Photoresponsive Molecular Tweezers. Photoregulated Ion Capture and Release Using Thioindigo Derivatives Having Ethylenedioxy Side Groups

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Abstract: Two trans–cis photoisomerizable thioindigos having $CH_3OCH_2CH_2OC(O)$ or $CH_3O(CH_2CH_2O)_3C(O)$ side groups at the 7 and 7′ positions, T-1 and T-2, respectively, were synthesized with the aim of controlling the following three functions for achieving fully photoregulated ion transport across a liquid membrane: (1) "all or nothing" type metal ion binding ability, (2) binding ability not only for alkali-metal ions but also for soft metal ions, and (3) photocontrol by visible light. Solvent extraction of metal ions with T-1 revealed that the trans form had no binding ability to any of the metal ions, whereas K^+, Rb^+, and Na^+ were selectively extracted ($Na^+ < Rb^+ < K^+$) by the photogenerated cis form. The cis form, in addition, had high binding ability to Ag^+, Hg^+, Hg^{2+}, and Cu^{2+} in comparison to alkali-metal ions. Ion transport experiments across a liquid membrane showed that repeating the cycles of alternate photoirradiation of 529- and 488-nm light, which caused isomerization of T-1 from the trans to the cis form (529 nm) and from the cis to the trans (488 nm), resulted in the transportation of Ag^+ from aqueous phase I to II through a 1,2-dichloroethane membrane containing T-1.

Biological systems have developed various kinds of photoactive organs to adapt themselves to the environmental electromagnetic radiation, sunlight. In plants, for example, photosynthetic systems have been evolved to utilized light as an energy source. At the same time, organisms have developed other systems that measure and respond to the light intensity or duration to find favorable condition for survival. In the latter systems, the light is used as information. Photoresponsive systems, such as phototropism, phototaxis, or vision, are ubiquitous in nature.[1]

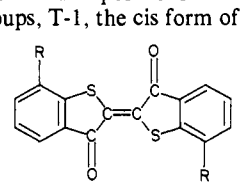
In a similar manner to biological systems, light can be used in organic chemistry not only as an energy source for chemical synthesis but also as an information source or a trigger for subsequent events. We have studied such application where light is used as a trigger or a signal for the reversible control of physical or chemical properties. Conformation of a polymer chain was reversibly changed from the compact to the extended form with a laser pulse by incorporating cis–trans photoisomerizable chromophores into the polymer backbone.[2,3] The laser pulse was used as a trigger for chain unfolding in this system. Another example is the photostimulated pH jump using hydroxide ion emitters.[4] The photoactive reagents can accelerate or retard chemical and biochemical reactions in aqueous systems by changing the pH by using light.[5,6]

In this paper, we would like to present results concerning photoresponsive molecular tweezers, in which ion pumps across a liquid membrane are fully controlled by photoirradiation. Although several attempts have been reported to photocontrol binding ability of metal ions to crown ethers or chelating agents,[7-10] the control was limited to the ion capture process, the capture and the transport across a liquid membrane being only slightly perturbed by the photoirradiation. Complexane-type ligands having two iminodiacetic acid groups at the 4 and 4′ positions of azobenzene, first prepared by Blank et al.,[8] and azobenzenophane-type crown ether, recently synthesized by Shinkai et al.,[11] are exceptional examples which showed the "all or nothing" change in ion binding. Upon photoirradiation, the former ligand changed the binding ability to Zn^{2+} in aqueous solution by bringing close together the two iminodiacetic acid groups, while the latter crown ether changed the ability by distorting the crown ring structure.

In order to overcome the incompleteness of photoregulation and to achieve ion selective and fully photoregulated ion transport across a liquid membrane, we developed a new concept to control ion binding ability, i.e., photoresponsive molecular tweezers. When the host ring molecular structure is split into two parts and incorporated into the trans–cis photoisomerizable chromophores as shown in Figure 1, the trans form has no acceptable site for guest ions. When the chromophore is converted to the cis form, the cavity capable of selectively adopting certain guest ions is reconstructed. We have synthesized thioindigo derivatives that have oxyethylene side groups with the aim of controlling the following three functions: (1) "all or nothing" type metal ion binding ability, (2) binding ability not only for alkali-metal ions but also for soft metal ions, such as Ag^+ and Cu^{2+}, and (3) photocontrol by visible light.

