New Fluorophores Based on Non-Cyclic Crown Ethers for Alkali and Alkaline Earth Metal Cation

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Abstract. Recent advances regarding podand derivatives which are non-cyclic crown ethers incorporating functional groups have been reviewed. Particular attention has been paid to fluorophore appended non-cyclic crown ethers as sensors for cation detection. Their complexation behavior with alkali and alkaline earth cations and interactions between their terminal groups is also discussed in detail.
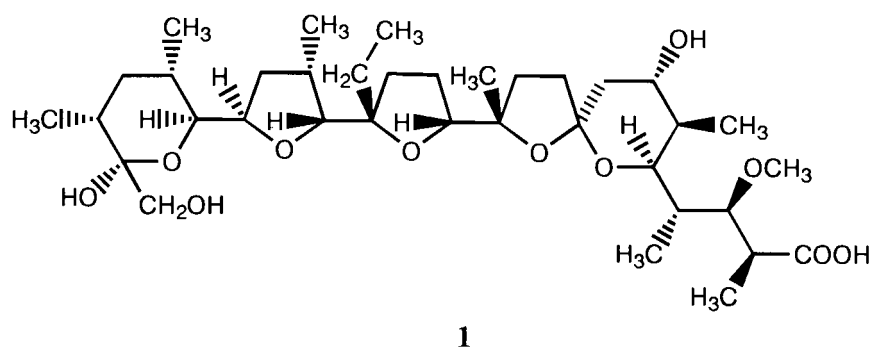
Key words: non-cyclic crown ether, pseudo-cyclic structure, alkaline earth ions, conformational change, fluorescence spectra, fluorescence detecting system.

1. Introduction

It is known that tetraethylene glycol dimethylether (glyme), polyethylene glycol and their ethers solvate alkali metals and their salts [1, 2]. Although the complexation ability of these non-cyclic ether derivatives is not so strong compared with that of crown ethers [3], the conformation of these compounds changes drastically from a linear structure to a cyclic structure on complex formation with metal ions. Much attention has been focused on non-cyclic crown ether derivatives owing to their interesting and significant conformational changes.

To compensate the low binding ability for metal ions, many efforts have been made, such as constructing a pseudo-cyclic structure through head-to-tail interaction on non-cyclic crown ethers. The pseudo-cyclic structure plays important roles not only in artificial ionophores but also in natural ionophores for the selectivity of metal cations and increase of the binding force. If this conformational change of non-cyclic crown ethers could be converted into physical signs, such as UV absorption and fluorescence etc., one would establish more sensitive cation sensors compared with crown ethers. This paper describes a new approach for the development of a fluorimetric alkali and alkaline earth metal sensor based on non-

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Formula 1.

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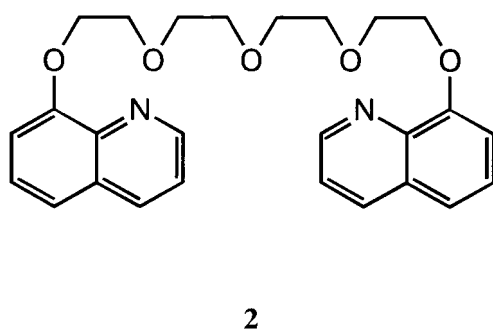
Formula 2.

cyclic crown ethers, and the complexation behavior of related compounds is also reviewed.

