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'Purposive' Molecular Design for Multifunctional Artificial Receptors

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Abstract. This account describes recent examples of multifunctional artificial receptors, which demonstrates our approach to purposive molecular design. The paper is divided into two parts. The first deals with novel crowned spirobenzopyrans as dual-mode signal transducers. The new crowned spirobenzopyrans complement previous crowned spirobenzopyrans from the viewpoint of molecular devices, and a detailed comparison between them is given. The second part is concerned with polypyridine-macrocyclic structures as ribofuranoside receptors. The design of the ribofuranoside receptors was based on the multipoint hydrogen bond complementarity between the receptors and methyl β-(D)-ribofuranoside. The binding affinity of the receptors was very high, so that even native ribose was extracted by them into nonpolar solvents.

Key words: molecular design, spirobenzopyran, signal transducer, polypyridine macrocycle, ribofuranoside receptor.

1. Introduction

Artificial molecular recognition chemistry started with the great serendipity of Pedersen in 1967 [1]. During the last three decades, artificial models developed in molecular recognition chemistry have demonstrated the importance of complementarity in size, shape, and functional groups at the molecular level for selective host–guest binding [2]. Recent investigations in the field reveal a shift of attention from single intermolecular interactions to combinations of them, as well as synchronizing the recognition process with other functions such as signal transduction, allosteric effect, etc. [3]. Now, the aim of molecular recognition chemistry is *no longer whether something can be bound or not, but what is to be bound, and how*. Thus, molecular design for artificial enzymes and receptors must be purposive, not serendipitous.

In 1990 we introduced conceptually new artificial receptors, crowned spirobenzopyrans **2**, in which recognition of alkali-metal cations induces a configurational change in the receptor frameworks accompanied by a signal (coloration) [4]. The molecular design of the crowned spirobenzopyrans was fully purposive, not serendipitous. The final aim of our research is to create 'intelligent' supramolecules and supramolecular systems, in which several conjugated functions are induced

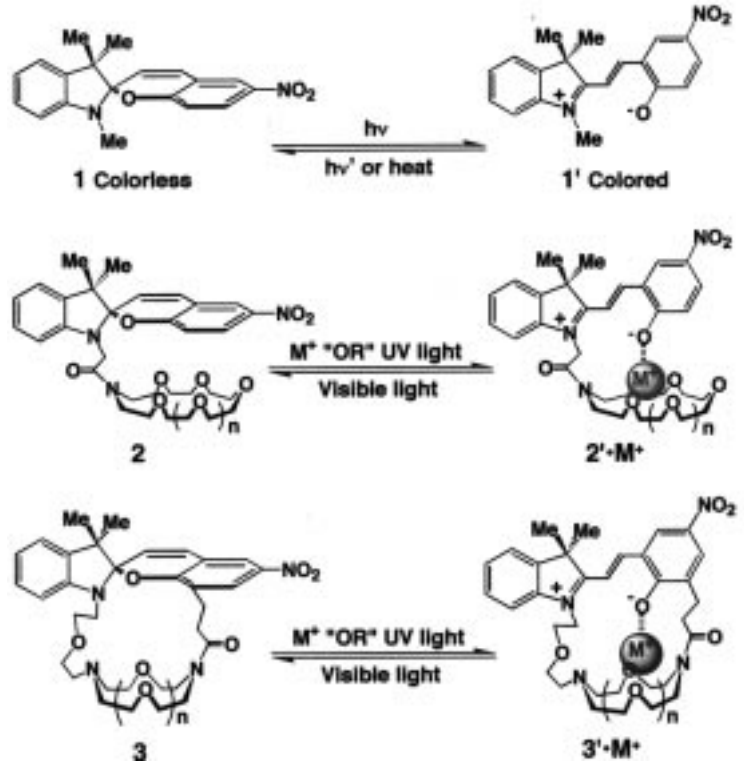
by molecular recognition and the whole process is completely regulated at our will. Our overall goal in this area is to develop such purposively-designed artificial receptors for each key biologically relevant molecule [5]. This account describes our recent examples of artificial receptors, from which our approach on molecular design will be well demonstrated.