Results and Discussion

1. Structure of Photoresponsive Host Molecules. The crown ether structure was chosen as a host molecular framework. Ethylenedioxy groups, which are a constituent unit of crown ether, were introduced at the 7 and 7′ positions of thioindigo by ester linkages. When the 7 and 7′ positions are substituted by single ethoxylenedioxy groups, T-1, the cis form of the molecule is able



T-1, R=$COOCH_2CH_2OCH_3$
T-2, R=$CO(OCH_2CH_2)_3OCH_3$

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(2) (a) Irie, M.; Hayashi, K. J. *Macromol. Chem.* **1979**, *A13*, 511. (b) Irie, M.; Hirano, Y.; Hashimoto, S.; Hayashi, K. *Macromolecules* **1981**, *14*, 262.
(3) Irie, M.; Schnabel, W. *Macromolecules* **1981**, *14*, 1246.
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(6) Irie, M.; Schnabel W. *Macromol. Chem. Rapid. Commun.* **1984**, *5*, 413.
(7) (a) Shinkai, S.; Nakaji, T.; Nishida, Y.; Ogawa, T.; Manabe, O. *J. Am. Chem. Soc.* **1980**, *102*, 5860. (b) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O. *Ibid.* **1981**, *103*, 111. (c) Shinkai, S.; Ogawa, T.; Kusano, Y.; Manabe, O.; Kikukawa, K.; Goto, T.; Matsuda, T. *Ibid.* **1982**, *104*, 1960. (d) Shinkai, S.; Minami, T.; Kusano, Y.; Manabe, O. *Ibid.* **1982**, *104*, 1967.
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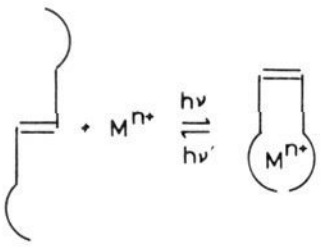

Figure 1. Photoresponsive molecular tweezers.

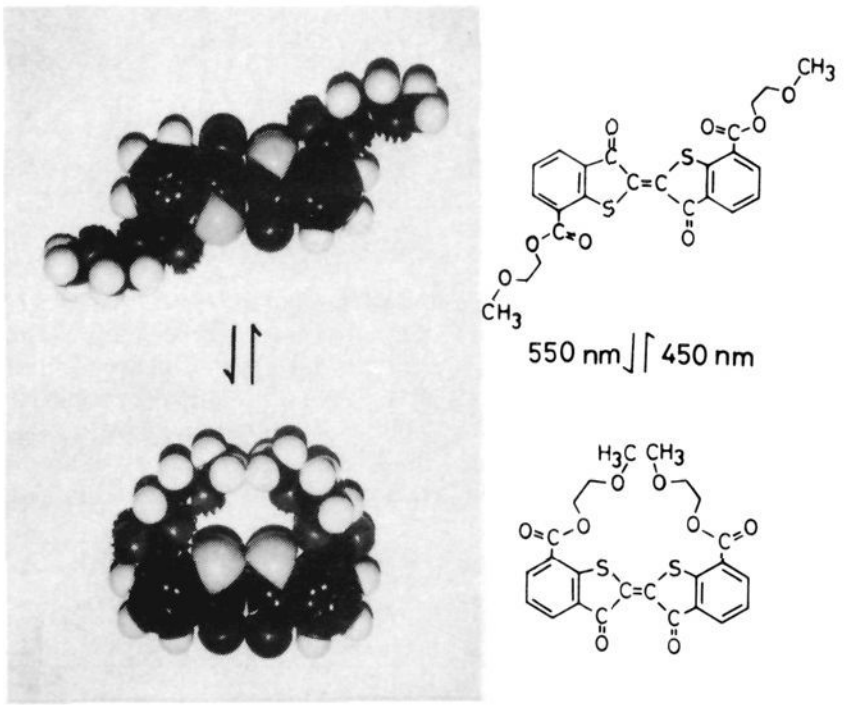

Figure 2. Molecular models (CPK model) and their structures of photoresponsive thioindigo host molecule (T-1). The upper structure is the trans form and the lower structure is the cis form.

to form a cavity similar to that of tetraoxydithia crown ether as shown in Figure 2. The trans form, on the other hand, has a rodlike structure as the most stable conformation and no longer makes a cavity capable of accepting guest ions.

When two ethylenedioxy groups are introduced at the 7 and 7′ positions of thioindigo, T-2, the trans form has possibility of making a cavity similar to that of a tetraoxythia crown ether, whereas the cis form cannot make a distinct cavity structure due to steric crowding of the oxyethylene chains.

