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Guest-Templated Selection and Amplification of a Receptor by Noncovalent Combinatorial Synthesis**

Mercedes Crego Calama, Peter Timmerman, and David N. Reinhoudt*

Template-directed synthesis, using molecular recognition to favor the formation of one particular product, plays an essential role in important biological processes, such as protein synthesis and self-replication. It has been widely used in a variety of macrocyclization reactions^[1] and (in)organic self-assembly processes.^[2] Molecular imprinting of synthetic receptors by guest templation, a process first realized in polymers,^[3] has recently received enormous attention as a way to direct the molecular evolution of a dynamic mixture of synthetic receptors.^[4–7] Thermodynamic equilibration of these receptor systems is achieved through the reversible formation of *covalent* bonds, namely, *cis–trans* isomerization,^[4] transesterification,^[5, 8] or disulfide bond formation.^[6] Here we describe the first example of guest-templated selection of a

receptor in a dynamic *noncovalent* combinatorial mixture, in which the different receptors equilibrate through the reversible formation of multiple hydrogen bonds.

Recently we have reported^[9] the noncovalent synthesis^[10] of a family of hydrogen-bonded assemblies $\mathbf{1}_3 \cdot (\text{DEB})_6$ (DEB = 5,5-diethylbarbituric acid), consisting of nine different components held together by 36 cooperative hydrogen bonds. Structural diversity at the supramolecular level can be generated in an extremely simple way, by mixing the various components **1** (**a, b, ...N**; Figure 1) under thermodynamically controlled conditions.^[11] In this way a library of 220 different noncovalent assemblies can be synthesized simply by assembling a mixture of ten different components derived from **1**.^[12] The composition of these libraries is statistical as determined for the model system $\mathbf{1a}_{3-n} \cdot \mathbf{1b}_n \cdot (\text{DEB})_6$ ($n = 0–3$), which exists as a 1:1:3:3 mixture of homomeric ($\mathbf{1a}_3 \cdot (\text{DEB})_6$ and $\mathbf{1b}_3 \cdot (\text{DEB})_6$) and heteromeric ($\mathbf{1a} \cdot \mathbf{1b}_2 \cdot (\text{DEB})_6$

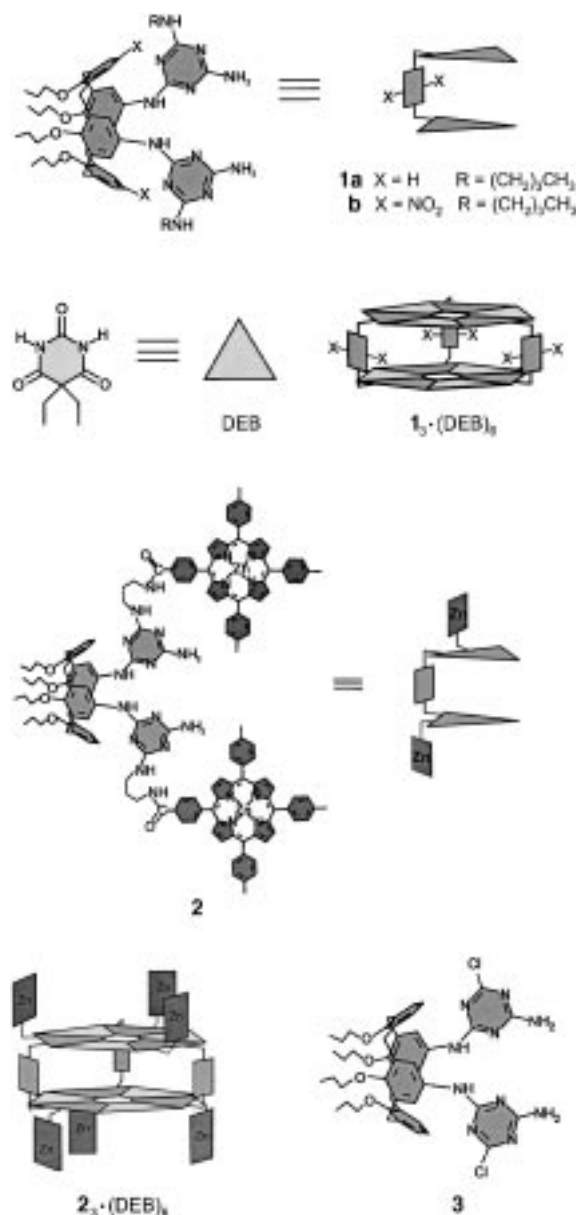


Figure 1. Molecular structures and schematic representations of the molecular components **1–3** and the hydrogen-bonded assemblies $\mathbf{1}_3 \cdot (\text{DEB})_6$ and $\mathbf{2}_3 \cdot (\text{DEB})_6$.