2. Novel Crowned Spirobenzopyrans as Dual-Mode Signal Transducers [6]

Colorless spiropyran derivatives **1** are an important class of photochromic and thermochromic compounds which can be converted to the corresponding zwitterionic colored merocyanine isomers **1**′ by light and/or heat [7]. The isomerization is unique in terms of the associated large changes in the structural and electric characteristics of the molecules. When the factor affecting this equilibrium is a chemical species, especially a specific substrate, new functions of the spiropyrans appear, i.e., structural change and signaling based on molecular recognition. Our own approach began with utilization of spiropyrans as a signal-transduction module. We have reported various crowned spirobenzopyrans **2** and cryptand spirobenzopyrans **3**, in which a strong interaction between the complexed cations and the *p*-nitrophenolate oxyanion of the merocyanine form **2**′ and **3**′ was responsible for the isomerization from the spiropyran to merocyanine (Scheme 1) [4, 5, 8].

The isomerization of the previously reported spirobenzopyrans **2** and **3** to the open-chain colored merocyanines was induced by recognition of alkali-metal and alkaline-earth metal cations *as well as* by UV irradiation. Thus, in terms of molecular devices, **2** and **3** can be considered to perform 'OR'-gate-type dual-mode signal transduction by synchronizing molecular recognition processes with their photochromism [9]. Sophisticated signal transduction at the molecular level also requires *simultaneous (AND)-type* counterparts. This idea led us to develop the new crowned spirobenzopyrans which could only be responsive to the combination of ionic and photonic stimuli [10].

We have reported advanced crowned spirobenzopyrans in which molecular recognition induces a structural change in the molecule accompanying coloration that results in the proximity of two remote sites in the spirobenzopyrans [8a]. Thus, we prepared the crowned spirobenzopyran **4** possessing a monoaza-crown ether, a propynyl, and an indane group. Alkali-metal cation-induced isomerization of **4** caused the propynyl-Me groups to approach the π-electrons of the indane-benzene ring, and the changes in the chemical shift of the Me groups were detected by NMR. During this study, we noted that photoinduced isomerization of **4** was slower than those of **2** and **3**. Although it may be difficult to determine all of the factors contributing to the slow photo-isomerization of **4**, in striking contrast to the previous crowned spirobenzopyrans **2** and parent spirobenzopyran **1**, we anticipate that the presence of the 3′-(benzo-15-crown-5) substituent is essential for blocking ready isomerization. Thus, we decided to utilize **4** as a basic skeleton of the simul-



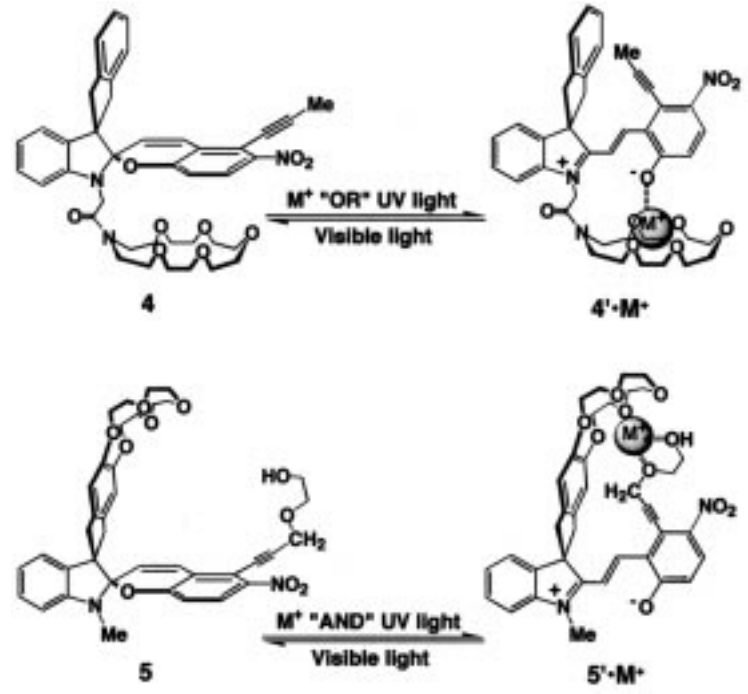
Scheme 1a.

taneous (AND)-type crowned spirobenzopyrans. In searching for an ideal crowned spirobenzopyran for this purpose, structure **5** was developed.