2. Photoisomerization. Thioindigo is known to change its absorption spectrum when the configuration changes from the trans to the cis form. The absorption maximum at 542 nm due to the trans form is replaced by a maximum at 481 nm due to the cis form upon irradiation with 550-nm light.

Similar spectral changes were observed for T-1 and T-2. Figure 3 shows the photostationary-state absorption spectra of T-1 in 1,2-dichloroethane under irradiation with 550- and 450-nm light. The spectrum under irradiation with 450-nm light was identical with the dark adapted spectrum, which was measured after the compound had been stored in the dark for several days at room temperature. This suggests that thioindigo almost completely converts to the trans form upon 450-nm-light irradiation. The absorption maximum at 533 nm is ascribable to the trans form of the compound and the maximum at 484 nm to the cis form.

The dotted line of Figure 3 shows the estimated spectrum of the pure cis form. Although the isolation of the cis form by column chromatography was unsuccessful, the absence of fluorescence of the cis form made it possible to estimate ϵ values. The method of Ross and Blanc[12] was used to estimate ϵ values for the cis form, and the method of Fischer[13,14] was employed for estimation of the trans form. No appreciable difference was discerned between the estimated pure trans form spectrum and the photostationary one. The absolute concentrations of the trans and cis forms under photoirradiation were derived from the ϵ values.

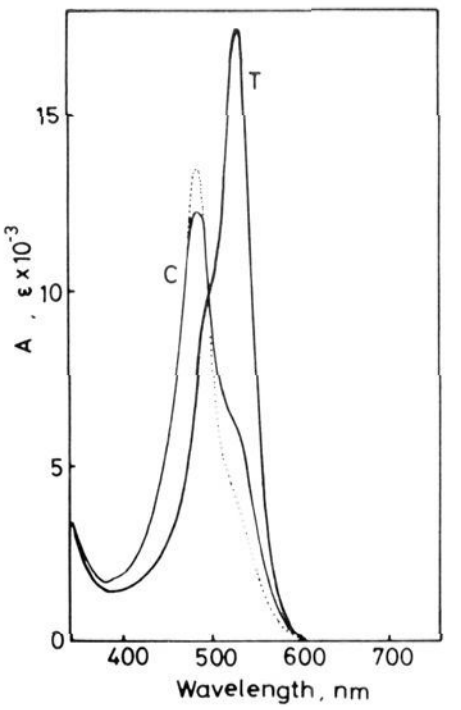

Figure 3. Absorption spectra of T-1 in 1,2-dichloroethane. T and C are the photostationary-state spectra under irradiation with 450- and 550-nm light, respectively. The dotted line is the estimated spectrum of the pure cis form.

Table I. Extraction of Alkali Metal Picrates with T-1[a]

solvent	photoirradiation wavelength, nm	picrate salts extracted, %				
		Li^+	Na^+	K^+	Rb^+	Cs^+
benzene	450 (trans)	<1	<1	<1	<1	<1
	550 (cis, 0.82)	<1	<1	9	3	<1
1,2-dichloroethane	450 (trans)	<1	<1	<1	<1	<1
	550 (cis, 0.82)	<1	2	13	6	<1

[a] Aqueous phase, aqueous solution containing 1×10^{-2} M metal nitrate and 2×10^{-5} M picric acid; organic phase, benzene or 1,2-dichloroethane solution containing 4×10^{-5} M T-1.

Similarity of the absorption spectra with thioindigo in the λ_{max} and ϵ values suggests that the introduction of ethylenedioxy groups at the 7 and 7′ positions scarcely affects the electronic structure of the thioindigo group.

3. Solvent Extraction of Metal Ions with T-1 and T-2. The binding ability to metal ions of *trans*-T-1 and *cis*-T-1 was estimated by solvent extraction of metal picrates from water to benzene or 1,2-dichloroethane.[15,16] The result of alkali-metal picrates is summerized in Table I. *trans*-T-1 had no binding ability to any of the alkali-metal ions, whereas K^+ and Rb^+ were extracted into benzene from the aqueous phase by the photogenerated cis form. In polar 1,2-dichloroethane, Na^+ was also extracted with *cis*-T-1 in addition to K^+ and Rb^+ and the amount of the extracted metal picrates increased.