## 2. A Naturally Occurring Non-Cyclic Ionophore and the Role of Pseudo Cyclic Conformation

Monensin **1** is a naturally occurring non-cyclic ion carrier which is constructed with three tetrahydrofuran units and two tetrahydropyran units having hydroxy and carboxy groups at its terminals [4, 5]. In alkaline condition, **1** forms a pseudo-cyclic structure like a crown ether via an intramolecular head-to-tail hydrogen bond between the carboxylate anion and the hydroxyl group. This pseudo cyclical compound **1** binds alkali metal ions strongly, and **1**·Na$^+$ passes through lipophilic biological membranes. On the other hand, in acidic conditions the complex structure of pseudo cyclical compound **1** with alkali metal ion is broken down by the protonation on the carboxylate anion, and the metal ion is released.
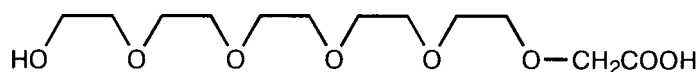
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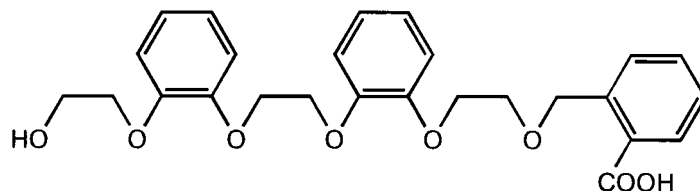
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Formula 4.

3. Artificial Non-Cyclic Crown Ethers and Their Complexation Behavior

The early study on artificial non-cyclic crown ether derivatives, podands, was carried out by Vögtle et al. [6, 7]. They demonstrated that the oligo-oxyethylene compound **2**, appending two quinoline units at its terminals, strongly bound K^+ by electrostatic interaction between the ion and the oxygen atoms with the aid of $\pi-\pi$ interaction between the end capped quinolines. Their study also indicated that quinoline moieties, which are strong ligands themselves, increased the rigidity around the oxyethylene part, and significantly contributed to stabilization of the complex of K^+. Thus, non-cyclic polyether compounds have been used as ion selective ionophores for active cation transporters and extraction reagents. Some podand derivatives incorporating ionophoric functional groups located at the terminals of molecules exhibit excellent properties as carriers for metal ions.

Nakahama et al. [8–11] demonstrated that a series of synthetic carboxylic ionophores **3**, **4** exhibit high selectivity for K^+ over Na^+ in the ion transport experiment across a dichloromethane liquid membrane. This excellent selectivity for K^+ was explained by the high lipophilicity of the K^+ complex with a definite helical conformation in the liquid membrane. This consideration was further supported by X-ray crystal structure analysis of the complex [12, 13]. Synthetic ionophores **5**, **6** [14] and **7** [15, 16] having a similar structure have been synthesized. These ionophores could show reversible conformational change between the pseudo-cyclic structure and the linear structure using interactions between the hydroxyl group or the quinoline moiety and the carboxylate anion. These compounds also showed abilities of ion carriers across biological and artificial membranes by the same mechanism as mentioned above. Recently, a non-cyclic polyether dicarboxylic acid ionophore was employed as an extraction reagent for the separation of Pb^{2+} from weakly acidic aqueous solution by liquid chloroform membrane [17].
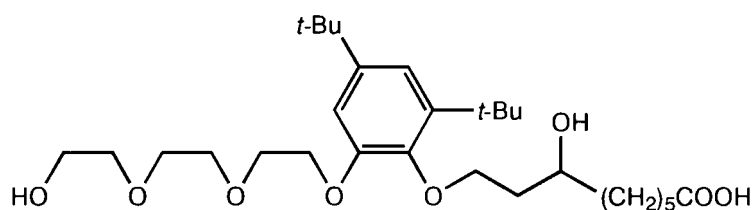
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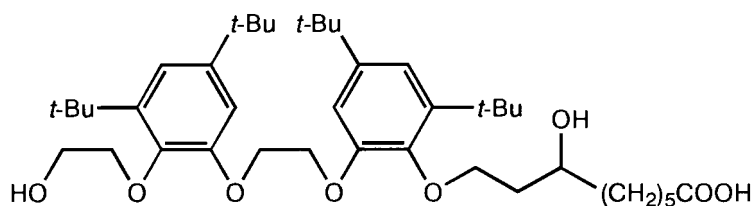
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Formula 6.

