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MOLECULAR DESIGN AND SYNTHESIS OF SIGNAL TRANSDUCER RECEPTORS

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Abstract This article deals with the performance of representative artificial signal transducer receptors we have synthesized so far for biologically important chemical species.

INTRODUCTION

A naturally occurring receptor is generally defined as a complex molecule or molecular assembly that, upon recognition of a specific substrate, undergoes a structural change that usually induces a series of functions such as allosteric effect and signal transduction, which eventually results in a physiological response.[1]

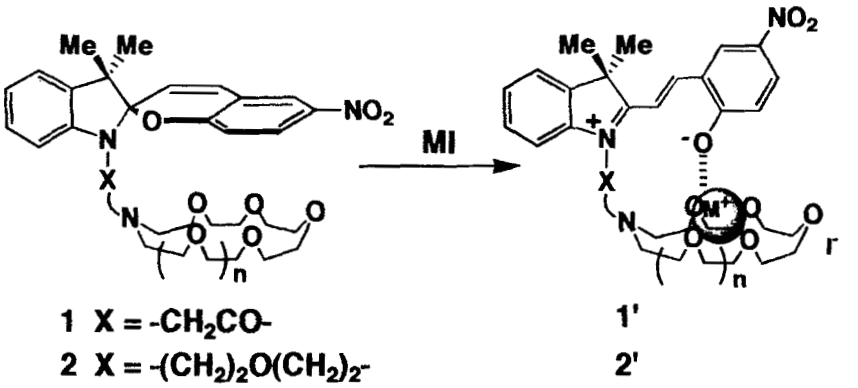
The final aim of our research is to create "intelligent" supramolecules and supramolecular systems, in which several conjugated functions are induced by molecular recognition and the whole process is completely regulated at our will. In 1990, we introduced conceptually new artificial receptors, in which recognition of alkali-metal cations induces a configurational change in the receptor frameworks accompanying signaling (coloration).[2] Our initial goal in this area is to develop such specific receptors for each of key molecules.[3] In this article, I describe a series of signal transducer receptors possessing a spiropyran unit as a signaling site for biologically important chemical species. The spiropyran receptors were designed to enable molecular recognition information to be signaled as isomerization of the spiropyran unit to the merocyanine structure.

CROWNED SPIROBENZOPYRANS

Our own approach began with the crown ether chemistry because crown ethers act almost exclusively on ionic substrates, and the selectivity for metal ions has well been documented. We hoped that the strong interaction between the complexed cations and

p-nitrophenolate oxy-anion of the merocyanine form could be responsible for the isomerization from the spiropyran to merocyanine. Thus, crowned spirobenzopyrans **1** and **2** were developed.[2,4] Isomerization of these spirobenzopyrans to the open colored merocyanines **1'** and **2'** was induced by recognition of alkali-metal cations and the selectivity of the coloration was found to be governed by several factors: (1) the size of the crown ring, (2) the position of recognition, (3) electric properties of both the complexed cations and the merocyanine dipoles, and (4) the length of the alkyl chains connecting the spirobenzopyran units and the crown ring units (Figure 1).

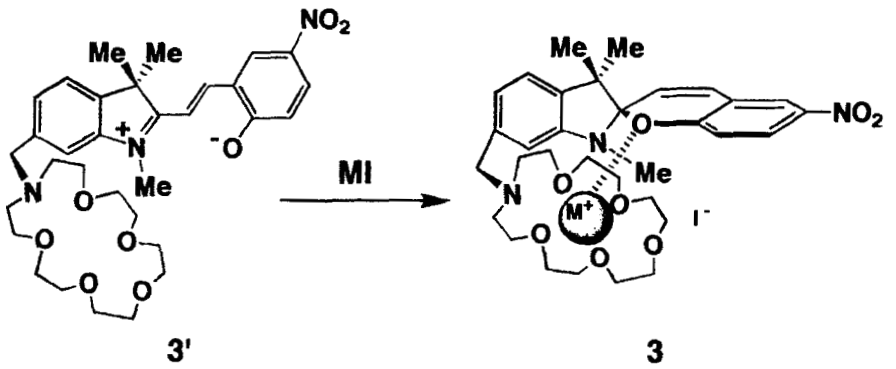
FIGURE 1



1 X = -CH_2CO-
2 X = -$(CH_2)_2O(CH_2)_2$-

1'
2'