The absence of metal ion extraction with *trans*-T-1 indicates that the single ethylenedioxy chain in the trans form cannot form a cavity to accept metal ions. Cooperative action of the double ethylenedioxy chains in the cis form, on the other hand, can make a cavity, as predicted by a molecular model shown in Figure 2, to accept Na^+, K^+, and Rb^+ ions. The cavity is made of four oxygen and two sulfur atoms as donor groups, similar to 1,4,7,10-tetraoxa-13,16-dithiacyclooctadecane.

The extractability under the photostationary state with 550 nm increases in the order $Na^+ < Rb^+ < K^+$. This order of extractibility is identical with the binding ability of dibenzo-18-crown-6.[14] The ion selectivity indicates that the cavity size is of the same order of magnitude as K^+ and also the cavity has a rigid enough structure to select the guest ions. The selectivity depended on the polarity of solvents and decreased in polar 1,2-dichloroethane.

Apart from the cavity size, the nature of the constituent donor atoms of the cavity plays an important role in the selectivity. The

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Table II. Extraction of Metal Picrates with T-1

photoirradiation wavelength, nm	picrate salts extracted,[a] %					
	Ag^+(a)	Hg^+(b)	Hg^{2+}(c)	Zn^{2+}(d)	Cu^{2+}(d)	Cd^{2+}(d)
450 (trans)	<1	<1	<1	<1	<1	<1
550 (cis, 0.82)	46	13	10	2	18	3

[a] Aqueous phase, aqueous solution containing (a) 1×10^{-2}, (b) 1×10^{-3}, (c) 1×10^{-3}, and (d) 1×10^{-2} M metal nitrate and (a) 2×10^{-5}, (b) 2×10^{-5}, (c) 4×10^{-5}, and (d) 4×10^{-5} picric acid; organic phase, benzene solution containing 4×10^{-5} M T-1.

Table III. Extraction of Metal Picrates with T-2[a]

photoirradiation wavelength, nm	picrate salts extracted, %	
	K^+	Ag^+
450 (trans)	14	23
550 (cis, 0.72)	10	20

[a] Aqueous phase, aqueous solution containing 1×10^{-2} M metal nitrate and 2×10^{-5} M picric acid; organic phase, benzene solution containing 4×10^{-5} M T-2.

incorporation of soft sulfur atoms in the cavity molecular structure enhances the acceptance of soft metal ions, such as Ag^+, and hampers simultaneously the acceptance of hard alkali-metal ions.[15]

Table II summarizes the results of the extraction of soft transition-metal ions with T-1. Ag^+, for example, was extracted as much as 46% with photogenerated *cis*-T-1, while no detectable extraction was observed when *trans*-T-1 was used. The trans form has no binding ability to any metal ions.

The high extractability of soft transition-metal ions, such as Ag^+, Hg^+, Hg^{2+}, and Cu^{2+} by *cis*-T-1, in comparison to alkali-metal ions, unambiguously indicates that sulfur atoms are incorporated in the host cavity molecular framework. High binding ability to Ag^+ and low ability to K^+ are also observed in the case of 2,3,4-(4′-methylbenzo)-1,4-dithia-7,10,13,16-tetraoxacyclooctadec-2-ene.[15]

Elongation of the ethylenedioxy chain gave a contradictory result as shown in Table III. When the side arm has two ethylenedioxy chains, T-2, the trans form can capture metal ions more efficiently than the cis form. In addition, the difference in the binding ability between the soft transition-metal ion (Ag^+) and the hard alkali-metal ion (K^+) was not so remarkable as with T-1. These results suggest that the single long oxyethylene chain itself can capture metal ions without any assistant of another chain and the cavity structure is possibly composed of four oxygen and only one sulfur atoms.

The decrease in the extractability of *cis*-T-2 is ascribable to the crowded nature of the double chains in the cis form. Molecular model experiments suggest that two cavities composed of four oxygen and one sulfur atoms can be formed in the trans form in both sides of thioindigo, while coexistence of the two cavities in the same side is impossible in the cis form because of steric hindrance.

4. Ion Transport across a Liquid Membrane. The all or nothing type change in ion binding ability of the photoisomerizable thioindigo with ethylenedioxy side chains suggests its possible application for fully photoregulated ion transport across a membrane; both ion capture and release processes are fully controlled by photoirradiation. We thus examined the effect of photoirradiation on Ag^+ transport across the 1,2-dichloroethane membrane in a H-type cell.