4. New Fluorophores for Cations Based on Non-Cyclic Crown Ethers

If fluorophores are located at the ends of non-cyclic crown ethers as a detecting moiety and as a "glue" for making the pseudo-cyclic structure, information about the conformational change at the binding event will be converted into fluorescence spectral changes. In other words, we can monitor a complexation process by means of the change in the fluorescence spectrum. It is also known that the fluorescence spectrum of fluorophores is sensitive to microenvironments. The usual fluorophore is a planar aromatic molecule and tend to stack each other. One can expect that fluorophores will show an excellent probe and an attachment for stabilization of the pseudo-cyclic structure of the complex.
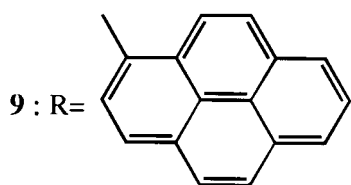

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Formula 7.

8 : R=

Formula 8.

9 : R=
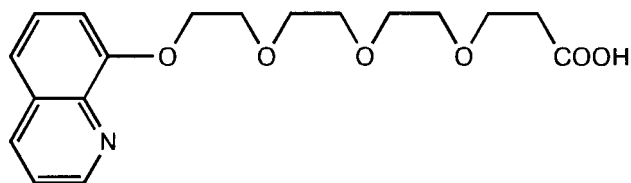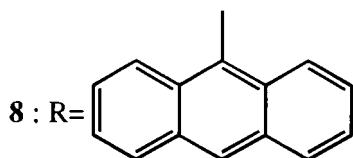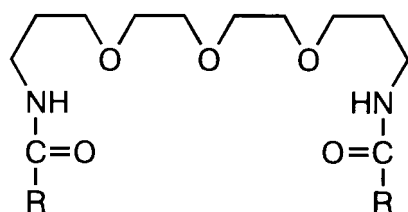
Formula 9.

On the basis of this idea, recently, we have synthesized several novel fluorescent reagents [18] which have two fluorescent chromophores (**8:** anthracene, **9:** pyrene, and **10:** fluorene etc.) at both terminals of 1,13-diamino-4,7,10-trioxatridecane symmetrically and asymmetrically substituted [19], and their complexation behavior with alkali and alkaline earth cations were discussed. Figure 1 shows fluorescence spectra of **8** as a function of concentration of $CaClO_4$ in acetonitrile at 25 °C. Through the complexation with Ca^{2+}, the shape and the peak of the fluorescence spectra of **8** significantly changed from a relatively structured band with three peaks around 400 nm to a structureless band at 490 nm. The peak around 400 nm of uncomplexed species and the broad peak at 490 nm of the complexed species could be attributed to fluorescence from an anthracene monomer and dimer, respectively. This phenomenon indicated that the structure of the ligand changed on complexation, and two anthracenes approached each other and then stacked. This large Storks shift change of anthracene, which came from the large conformational
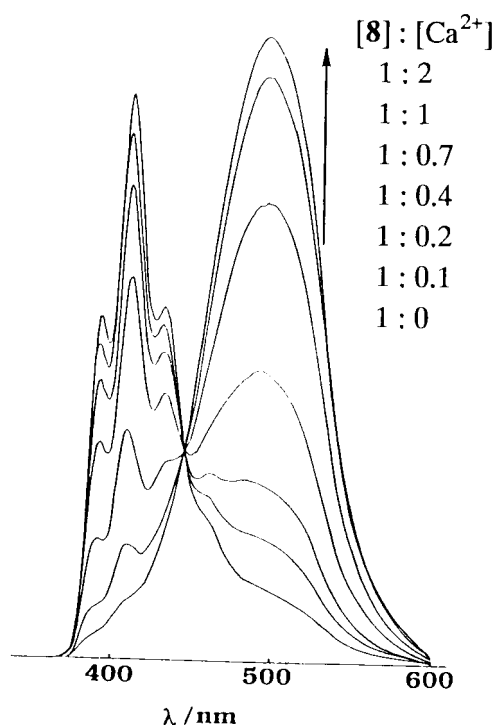

10 : R=
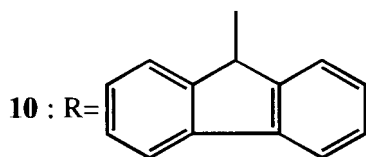
Formula 10.