FIGURE 2



3' **3**

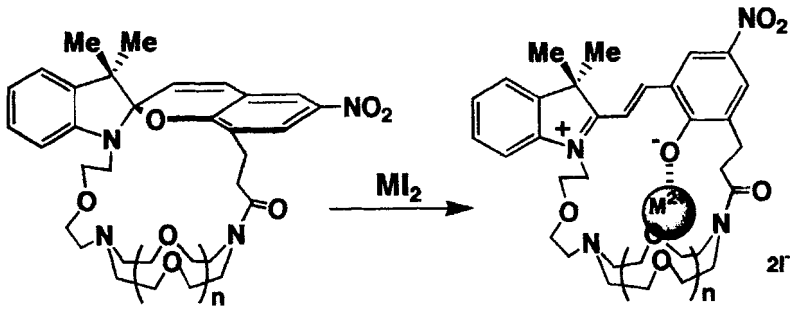
On the other hand, crowned spirobenzopyran **3** was designed to recognize cations in which the complexed cations could interact with the ether oxygen of the closed spiropyran and not the phenolate oxygen of the opened merocyanine (Figure

2).[4] Indeed, isomerization of **3** to the colored mertocyanine **3'** was most strongly suppressed by the presence of a potassium cation which was expected to be most strongly recognized by the crown ring.

CRYPTAND SPIROBENZOPYRANS

The spirobenzopyrans bearing a short linkage **1** showed color selectivities for Li^+ (n=1) and Na^+ (n=2). Selective coloration, however, for larger alkali-metal cations could not be obtained even in the cases of the n>2 crowned spirobenzopyrans. While the spirobenzopyrans **2**, in which the spirobenzopyran moiety were much further separated from the crown ether units by alkyl chains than **1**, showed a small selective coloration for larger alkali-metal cations, such as K^+ and Cs^+, the molar absorptivities in the presence of alkali-metal iodides were considerably smaller when compared to those of **1**. We thought that the low coloring efficiency might result from the entropic and enthalpic disadvantages: reduced probability of the existence of the complexed cations in the neighborhood of the phenolate oxygen of the merocyanines, and from the weak electrostatic interaction between the complexed large univalent cations and the *p*-nitrophenolate dipole of the merocyanines. Taking into account the above points, we developed cryptand type crown spirobenzopyrans **4** (Figure 3).[5]

FIGURE 3



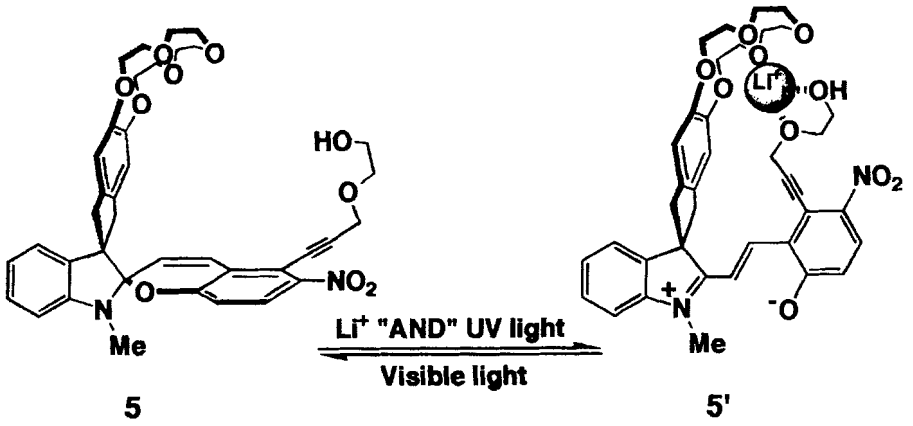
The absorption spectra of **4** were scarcely affected upon addition of any alkali-metal iodides in CH_3CN. In the ^1H NMR spectra of **4** in CD_3CN, however, the downfield shifts (aromatic and crown ring regions), split (crown ring and alkyl linkage regions), and sharpening (aromatic region) of the signals in the spiropyran forms were observed after the addition of KI. This result clearly indicated that the alkali-metal

cations were bound to the macrocycle of **4**, and that the colorless form was attributed to the weak electrostatic interaction between the complexed univalent cations and the *p*-nitrophenolate dipole of the merocyanines. On the other hand, addition of alkaline-earth metal iodides to these CH_3CN solutions gave rise to changes in their spectra. Thus, **4a** and **4b** revealed the highest coloration for Ca^{2+} and Sr^{2+}, respectively. Titration experiments demonstrated that almost *1 equiv of* SrI_2 is enough to obtain the maximum coloration of **4b**.