As a model system of the ion transport across the membrane, we, at first, confirmed to what extent ion extraction into the organic phase and ion release into the aqueous phase can be regulated by photoirradiation in a single tube. $AgNO_3$ and picric acid were dissolved in the aqueous phase and T-1 in 1,2-dichloroethane. After photoirradiation for 60 s with 529-nm (0.1 W) light of an Ar ion laser, which causes isomerization of T-1 from the trans to the cis form, the decrease of the metal picrate concentration in the aqueous phase was followed spectroscopically. The decrease corresponds to the Ag^+ concentration extracted into the organic phase.

Figure 4 shows the time dependence of the Ag^+ extraction into the organic phase after being "switched on" with a 60-s burst of

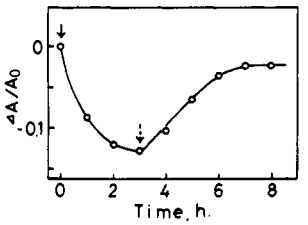


Figure 4. Photoregulated capture and release of Ag^+ by T-1 in a single test tube. The extractability was estimated from the decrease of the absorption ($\Delta A/A_0$) of the metal picrate in the aqueous phase. Initial conditions are following: aqueous phase, aqueous solution containing 1×10^{-2} M $AgNO_3$ and 2×10^{-5} M picric acid; organic phase, 1,2-dichloroethane solution containing 4×10^{-5} M T-1; (↓) irradiation for 60 s with 529-nm (0.1 W) light; (↓) irradiation for 30 s with 488-nm (0.1 W) light.

Table IV. Photoregulated Capture and Release Cycles of Ag^+ by T-1[a]

photoirradiation wavelength, nm	picrate salts extracted, %				
	1st	2nd	3rd	4th	5th
488 (trans, 0.87)	0[b]	10	12	14	14
529 (cis, 0.75)	40	40	41	42	42

[a] Aqueous phase, aqueous solution containing 1×10^{-2} M $AgNO_3$ and 2×10^{-5} M picric acid; organic phase, 1,2-dichloroethane containing 4×10^{-5} M T-1. [b] Organic phase contains dark adapted T-1.

529-nm laser light. Ag^+ was captured by photogenerated *cis*-T-1, and 13% of the ions was extracted into the organic phase in 3 h. After the extraction ceased, the organic phase was irradiated for 30 s with 488-nm (0.1 W) light of an Ar ion laser to isomerize T-1, having captured Ag^+, from the cis to the trans form. The content of the picrate in the aqueous phase increased slowly and reached a final concentration 2% lower than the initial concentration. Without 488-nm irradiation, increase of Ag^+ concentration in the aqueous phase in the dark was negligibly small, less than 2% in 5 h. This suggests that the ion dissociation constant of the cis form is very low.

The increase in the concentration is unambiguously brought about by the photostimulated release of Ag^+ from the host molecules. When the host molecules isomerize from the cis to the trans form, they release Ag^+ because the trans form has no binding ability to Ag^+. The relatively slow increase in the concentration suggests that the diffusion of the metal picrate across the water–organic phase boundary is slow because of its small area, which is not disrupted by gentle stirring applied to the system. The organic phase is considered to be temporarily supersaturated with respect to the metal picrate. Of the Ag^+ extracted into the organic phase, 2% remained captured in this phase by *cis*-T-1. This is due to the fact that the 488-nm light can only partially (87%) convert the cis into the trans form.

The cycle of ion extraction and release was repeated 5 times under vigorous stirring conditions to examine the reversibility. Vigorous stirring accelerated the ion extraction and releasing processes in less than 20 min and also increased the extractability. As can been seen from Table IV, the photoresponsive tweezers have quite good reversibility.

The photoactive function of the host molecule may be expressed as follows. The host molecule acts as a metal ion acceptor when it receives a photosignal of 529-nm light, whilst it changes its function to a metal ion emitter when it receives a signal of 488-nm light.

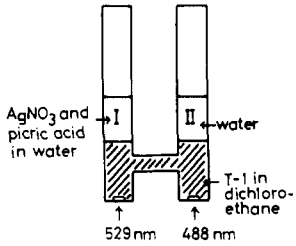


Figure 5. H-type cell for ion transport experiments.