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and $1\mathbf{a}_2 \cdot 1\mathbf{b} \cdot (\text{DEB})_6$ assemblies. However, none of the assemblies in this mixture contains a functional binding site for guest complexation.

To study the guest-templated selection of receptor $2_3 \cdot (\text{DEB})_6$ in the noncovalent combinatorial mixture $2_{3-n} \cdot 1\mathbf{b}_n \cdot (\text{DEB})_6$ ($n=0-3$, Figure 2), we synthesized dimelamine 2 , with two opposed zinc-porphyrin moieties.^[13] It is known from previous work by Sanders and Anderson^[14] that zinc porphyrins complex pyridine derivatives with moderate affinity ($K_a = 3 \times 10^3 \text{ M}^{-1}$ in CDCl_3) and that the binding of tripyridines to cyclic multiporphyrin arrays is much stronger ($K_a \approx 10^{10} \text{ M}^{-1}$ in CDCl_3) as a result of cooperativity between the porphyrin centers.^[15] Similarly, we anticipated that all four assemblies in the dynamic mixture $2_{3-n} \cdot 1\mathbf{b}_n \cdot (\text{DEB})_6$ ($n=0-3$) will bind the tripyridine 4 with very different affinities depending on the number of preorganized zinc-porphyrin centers that cooperate in the binding process. The addition of 4 to a statistical mixture (1:3:3:1) of the assemblies $2_{3-n} \cdot 1\mathbf{b}_n \cdot (\text{DEB})_6$ ($n=0-3$) will then shift the thermodynamic equilibrium of the mixture towards the strongest 4 -binding assembly, the homomeric $2_3 \cdot (\text{DEB})_6$, thereby reducing the concentrations of the heteromeric assemblies $2 \cdot 1\mathbf{b}_2 \cdot (\text{DEB})_6$ and $2_2 \cdot 1\mathbf{b} \cdot (\text{DEB})_6$ (see Figure 2). In this way, the tripyridine 4 serves as a guest molecule that drives the chemical evolution of assembly $2_3 \cdot (\text{DEB})_6$ in the dynamic mixture $2_{3-n} \cdot 1\mathbf{b}_n \cdot (\text{DEB})_6$ ($n=0-3$).

First we studied the hydrogen-bond directed formation of the all-porphyrin assembly $2_3 \cdot (\text{DEB})_6$ alone and its binding to 4 . Assembly $2_3 \cdot (\text{DEB})_6$ contains two identical binding sites, one on top and one on the bottom of the assembly, each composed of three zinc-porphyrin moieties. Mixing of free 2 , the ^1H NMR spectrum of which mainly shows broad resonances (Figure 3A), with 2.0 equivalents of DEB in CDCl_3 , leads to the clean self-assembly of $2_3 \cdot (\text{DEB})_6$ as judged from the characteristic signals at $\delta = 13.3$ and 14.1 for