Figure 1. Fluorescence spectra of **8** and its Ca^{2+} complex, as excited at 332 nm. [**8**] = 5 × 10^{-5} mol dm^{-3} in acetonitrile at 25 °C.

changes, confirmed the binding event clearly. In the presence of Sr^{2+} or Ba^{2+}, the same spectral changes were observed. Unfortunately, compounds **9** and **10** (the analogues of **8**) did not show spectral changes on addition of any metal salts. The fluorescence spectrum of **9** only indicated that of dimer pyrene, suggesting the presence of the strong interaction of pyrene units in the ground state before complexation. On the other hand, **10** showed only monomer type fluorescence spectra in the presence and absence of $CaClO_4$. This may be caused by weak interaction between the fluorene units. In the presence of alkali metal or ammonium ion, only small spectral changes were observed for **8–10**. This observation suggests that the complexation ability of these reagents to alkali metal ions or ammonium ion is quite small. Compound **8** forms 1 : 1 complex with alkaline earth metal ions; the order of the complex formation constants was $Ca^{2+}>Sr^{2+}>Ba^{2+}>Mg^{2+}$. The complex formation constants are summarized in Table I. As shown in Table I, **8** formed the most stable complex with Ca^{2+}; this may stem from the suitable enclosure of Ca^{2+} by the oxygen atoms of the polyether and carbonyl moieties like an 18-crown–6 molecule. This pseudo-cyclic structure causes a dimer-like interaction between two anthracene units. On the other hand, the anthracene units of free **8** existed as a monomer.
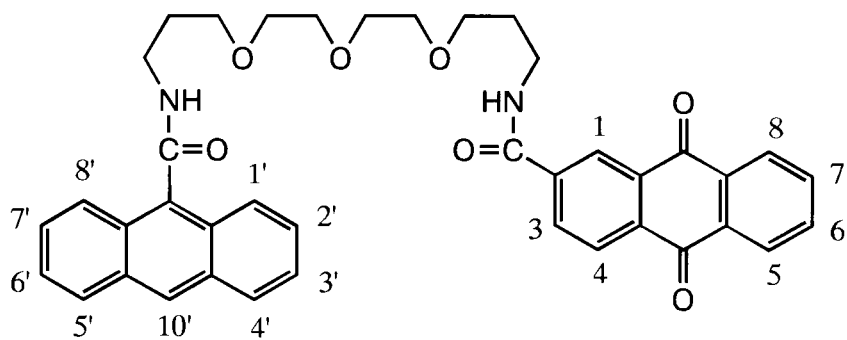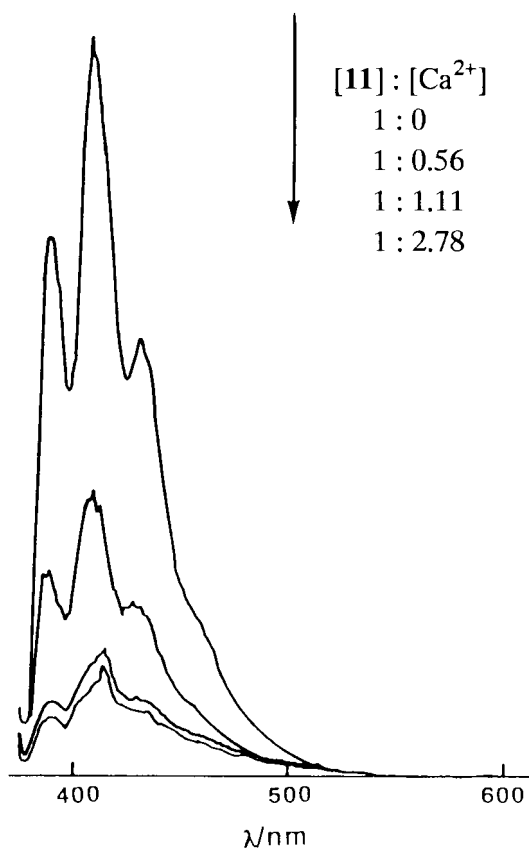
Formula 11.