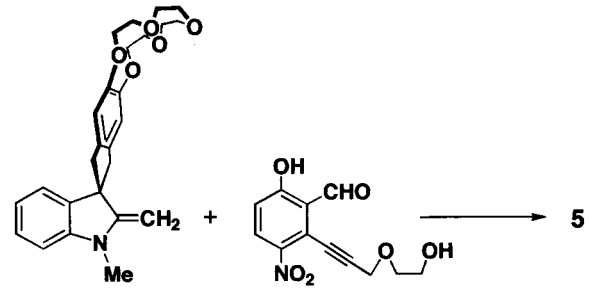
The design of the simultaneous-type crowned spirobenzopyran **5** was based on the fact that the crown-bound cations could interact with the ether oxygens of the oxyethylene sidearm and not the phenolate oxygen of the opened merocyanine form **5′**. Thus, we expected that the absence of a strong electrostatic interaction between crown-bound cations and the phenolate oxygen of **5′** would prevent ready thermal isomerization of **5** to **5′** · M^+, in contrast with **2** and **3**, and that the photoisomerized, cation-binding merocyanine form **5′** · M^+ would be stabilized by the additional interaction of the lariat oxyethylene sidearm with the cations. The appropriateness of the molecular design was reinforced by computer modeling.

The synthetic strategy for preparing the new crowned spirobenzopyrans is similar to that reported for the previous crowned spirobenzopyrans. The new crowned spirobenzopyran **5** was synthesized from two key intermediates, benzo-15-crown-5-possessing a 3*H*-indole derivative and 6-alkynyl-5-nitrosalicylaldehyde by enamine-passed aldol-type cyclization in the final step (Scheme 2).

Most spirobenzopyrans exist mainly as the closed spiropyran form [7]. This is true even in the cases of crowned spirobenzopyrans [4, 8]. The new crowned



Scheme 1b.



Scheme 2.

spirobenzopyran **5** also revealed no absorption bands above 350 nm in aprotic solvents such as $CHCl_3$, CH_3CN, etc., indicating a closed spiropyran form. Indeed, an almost colorless solution was obtained after dissolving **5** in such solvents. The absorption spectra were scarcely affected upon addition of any alkali-metal iodides in CH_3CN, even after several days in the dark. On the other hand, immediately after the addition of LiI, new absorption bands (λ_{max} = 530 nm, ϵ = 10 000) appeared for **2** (n = 1). In the ^{1}H NMR spectra of **5** in CD_3CN, however, the downfield shifts and split of the signals for the crown rings in the spiropyran form (3.6 $\sim$ 4.2 ppm) were observed after the addition of LiI. This observation suggested that the colorless form was attributed to no isomerization of $\mathbf{5}' \cdot Li^+$ to $\mathbf{5}' \cdot Li^+$. The complexation

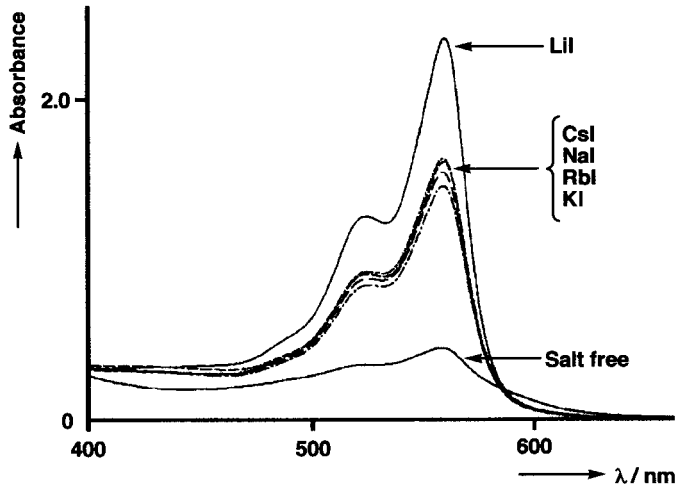


Figure 1. Electronic absorption spectra of **5** (0.1 mM) in CH_3CN in the presence of alkali-metal iodides (0.5 mM) after 1 h irradiation (360 nm).