AND-GATE TYPE CROWNED SPIROBENZOPYRANS

The isomerization of crowned and cryptand spirobenzopyrans **1** ~ **4** to the open-chain colored merocyanines was induced by recognition of alkali-metal cations as well as UV-irradiation. Thus, according to the perspective of molecular devices, the spirobenzopyrans can be considered to perform "OR" gate type dual-mode signal transduction by synchronizing molecular recognition processes with their photochromism. An idea that sophisticated logic operation also necessitate "AND" gate type counterparts led us to develop the new crowned spirobenzopyrans that could only be responsive to the combination of ionic and photonic stimuli. In searching for an ideal crowned spirobenzopyran for this purpose, the structure **5** was developed (Figure 4).[6]

FIGURE 4



5 **5'**

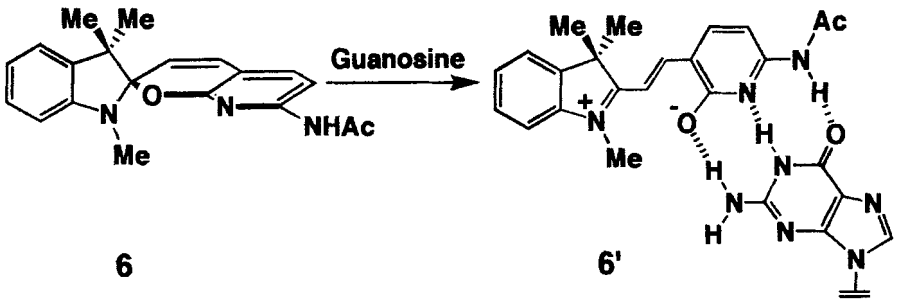
The absorption spectra of **5** were scarcely affected upon addition of any alkali-metal iodides in CH_3CN. In the ^1H NMR spectra of **5** in CD_3CN, however, the

downfield shifts and split of the signals for the crown rings in the spiropyran form were observed after the addition of LiI. This result suggested that the lithium cations were bound to the macrocycle of **5**, and that the colorless form was attributed to no isomerization of **5**•Li^+ to **5** '. Subsequently, irradiation (360 nm) of the metal iodides-contained CH_3CN solutions of **5** gave rise to changes in their spectra, and new absorption bands appeared. Noteworthy is that selective coloration for LiI was observed, reflecting that merocyanine structure **5** ' was most strongly stabilized by Li^+, and that only photoirradiation (without metal iodide) showed a negligible change in its spectrum.

SPIROPYRIDOPYRANS

The design of the spiropyridopyran **6** was based on the triple hydrogen bond complementarity between the acetamidopyridopyran unit of **6** or the acetamidopyridone anion unit of the open merocyanine form **6** ' and guanine.[7] We expected that equilibrium between the colorless spiropyridopyran and the colored merocyanine would be shifted to the latter one by recognition of guanine (Figure 5).

FIGURE 5



The spiropyridopyran **6** showed only weak absorption bands above 350 nm in nonpolar solvents, indicating that **6** exists mainly as the closed spiropyran form. In CH_2Cl_2, however, addition of 2',3',5'-tris-*O*-(*tert*-butyldimetylsilyl)guanosine (10 equiv) to **6** produced changes in the absorption spectra, and the strong absorption bands appeared. On the other hand, only negligible changes were observed upon addition of other nucleoside derivatives. Furthermore, the spiropyridopyran could distinguish guanosine derivatives from *N*-methylated ones on the basis of coloration.

CONCLUSION

This article emphasized the performance of signal transducer receptors possessing a spiropyran unit as a signaling site. The receptors were designed to enable the information of molecular recognition to be signaled as changes for the optical properties of the receptors. The signaling process synchronized with the configurational changes for the receptors, in which we could add further functions to the receptors such as transmission of recognition information.[8] Although the work described here was not purposely directed toward analytical application, some of the systems mentioned seem to have a great potential as molecular sensors. Larger and more complex biologically essential substrates such as peptides, oligonucleotides, and carbohydrates will be future targets for our receptors.[9]

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