Figure 2. Fluorescence spectra of **11** and its Ca^{2+} complex, as excited at 372 nm. [**11**] = 1. 8 × 10^{-5} mol dm^{-3} in acetonitrile at 25 °C.

Table I. Summary of complex formation constants of **8**, **11**, and **12** for various metal ions in acetonitrile at 25 °C

Fluorophore	Metal ion	$\mathrm{Log_{10}K}$[a]
8[c]	Li^+	2.73
	Mg^{2+}	4.67
	Ca^{2+}	6.41
	Sr^{2+}	5.25
	Ba^{2+}	4.81
11[d]	Mg^{2+}	5.53
	Ca^{2+}	6.43
	Sr^{2+}	6.10
	Ba^{2+}	5.71
12[e]	Tb^{3+}	$\mathrm{Log_{10}K_1} = 6.59$[b]
		$\mathrm{Log_{10}K_2} = 4.17$[b]

[a] $K = [L \cdot M]/([L][M])$.
[b] $K_1 = [L \cdot Tb^{3+}]/([L][Tb^{3+}])$, $K_2 = [L_2 \cdot Tb^{3+}]/([L][Tb^{3+} \cdot L])$.
[c] Ref. 18.
[d] Ref. 19.
[e] Ref. 21.

Table II. Induced chemical shift changes (ppm) of aromatic protons in **11**[a] after complexation with various metal ions in acetonitrile-d_3[b]

Metal	Anthracene unit					Anthraquinone unit				
	H–1′, 8′	H–2′, 7′	H–3′, 6′	H–4′, 5′	H–10′	H–1	H–3	H–4	H–5, 8	H–6, 7
Mg^{2+}	–[c]	−0.03	−0.12	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
Ca^{2+}	−0.09	0.0	−0.09	−0.35	−0.36	−0.44	−0.70	−1.03	+0.08, –[c]	+0.01, –[c]
Sr^{2+}	−0.03	−0.01	−0.04	−0.17	−0.16	−0.26	−0.53	−1.07	+0.05, −0.2	+0.01, –[c]
Ba^{2+}	−0.05	−0.03	−0.06	−0.23	−0.23	−0.23	−0.43	−0.87	+0.06, –[c]	+0.03, 0.0

−: higher magnetic field, +: lower magnetic field.
[a] Ref. 19.
[b] These assignments were determined by H-H COSY and NOESY spectra.
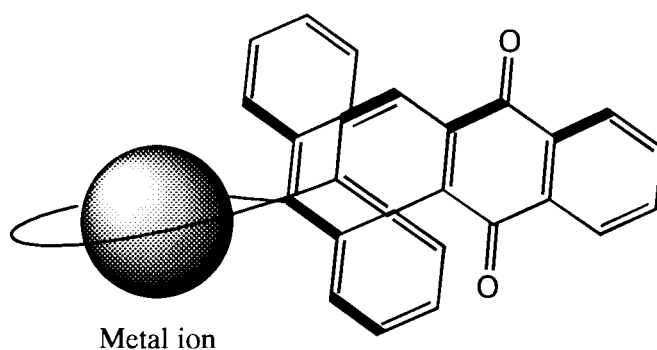[c] These could not be assigned because of too complicated spectra.

Figure 3. Proposed complex structure of **11**·Ca^{2+}. The oxyethylene moiety and amide groups are omitted for clarity.