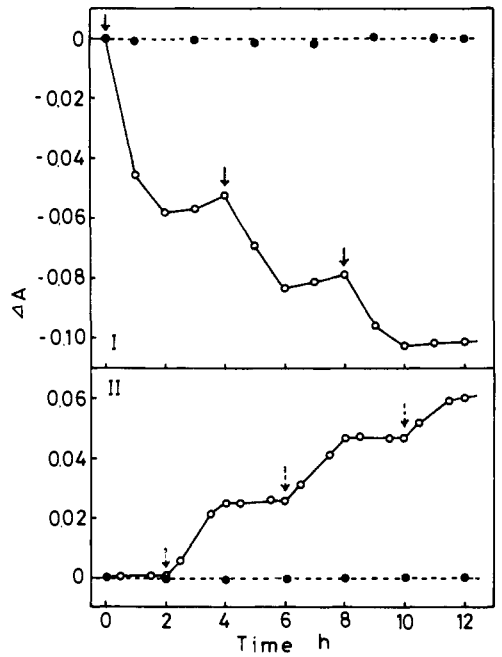


Figure 6. Photoregulated Ag^+ transport across a liquid membrane containing T-1. Aqueous phase I, aqueous solution containing 1×10^{-2} M $AgNO_3$ and 2×10^{-5} M picric acid; liquid membrane, 1,2-dichloroethane containing 4×10^{-5} M T-1; aqueous phase II, pure water. Initial absorbance at 357 nm of the metal picrate in aqueous phase I was 0.30. (↓) Irradiation for 60 s with 529-nm (0.1 W) light. (↓) Irradiation for 30 s with 488-nm (0.1 W) light. (●) In the dark.

The results of the single tube experiments suggest that it is possible, in principle, to control ion transport through a liquid membrane both at the ion capture and at the ion release stages.

Ion transport experiments were carried out as follows, by using a H-type cell shown in Figure 5. In aqueous phase I, $AgNO_3$ and picric acid were introduced. 1,2-Dichloroethane was used as the organic phase, in which T-1 was dissolved. Aqueous phase II was pure water. The initial pH of both aqueous phases was adjusted to 5.5 by the addition of an appropriate amount of acid (HCl) or alkaline (NaOH) aqueous solutions.

Figure 6 shows the results of the photoregulated Ag^+ ion transport. In the dark, no ion transport from I to II was observed as shown by the filled circles. Upon irradiation of the organic phase just below aqueous I for 60 s with 529-nm (0.1 W) light from an Ar ion laser, the concentration of the metal picrate in aqueous phase I started to decrease and around 20% was extracted into the organic phase after 2 h. During this time, an appreciable amount of metal picrate was not released into aqueous phase II.

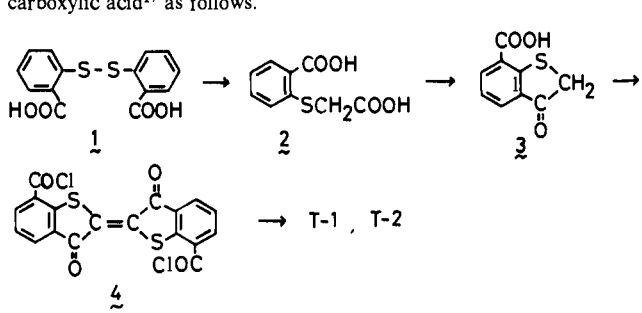
After 2 h of extraction, the organic phase below aqueous phase II was irradiated for 30 s with 488-nm (0.1 W) light. Then, the Ag^+ extracted into the organic phase was released into aqueous phase II, and the concentration of the metal picrate began to increase in phase II. The slight increase in the concentration in aqueous phase I suggests that a small amount of the ejected Ag^+ diffused to the organic phase below aqueous phase I and was released into phase I. In 2 h, half of the extracted ions were released into aqueous phase II. The rest of the ions are considered to be still captured by the remaining *cis*-T-1. This is expected since only 50% of the organic phase is irradiated by 488-nm light, and so the conversion of cis to trans cannot exceed 50%.

A second photoirradiation by 529-nm light of the organic phase below phase I further decreased the content of the metal picrate in phase I, and the second irradiation by 488-nm light further increased the picrate content in aqueous phase II. Repeating the cycles of alternate photoirradiation of 529- and 488-nm light resulted in the transportation of Ag^+ from aqueous phase I to II. Both the metal ion capture and release processes are fully controlled by photoirradiation. The association constant of Ag^+ to the cis form T-1 estimated from the extraction experiments[15] gave a value of over 10^6 M^{-1}. The high association constant prevents rapid thermal release of Ag^+ from organic phase to aqueous phase II. This makes it possible to control the ion releasing process by photoirradiation.

In this ion transport process, the rate-limiting step is considered to be the diffusion of metal picrates and host molecules across the aqueous–organic phase boundary. The solution was gently stirred to avoid quick mixing of the organic phase, which would complicate the ion release process. To accelerate the ion transport rate, it is necessary to enlarge the boundary area, for example, by employing countercurrent extraction.