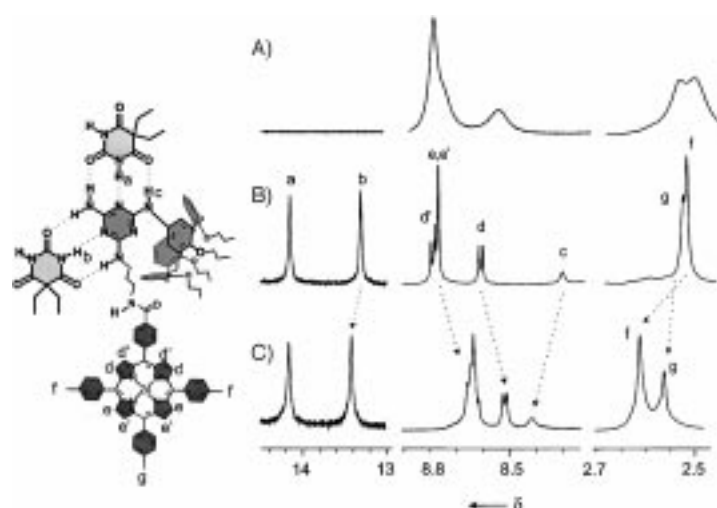


Figure 3. Parts of the ^1H NMR spectra of A) free **2**; B) assembly $2_3 \cdot (\text{DEB})_6$; C) assembly $2_3 \cdot (\text{DEB})_6$ plus 2.0 equiv of **4**. All spectra were recorded at 300 MHz in CDCl_3 at room temperature.

the hydrogen-bonded NH_a and NH_b protons (Figure 3B). Complexation studies of $2_3 \cdot (\text{DEB})_6$ with **4** showed the quantitative formation of the corresponding complex $2_3 \cdot (\text{DEB})_6 \cdot 4_2$ and clearly proved the 1:2 stoichiometry. For example, addition of 1.4 equivalents of **4** to assembly $2_3 \cdot (\text{DEB})_6$ causes several signals in the ^1H NMR spectrum to shift, but the signals of the resulting spectrum are severely broadened, most probably as a result of the slow exchange between assembly $2_3 \cdot (\text{DEB})_6$ and the 1:2 complex $2_3 \cdot (\text{DEB})_6 \cdot 4_2$. However, when 2.0 equiv of **4** are present, a well-defined spectrum with sharp peaks is obtained in which some of the porphyrin and dimelamine proton signals are shifted significantly (Figure 3C). The NH_b and NH_c proton signals both shift downfield ($\Delta\delta = 0.10$ and 0.14 , respectively), while the NH_a proton signal is unaffected. In contrast, all

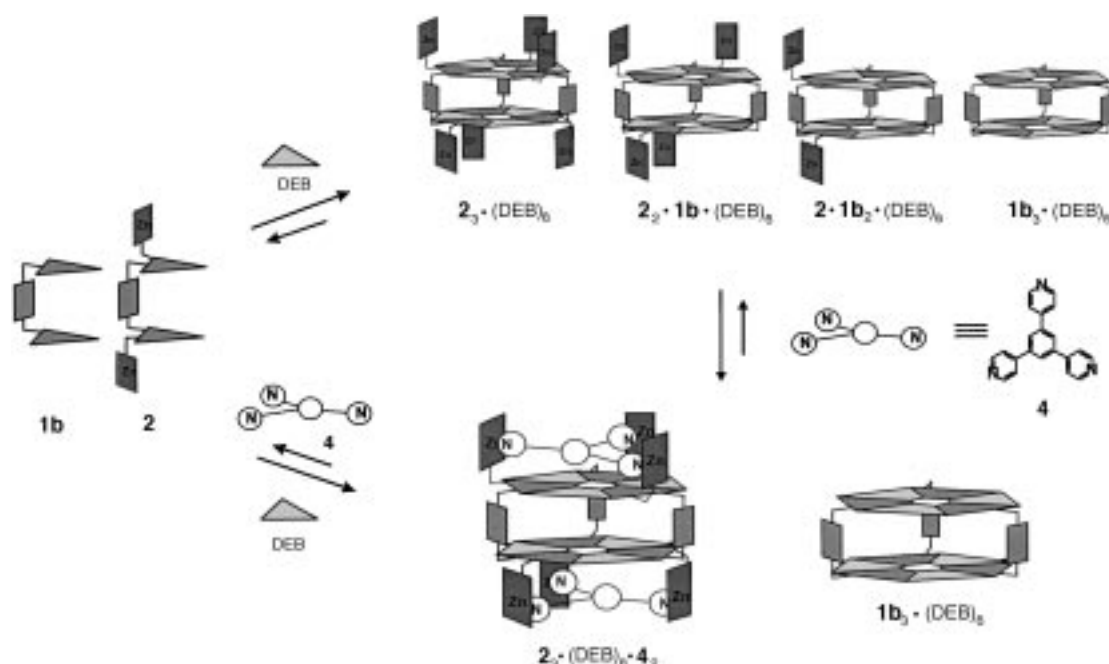


Figure 2. Schematic representation of the self-assembly of the 4-component dynamic mixture $1\mathbf{b}_{3-n} \cdot 2_n \cdot (\text{DEB})_6$ ($n=0-3$) and posterior templated selection of the best receptor upon the addition of guest molecule **4**.