was also demonstrated by FAB mass experiments. Subsequent irradiation (360 nm) of the alkali-metal iodide-containing CH_3CN solutions of **5** gave rise to changes in their spectra, and new absorption bands appeared. Figure 1 shows that a slight, selective coloration for LiI was observed, and that only photoirradiation (salt free) of **5** resulted in a minor change in its spectrum, suggesting the suppression of its photochromic property in the absence of the cations. Previous crowned spirobenzopyrans **2** revealed cation-induced hypsochromic band shifts of Li^+, Na^+, K^+, Rb^+, and Cs^+, which decreased in that order, explained in terms of the electrostatic interactions between the complexed cations and the *p*-nitrophenolate dipole of the merocyanine [4]. On the other hand, the same λ_{max} (560 nm) of $\mathbf{5}' \cdot M^+$, irrespective of the presence of all kinds of alkali-metal cations, indicated no interaction of the crown-bound metal cations with the *p*-nitrophenolate oxygen of **5**′ [4, 5, 7, 8].

Various NMR techniques demonstrated that the emerging absorption bands could be assigned to the merocyanine structure **5**′. The interaction of the crown-bound Li^+ and the incoming oxyethylene sidearm but not the *p*-nitrophenolate oxygen of **5**′ was also verified by the downfield shift (0.25 ppm) of the propargyl methylene protons by comparison with those of **5**, in agreement with the UV spectra. The colored solution was stable and did not bleach thermally in dark conditions at room temperature even after 30 days, while the photoisomerized colored form of the parent spirobenzopyran **1** was so labile as to disappear completely after 10 min under identical conditions. Partial re-isomerization of $\mathbf{5}' \cdot M^+$ to the colorless spiropyran form $\mathbf{5} \cdot M^+$ occurred upon irradiation with >480 nm light, although the nitro-substituted spirobenzopyrans such as **5** are so liable to fatigue that substantial decomposition was observed during a few repetitions of the photochromic cycle.

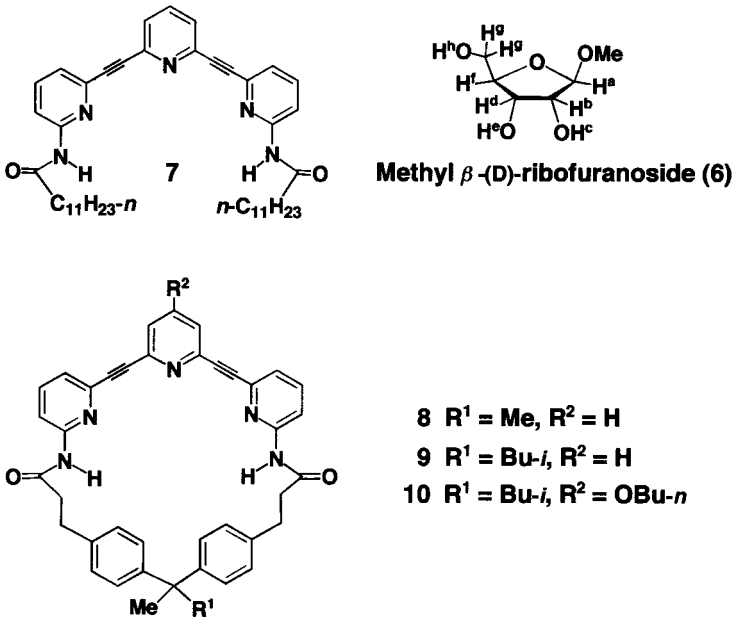
The results obtained here show that the crowned spirobenzopyran **5** can operate well as a dual-mode signal transducer. Thus, the new crowned spirobenzopyran **5**

could transmit information on two different simultaneous stimuli (ion and photon) according to changes in its optical properties. The dual-mode signal transducer molecules developed here are expected to contribute to molecular-based device technologies, although significant improvements, including selectivity, response, and fatigue resistance, are still needed.