Experimental Section

Materials. T-1 and T-2 were synthesized from 2,2′-dithiodisalicylic acid via (*o*-carboxyphenyl)thioacetic acid and 1-thio-3-oxoindanyl-7-carboxylic acid[17] as follows.



(*o*-Carboxylphenyl)thioacetic Acid (2). A mixture of 2,2′-dithiodisalicylic acid (**1**) (153 g), chloroacetic acid (113 g), and sodium hydroxide (100 g) in water (100 mL) was boiled for 3 h. A further 36 g of sodium hydroxide in a small amount of water was added after 1 h of boiling. The reaction mixture was cooled to room temperature and neutralized with 20% hydrochloric acid. The brown precipitate was filtered and dried. The crude product was recrystallized from ethyl acetate to give brown needle crystals: mp 217–218 °C. Anal. Calcd for $C_9H_8O_4S$: C, 50.93; H, 3.81; S, 15.10. Found: C, 50.73; H, 3.82, S, 15.19.

1-Thio-3-oxoindanyl-7-carboxylic Acid (3). (*o*-Carboxyphenyl)thioacetic acid (21.2 g) was boiled with an excess of thionyl chloride under a nitrogen atmosphere, of which the excess was removed in vacuo. To the resulting unisolated acid chloride in *o*-dichlorobenzene (300 mL) was gradually added powdered aluminium chloride (16 g). The temperature was finally raised to 50 °C. The whole reaction finished in 1 h. Ice and sodium hydroxide were added until the mixture became alkaline. The aqueous layer after extraction with ether was acidified with 20% hydrochloric acid to give a brown precipitate. The precipitate was washed with water and then dried. The crude product was recrystallized from water and then acetone to give reddish-brown needles: mp 310–311 °C. Anal. Calcd for $C_9H_6O_3S$: C, 55.66; H, 3.12; S, 16.51. Found: C, 55.38; H, 2.96; S, 16.20.

7,7′-Bis(chlorocarbonyl)thioindigo (4). 1-Thio-3-oxoindanyl-7-carboxylic acid was refluxed with excess thionyl chloride for 3 h. The excess thionyl chloride was removed in vacuo and resulting product was used for the next step without isolation.

7,7′-Bis((methoxyethylene)oxy)carbonyl)thioindigo (T-1). To the unisolated acid chloride obtained above in a mixed solvent of benzene (6 mL) and pyridine (3 mL), ethylene glycol monomethyl ether (1.5 mL) was added slowly, and the solution was stirred for 30 h at room temperature. After the solvent was removed, the product was washed with water and then dried. The crude product was recrystallized from benzene: ^1H NMR (Me_2SO-d_6) 3.3 (s, 6 H, CH_3), 3.8 (m, 4 H,

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CH_2CH_2OCO), 4.5 (m, 4 H, CH_2OCO), 7.6 (t, 2 H, ArH), 8.2 (d. 2 H, ArH), 8.3 (d, 2 H, ArH); mass spectrum, m/e M^+ 500. Anal. Calcd for $C_{24}H_{20}O_8S_2$: C, 57.59; H, 4.03; S, 12.81. Found: C, 57.53; H, 3.91; S, 12.78.

7,7'-Bis(((2-((2-methoxyethylene)oxy)ethylene)oxy)ethylene)-oxy)carbonyl)thioindigo (T-2). The synthetic procedure was the same as for T-1. Triethylene glycol monomethyl ether was used instead of ethylene glycol monomethyl ether: ^1H NMR (Me_2SO-d_6) 3.3 (s, 6 H, CH_3), 3.5 (m, 16 H, CH_2), 3.8 (m, 4 H, CH_2CH_2OCO), 4.5 (m, 4 H, CH_2OCO), 7.6 (t, 2 H, ArH), 8.2 (d, 2 H, ArH), 8.3 (d, 2 H, ArH); mass spectrum, m/e M^+ 676. Anal. Calcd for $C_{32}H_{36}O_{12}S_2$: C, 56.79; H, 5.36; S, 9.48. Found: C, 56.76; H, 5.53; S, 9.55.

