 10b). Although experimental evidence is accumulating, the precise details of the inversion mechanisms are still unknown. A pathway which is consistent with all of the experimental findings involves the following: (i) the initial formation of an electronically excited state in the pyramidal geometry, (ii) its geometric relaxation to a configuration which is approximately trigonal on sulfur, and (iii) a subsequent nonradiative decay to the ground state in a planar geometry (structurally similar to the thermal transition state) which evolves into one of the two possible configurations. The multiplicity of the excited state is still debated, although there is some evidence in favor of a singlet state as found in the present case.

(23) It was verified that the presence of SnCl$_2$ (1.5 mM) has a negligible influence on the relative absorption of 3.0 mM solutions of *cis*-**1** and *trans*-**1** in CD$_3$CN at 280 nm.

| [SnCl₂] (mM) | $t_{1/2}$ (s) | [*cis*-**1**]/[*trans*-**1**][a] |
|---|---|---|
| | $1.8 \times 10^3$ | $5.2^b$ |
| 1.50 | $1.8 \times 10^3$ | $16^b$ |
| 3.00 | $1.2 \times 10^3$ | $>100^c$ |
| 6.00 | $7.5 \times 10^2$ | $>100^c$ |

*a* Measured at photoequilibrium. *b* Error ±10%. *c* No traces of *trans*-**1** were detected by ¹H NMR analysis.

solutions, thus indicating that complexation of SnCl₂ by *cis*-**1** is far more effective than complexation by *trans*-**1** in the reaction conditions.[24] This result can be explained by the formation of a chelated adduct between *cis*-**1** and SnCl₂ in which the tin ion is complexed by the two sulfinyl oxygen atoms of *cis*-**1** in its *exo-exo* conformation (Figure 2a).[25] In
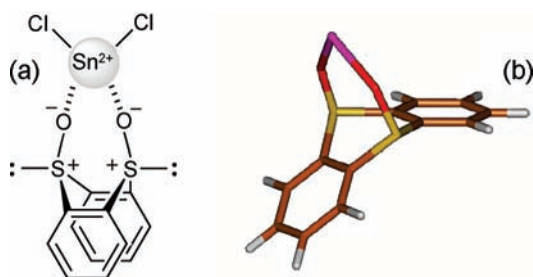


**Figure 2.** Chelated complex between SnCl₂ and *cis*-**1** in its *exo-exo* conformation.

Figure 2b is reported the structure of the tin(II) complex of *cis*-**1** calculated at the B3LYP/6-31+G(d)/sddall level of theory (see Figure S7, Supporting Information).

Even though *cis*-**1** is much more stable in its *endo-endo* conformation,[13] theoretical calculations indicate that the *exo-exo* tin complex is ca. 83 kcal/mol more stable than the *endo-endo* tin complex in a vacuum (see Figure S6, Supporting Information).

It seems likely that complexation of SnCl₂ acts as a kinetic trap for *cis*-**1**. It hinders the pyramidal inversion at the sulfur stereogenic centers so that once the SnCl₂ complex of *trans*-**1**

is transformed into the SnCl₂ complex of *cis*-**1** upon irradiation, the latter cannot revert to the former.[26]

Interestingly, the *trans*-**1** → *cis*-**1** photoinversion process is also more rapid in the presence of SnCl₂ and becomes increasingly faster on increasing the SnCl₂ concentration (see Table 2).[27] This effect might be due to a photosensitizing effect of the Sn(II) salt for the sulfoxide photoinversion. In order to check this hypothesis, we have investigated the effect of SnCl₂ on the photostereomutation process of a system containing only one sulfinyl group, namely, (*S*)-methyl *p*-tolyl sulfoxide, (*S*)-**2**. When a 3.5 mM solution of (*S*)-**2** in CH₃CN is irradiated at the absorbance maximum (243 nm) in the presence of an equimolar amount of SnCl₂ a significant decrease of the photoracemization rate is observed (see details and Figure S8, Supporting Information).

This finding suggests that SnCl₂ is not a photosensitizer for the *trans*-**1** → *cis*-**1** photoisomerization but its effect on the photoinversion rate is probably due to a stabilizing chelate binding of the TS, the structure of which is similar to that of the thermal TS[22] and most likely resembles that of the *cis* isomer.

In the present paper, we have demonstrated that photoequilibration of *trans*-**1** and *cis*-**1** can be used as source of diversity in the generation of a minimal dynamic library. Photoequilibrium in Scheme 1 can be shifted by irradiation of the solution at different wavelengths or by the presence of SnCl₂ that binds *cis*-**1** more efficiently than *trans*-**1**. These results suggest that the exploitation of photodynamic processes as a further degree of freedom in the constitution of dynamic libraries can offer an additional route to the development of DCC. Furthermore, photoreversible processes appear to be highly suitable for a "multiple reactions approach" to DCC.[6e,f,8,28] Systems endowed with a higher number of stereocenters, giving rise to more complex photodynamic libraries, are currently under investigation. The results of these studies will be reported in due time.

**Supporting Information Available:** Instrumentation, materials and methods, photoisomerization of *trans*-**1** and *cis*-**1** in the absence and in the presence of SnCl₂, photoracemization of (*S*)-methyl *p*-tolyl sulfoxide in the absence and in the presence of SnCl₂, and theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) All of the attempts to directly measure the association constants of *cis*-**1** and *trans*-**1** with SnCl₂ failed because of the interference of tiny but unavoidable amounts of water in the acetonitrile solution. Even a sample of freshly distilled CD₃CN contains a water concentration >2 mM. The water ¹H NMR signal changes in shape (broader) and in chemical shift (downfield shifted) when SnCl₂ is added to the solution during the titration, thus demonstrating interactions between water and the tin salt. As a consequence, any quantitative binding measurement concerning the association between SnCl₂ and both the thianthrene dioxide isomers does not seem allowed. Obviously, this interference increases when the concentration of the species to be titrated decreases.

(25) Formation of complexes of tin ions with sulfoxides by interaction with the sulfinyl oxygen is well documented: (a) Calligaris, M. *Coord. Chem. Rev.* **2004**, *24*, 8–351. (b) Hsu, C. C.; Geanangel, R. A. *Inorg. Chem.* **1980**, *19*, 110–119. The structures of chelated complexes of disulfoxides with triphenyltin chloride with bonding occurring through the sulfinyl oxygen atoms have been also reported: Filgueiras, C. A. L.; Celso, C.; Marques, E. V.; Johnson, B. F. G. *Inorg. Chim. Acta* **1982**, *59*, 71–74.

(26) Theoretical calculations at the B3LYP/6-31+G(d)/sddall level have been carried out for the structure of Sn²⁺ complexes of *cis*-**1**, *trans*-**1**, and thermal transition state (see Figure S7 in the Supporting Information). The transition state has now a geometry much more similar to the *exo-exo* conformer of *cis*-**1** than to the *endo-exo* of *trans*-**1**. This result, together with the assumption that the photochemical mechanism described in ref 22 does not change in the presence of Sn²⁺ should justify qualitatively the preferential formation of *cis*-**1**.

(27) Since no clear first-order kinetic profiles were observed for the photoisomerization in the presence of SnCl₂, $t_{1/2}$ values have been reported.

(28) Christinat, N.; Scopelliti, R.; Severin, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1848–1852.