3. Polypyridine-Macrocyclic Structures as Ribofuranoside Receptors [11]

Carbohydrates, sugars, have long been recognized only as structural and energy storage molecules. In the past two decades, carbohydrates have gained an accurate appraisal as the third major class of natural building blocks. Now, the role of carbohydrates has been found to be essential for viral adhesion to host tissues, associated inflammatory response, tumor cell metastasis, etc. [12]. Thus, artificial receptors that recognize and bind to specific carbohydrates are of current topical interest [13]. Among the various artificial receptors, however, only a few have been shown to be effective for the recognition of carbohydrates [14]. This is possibly because of the three-dimensional complexity of carbohydrate structures. As part of our program aimed at the development of multifunctional artificial receptors for biologically important molecules, we sought to construct receptors for β-ribofuranosides.

The multipoint hydrogen-bonding interaction was chosen as the main driving force in the recognition of β-ribofuranosides since it may not be easy to distinguish between the families of closely related stereoisomers of carbohydrates by using a single, strong interaction, such as electrostatic interaction. As a starting point for the design of ribofuranoside receptors, we chose the 2,2′:6′,2″-terpyridine skeleton with ethynediyl spacers as the binding site in the receptor molecules (Scheme 3). The decision was based on the utilization of strong O—H $\cdots$ N hydrogen bonds and consideration of the direction of three ribofuranoside-OH groups (2-C, 3-C, and 5-C). The basic recognition site was submitted to more functionalization, in which amide-type substituents were introduced at both the terminal pyridine rings. Thus, the 2-acylaminopyridine moiety can be expected to provide an additional hydrogen-bonding motif upon recognition of methyl β-(D)-ribofuranoside (**6**). Indeed, when 1 equiv. of **6** was added to a $CDCl_3$ solution of **7**, the ^{1}H NMR signals of not only the three OH protons of **6** but also the NH protons of **7** were shifted downfield. This finding suggests that all hydrogen acceptors and at least one donor of **7** take part in the complexation with **6**. The 1 : 1 stoichiometry was confirmed by continuous variation plots. Benesi–Hildebrand analysis gave the association constant: K_a = 30 M^{-1}. In the tripyridine receptor **7**, the *sp*-carbon spacers allow rotation about the pyridine–ethynediyl bonds, maintaining linearity along the pyridine–pyridine axis, so that the most predominant conformation of **7** is anticipated to be the *anti* form ($\mathbf{7}_{anti}$) in which the multipoint hydrogen-bonding interaction for ribofuranoside is no longer possible. Indeed, *ab-initio* calculation revealed that $\mathbf{7}_{anti}$ is more stable than $\mathbf{7}_{syn}$ by 2.44 kcal/mol (Figure 2) [5b]. One might postulate that the interaction between the receptor **7** and **6** loses the dif-



Scheme 3.

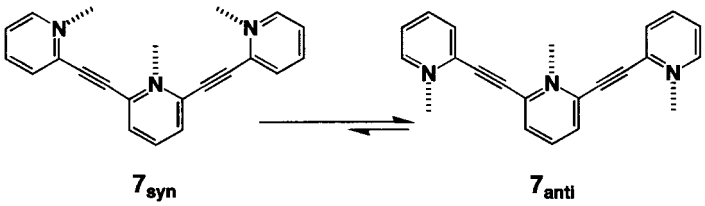
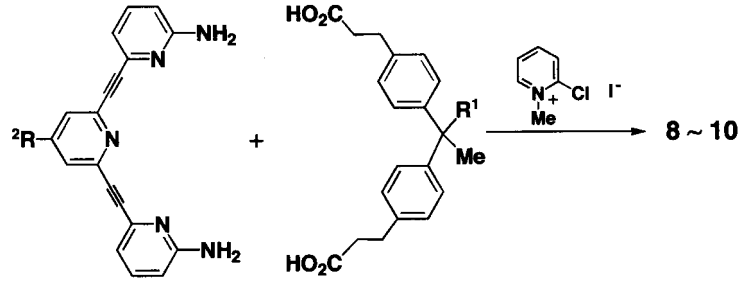


Figure 2. Structures for $\mathbf{7}_{syn}$ and $\mathbf{7}_{anti}$. The amide substituents were omitted for simplification of the *ab-initio* calculations.

ference between the free energies. In order to depress the free rotation about the pyridine–pyridine axis, macrocyclic structures were chosen. Thus, we designed and synthesized bisphenol derivative-bridged polypyridine-macrocyclic receptors **8**–**10**.