Photoisomerization. A xenon lamp (Osram 450 W) was used as a light source. Monochromatic light of 550 and 450 nm was obtained by passing the light through a band-pass interference filter (Toshiba KL-55 or KL-45) and a cutoff filter (Toshib VY-42). Lines of the Ar ion laser (Spectra-Physics 165) of 488 and 529 nm were also used to isomerize T-1 from the cis to the trans and from the trans to the cis form, respectively, in a single test tube or in a H-type ion transport cell. A laser beam is convenient for irradiation to the limited area. When used for the ion transport experiments, the laser beam irradiated a small area just below the aqueous-organic phase boundary.

Solvent Extraction. Equal volumes (15 mL) of benzene (or 1,2-dichloroethane) containing 4×10^{-5} mol/l T-1 or T-2 and an aqueous solution containing 1×10^{-2} mol/l metal nitrate and 2×10^{-5} mol/l picric acid was vigorously agitated for 30 min with a shaker (Yamato SA-31). T-1 and T-2 were irradiated with 450- or 550-nm light for 10 min prior to the extraction experiments. A similar extraction was performed with pure benzene (or 1,2-dichloroethane). The extractability was determined from the difference between these two absorbances of metal picrate in the aqueous phase. All the extractions were conducted at 25 °C.

Ion Transport across a Liquid Membrane. A H-type cell containing 40 mL of organic liquid membrane (1,2-dichloroethane) and two aqueous phases (15 mL each) was used. The cell was immerced in a water bath thermostated at 25 °C. The liquid membrane was stirred gently. Dissolved in the liquid membrane was 4×10^{-5} mol/l T-1. Aqueous phase I contained 1×10^{-2} mol/l $AgNO_3$ and 2×10^{-5} mol/l picric acid, and phase II was pure water. The ion transport was followed by measuring the decrease of the absorption of metal picrate in phase I and the increase in phase II.

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On a Tandem 1,2-Elimination/[1,7]-Sigmatropic Shift: Synthesis of Double Bond Shifted Isomers of Vitamin A

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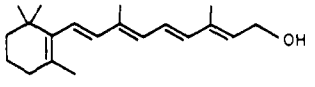
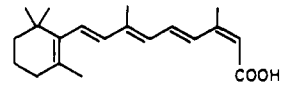
Abstract: The syntheses of four geometrical isomers of 18,14-*retro*-retinol (**7a–10a**) and two dehydro derivatives (**31b** and **32b**) are described. Treatment of the *cis*-benzoate **19** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded an 80% yield of the trienyne **20a**. Evidence for the formation of the latter by an initial 1,2-elimination to afford the putative **21** followed by a [1,7]-sigmatropic shift is provided. Thus, treatment of the pentadeuteriobenzoate **23** under identical conditions afforded **25**, in which a single deuterium atom is incorporated at the C_3, methyl position by way of an intramolecular process. Palladium-catalyzed coupling of the Grignard salt of **20a** (**20f**) with (*E*)-bromide **30a** followed by deprotection afforded dehydro-*retro*-retinol **31b**. The latter was catalytically reduced to the (10*Z*)-*retro*-retinol **8a**. A similar sequence applied to the (*Z*)-bromide **30b** afforded **32b** and the (10*Z*,12*Z*)-*retro*-retinol **10a**. A standard three-step sequence was used to convert **20a** to the tetraenal **33b**, which was condensed in a Wittig reaction with ylide **35** to afford after separation the *all-trans*- and (12*Z*)-*retro*-retinols, **7a** and **9a**, respectively.

A significant correlation between the role of retinoids (vitamin A) in controlling differentiation of epithelial cells and the development of malignancy in epithelial tissues has been clearly established.[1] The natural vitamin A (**1**) exhibits therapeutic and prophylactic activity in certain types of carcinomas but unfortunately causes toxic liver damage due to excessive localization in the liver. In contrast, the unnatural geometric isomer 13-*cis*-



1



2

retinoic acid (**2**) is far less toxic yet possesses similar biological efficacy in controlling cell differentiation.[1,2] Success of this sort has spurred a search for increasingly more effective retinoidal anticancer drugs.[3] The signal importance of retinoids in photobiological research (energy transduction and vision)[4] and acne therapy[5] provides further impetus for synthetic endeavors in the vitamin A field.

In the case of compounds which show toxic side effects, acceptable therapeutic indexes can still be obtained by designing analogues which show greatly enhanced beneficial activity. Although exactly how a retinoid such as **2** exerts its various biological effects is unclear, it would be quite plausible that it does so by binding to one or more proteins in one topologically specific form or another. For example, 13-*cis*-retinoic acid (**2**) may bind to a putative receptor in a side chain conformation, such as **3–6** or one

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