Although **8** shows excellent fluorescence signs through complexation with alkaline earth metal ions, it is difficult to study a structure of the complex due to the good symmetrical structure of **8** and only observation of the averaged peak positions in ^{1}H-NMR spectroscopy. To overcome this defect, Tahara et al. [19] synthesized a fluorescent reagent **11** bearing two chromophores asymmetrically (one side was anthracene (electron donor) and the other was anthraquinone (electron acceptor)). As shown in Figure 2, the formation of complex **11**·Ca^{2+} resulted in the quenching of emission of the anthracene. There is no spectral overlap between the fluorescence of anthracene and the absorption of anthraquinone, and the redox potential of anthracene (*ca.* -1.75 V in excited S_1 state) is more negative than that of anthraquinone (-0.70 V). Therefore, the quenching mechanism was concluded as follows: alkaline earth cations induced conformational change by which anthracene and anthraquinone approach each other, and intramolecular electron transfer from excited anthracene to anthraquinone occurred. The order of complex formation constants of the complexes was almost the same as in the case of **8**. However, the selectivity of **11** for alkaline earth metal ions was less than that of **8**. This may be caused by the lower rigidity of the pseudo cyclic structure of the complex of **11** due to a weaker interaction between anthracene and anthraquinone than that between two anthracenes in the ground state. The detailed ^{1}H-NMR study gave good information about the structures of the complexes. When **11** complexed with an alkaline earth metal ion, the etherial protons shifted down field, since the electron density of the oxygen atoms is reduced by the coordinated cation. Interestingly, the H-1, H-3, and H-4 protons of the anthraquinone moiety and the H-4′, H-5′, and H-10′ protons of the anthracene moiety showed large high magnetic field shifts. The induced chemical shift changes of aromatic protons in **11** in the presence of various metal ions are summarized in Table II. These induced shift changes of the aromatic protons should be attributed to a diamagnetic effect from the ring current of each aromatic unit. From these observations, the possible conformation of the complex was suggested in Figure 3.
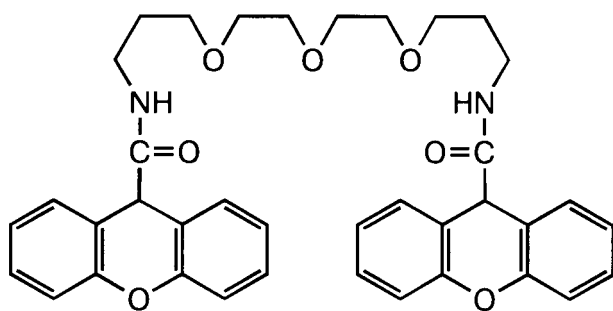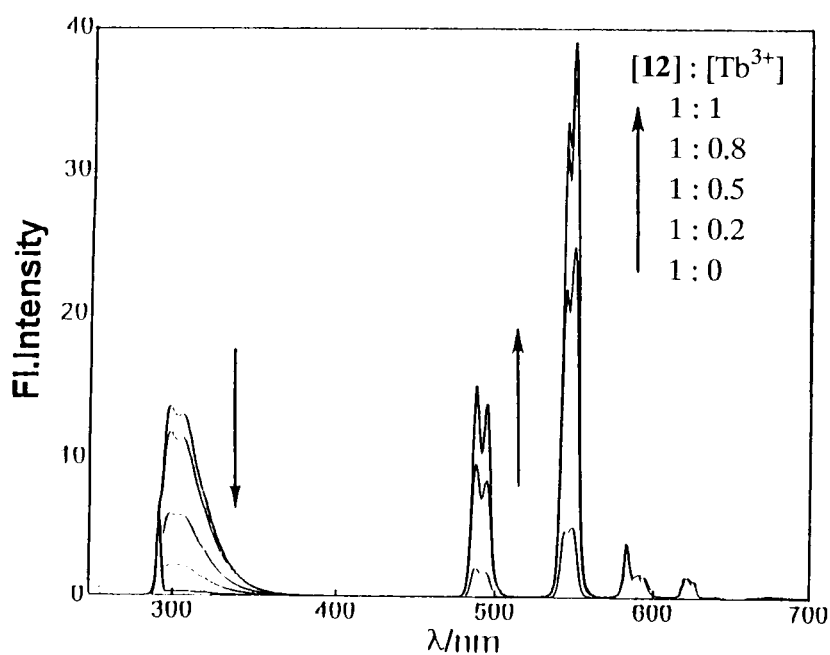
12

Formula 12.

Figure 4. Fluorescence spectra of **12** and its Tb^{3+} complex, as excited at 292 nm. [**12**] = 1 × 10^{-5} mol dm^{-3} in acetonitrile at 25 °C.