The polypyridine-macrocyclic receptors **8**–**10** were synthesized from two key intermediates, diaminoterpyridine derivatives and dicarboxylic acid derivatives by Mukaiyama's macrocyclization in the final step (Scheme 4). The diaminoterpyridine derivatives were prepared from 2,6-dibromopyridine and its derivative with 2-amino-6-ethynylpyridine by the Sonogashira reaction. The dicarboxylic acid derivatives were all synthesized from bisphenol derivatives as starting material.

Binding assays of the macrocyclic receptors **8**–**10** for **6** were carried out in a manner similar to that described for **7**, and the association constants are summarized in Table I. The macrocyclic receptors **8** and **9** display K_a of 2400 M^{-1} and 2500 M^{-1}, respectively, ca. 80-fold higher than corresponding acyclic **7**. Further-



Scheme 4.

Table I. Association constants for the binding of the receptors to **6** in $CDCl_3$ at 23 °C. Determination of binding constants was carried out under Benesi–Hildebrand conditions. The receptor concentration for **8** and **9**–**10** was 0.3 and 0.1 mM, respectively. The concentration of **6** was 2.7–6.0 and 0.9–2.0 mM for **8** and **9**–**10**, respectively. The chemical shifts of the receptor–NH protons were monitored as a function of **6** concentration

Receptors	8	9	10
K_a (M^{-1})	2400 ± 200	2500 ± 200	5200 ± 300

more, increasing the electron density of the pyridine nitrogen, a definite increase in K_a will be expected due mainly to enthalpic factors. Indeed, alkoxy-substitution at the 4′ position of the central pyridine ring showed a further increment of the association constants. Thus, **10** has a K_a value of 5200 M^{-1}, a notably high value for artificial carbohydrate receptors utilizing hydrogen bonds (Table I).

Useful information on the structures of the complexes was obtained by their ^1H NMR spectra. Treatment of a $CDCl_3$ solution of **6** (10 mM) with 1 equiv. of **8** resulted in several characteristic changes in the spectrum (Figure 3). Downfield shifts were observed for the OH protons of **6** (H^c: 2.6, H^e: 2.5, and H^h: 0.4 ppm), while OMe and CH_2OH protons were largely shifted upfield (OMe: 0.3 and CH_2OH: 0.4 and 0.2 ppm). The former shifts reflect the formation of a multipoint hydrogen bonded complex, and the latter may be attributed to the hydrophobic moieties of **6** being placed on the diphenylpropane-bridge that is perpendicular to the terpyridine site. Furthermore, the receptor signals of aromatic (terpyridine and diphenylpropane moieties) and ethylene protons showed substantial changes after the recognition of **6**, suggesting that **8** employs the recognition strategy of substrate-induced organization of the conformation (induced-fit mechanism) [15]. On the basis of the above observations, a possible recognition mode for the complex (**6** · **8**) is shown in Scheme 5.

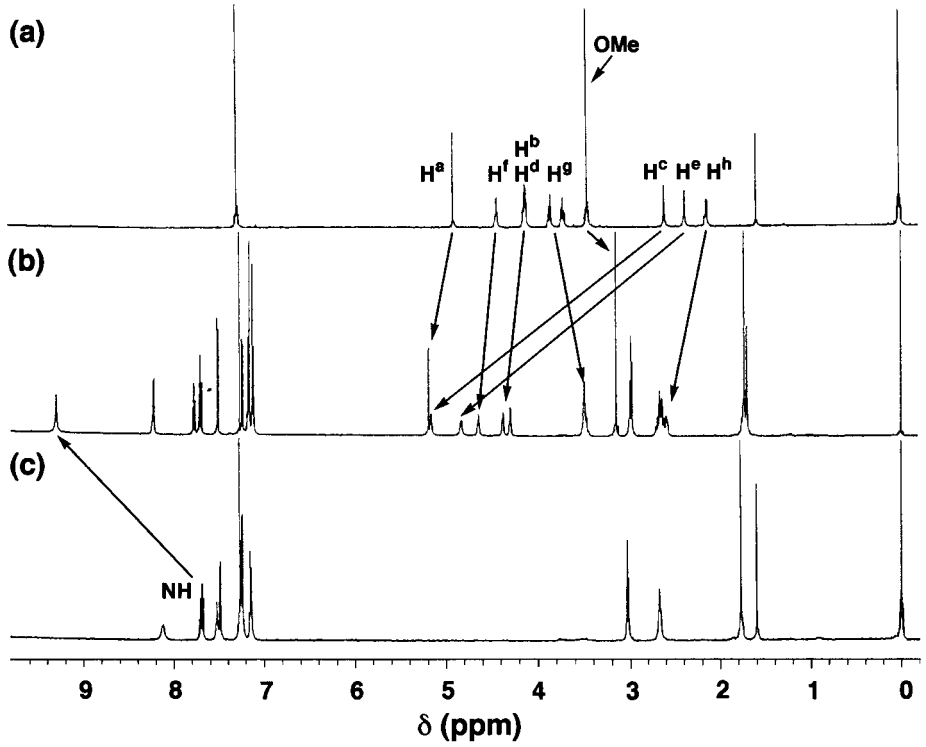
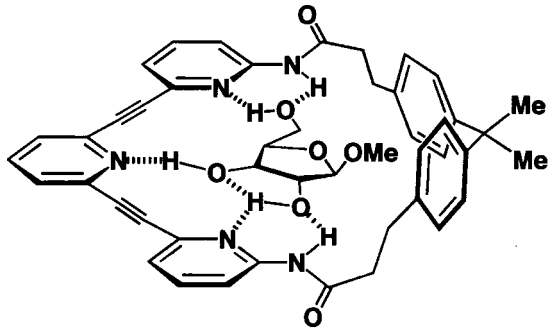


Figure 3. ^{1}H NMR spectra (500 MHz) of (a) **6**, (b) **6** · **8**, and (c) **8** in $CDCl_3$ at 23 °C.



Scheme 5.

The extraction of various monosaccharides into $CDCl_3$ containing **10** was carried out. Selective extraction of ribose by the receptors was observed: the extractabilities, or affinities to the receptors of various pentoses and hexoses decreased in the following order: ribose > deoxyribose ≅ lyxose ≅ xylose > fructose > arabinose > glucose ≅ mannose ≅ galactose. Noteworthy is that the extractability of ribose is higher than that of the more lipophilic deoxyribose. These results indicate that the binding affinities of the receptors for saccharides are governed not

only by hydrophobic interactions but also the whole size and the OH directions of saccharides, as well as as their shapes.

The polypyridine-macrocyclic structures represent rationally designed artificial ribofuranoside receptors, in which multipoint hydrogen-bonding interactions play a key role for the recognition. The binding affinity of the receptors for methyl β-(D)-ribofuranoside was very high, so that native ribose was extracted by them into nonpolar solvents. The driving force for the binding was found to be governed by not only hydrophobic interactions but also the whole size and the OH directions of saccharides.

4. Prospects

This article has emphasized the performance of the artificial receptors that we have recently synthesized. The starting point for our research is what kind of biologically relevant molecules are to be recognized, and how. Thus, the molecular design of the receptors was fully purposive, not serendipitous. This approach to the artificial receptors inevitably demands a sophisticated synthetic strategy. Furthermore, we must keep in mind that molecular recognition is no more than an initial process in the functioning of naturally occurring receptors. The time may have arrived for requiring molecular recognition chemistry to move to the next stage from synthesis of host structures to host functions i.e., real artificial receptors. Larger and more complex biologically essential substrates, such as peptides, oligonucleotides, and oligosaccharides, will be future targets for our receptors.

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