On the basis of a similar idea, several polyoxyethylene end capped naphthalenes via ester linkages were synthesized and the complexation behavior was investigated [20].

As another example of an application for non-cyclic crown ether derivatives, Suzuki et al. [21] reported the energy transfer luminescence of Tb^{3+} complexed with non-cyclic crown ether **12** containing xanthene as a sensitizer by using a similar methodology to that of the non-cyclic crown ethers. Figure 4 shows
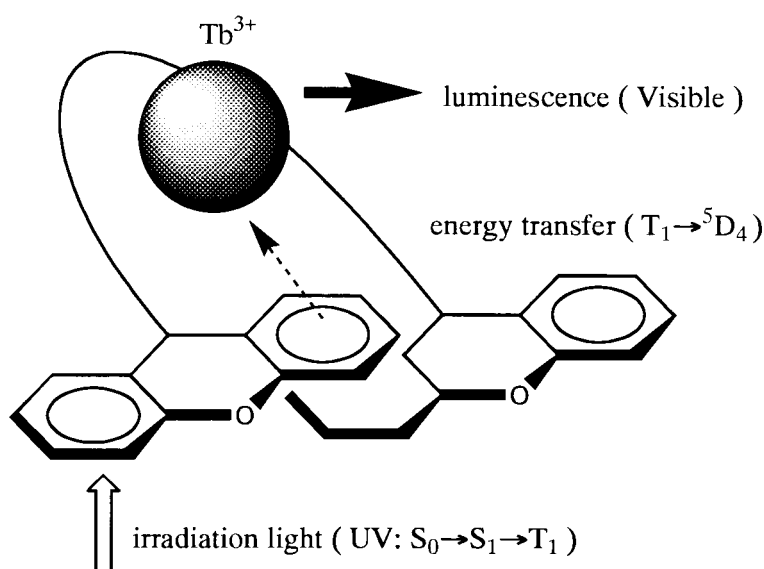
Figure 5. Proposed mechanism of intermolecular energy transfer luminescence of Tb^{3+} complexed with **12**. The oxyethylene moiety and amide groups are omitted for clarity.

fluorescence spectra of **12** complexed with Tb^{3+} in acetonitrile at 25 °C as a function of Tb^{3+} concentration. In the absence of Tb^{3+}, **12** gave an emission of xanthene monomer around 300 nm. On the other hand, **12**·Tb^{3+} indicated an increase of the intensity of four luminescence lines which corresponded to the transition from $^5D_4$ to $^7F_6$ (480 nm), $^7F_5$ (543 nm), $^7F_4$ (583 nm) and $^7F_3$ (620 nm) accompanied by the decrease of the xanthene monomer emission. This excellent sensitized property was explained as follows. UV light energy excited the xanthene moiety to the S_1 state, and this state was converted to the T_1 state immediately by intersystem crossing. This T_1 energy was transferred to Tb^{3+} ($^5D_4$) through intramolecular energy transfer (Figure 5). When an equimolar amount of **12** was added to the Tb^{3+} solution, the fluorescence intensity at 543 nm was about 400 times larger than that of Tb^{3+} itself. A titration curve of fluorescence intensity at 543 nm vs. Tb^{3+} concentration indicated that the emission intensity was gradually saturated with increase of $[Tb^{3+}]$ and reached an asymptotic value above $[Tb^{3+}]/[\textbf{12}] = 1$ showing a 1 : 1 complex at this point. A bending point was also observed at $[Tb^{3+}]/[\textbf{12}] = 0.5$ showing a 1 : 2 complex formation. Thus, on the assumption that **12** forms a 1 : 2 complex ($[Tb^{3+}] : [\textbf{12}]$) at low concentration of Tb^{3+} and a 1 : 1 complex at high concentration of Tb^{3+}, complex formation constants were evaluated (Table I). Compound **12** also showed about 1000 times higher complex formation constant compared with that of an analogous compound without the terminal fluorophores. This result supported the conclusion that interaction between both terminal xanthene moieties contributed significantly to stabilization of the complex like a dimer formation.

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