signals of the β -pyrrol protons ($H_{d,e}$) of the porphyrin moieties shift upfield ($-\Delta\delta = 0.10$ – 0.15). Moreover, the chemically nonequivalent H_e protons show an AB-pattern in the complex $2_3 \cdot (\text{DEB})_6 \cdot 4_2$, whereas the spectrum of the free assembly $2_3 \cdot (\text{DEB})_6$ exhibited only one single frequency at $\delta = 8.78$. Apparently, in the presence of guest molecule **4** the chemical difference between the two H_e protons is larger. Finally, the complexation of **4** causes a $\Delta\delta = 0.12$ ($\delta = 2.50 \rightarrow 2.62$) and $\Delta\delta = 0.04$ ($\delta = 2.51 \rightarrow 2.55$) shift for the H_f and the H_g proton signals, respectively, resulting in an exchange of their relative position in the spectrum. Addition of more than two equivalents of **4** does not shift any of the proton signals further than in the 1:2 complex $2_3 \cdot (\text{DEB})_6 \cdot 4_2$, indicating that the affinity of **4** for assembly $2_3 \cdot (\text{DEB})_6$ is very high indeed.

Subsequent to the formation studies, we investigated to what extent **4** can shift the thermodynamic equilibrium in the dynamic mixture $2_{3-n} \cdot 1b_n \cdot (\text{DEB})_6$ ($n = 0$ – 3). The mixture was prepared by mixing equimolar solutions of the individual assemblies $1b_3 \cdot (\text{DEB})_6$ and $2_3 \cdot (\text{DEB})_6$ in CDCl_3 at room temperature. The H_c – H_e ($\delta = 8.0$ – 9.0) and the H_f , H_g proton signals ($\delta = 2.5$ – 2.7) clearly illustrate the mixing process (Figure 4A–C).^[16] For the H_c proton signal of the mixture $2_{3-n} \cdot 1b_n \cdot (\text{DEB})_6$ ($n = 0$ – 3) at least five signals ($\delta = 8.3$ – 8.5) are present, while this proton appears as a single resonance at $\delta = 8.32$ for the pure homomeric assembly $2_3 \cdot (\text{DEB})_6$ (Figure 4A). Similarly, the H_d , H_e and the H_f , H_g protons of the mixture give rise to multiple resonances. Integration of the various proton signals clearly proves the almost statistical

composition of the mixture (30% versus 25% homomeric, 70% versus 75% heteromeric).^[17]

The addition of two equivalents of **4** to the dynamic mixture $2_{3-n} \cdot 1b_n \cdot (\text{DEB})_6$ ($n = 0$ – 3) shifts the thermodynamic equilibrium of the mixture towards the maximized formation of the strongest receptor $2_3 \cdot (\text{DEB})_6$. Evidence for this comes from the complete disappearance of the proton signals for the heteromeric assemblies $2 \cdot 1b_2 \cdot (\text{DEB})_6$ and $2_2 \cdot 1b \cdot (\text{DEB})_6$ (Figure 4D). From the five H_e proton resonances at $\delta = 8.3$ – 8.4 , only two signals for the homomeric assemblies $1b_3 \cdot (\text{DEB})_6$ and $2_3 \cdot (\text{DEB})_6 \cdot 4_2$ (marked with $\blacktriangle$) are present after addition of **4**. Similarly, three of the four resonances for the H_d protons at $\delta = 8.6$ – 8.8 disappear and only the single doublet at $\delta = 8.58$ for the 1:2 complex $2_3 \cdot (\text{DEB})_6 \cdot 4_2$ is observed. Finally, the six resonances for the H_f , H_g proton signals present in the library convert to the two singlets at $\delta = 2.55$ and 2.62 (Figure 4D) of the complex $2_3 \cdot (\text{DEB})_6 \cdot 4_2$ (Figure 4E).^[18] The assembly $1b_3 \cdot (\text{DEB})_6$ does not display any proton signals in this region (Figure 4B). These results clearly show that guest molecule **4** efficiently templates the formation of the strongest binding assembly in the library, $2_3 \cdot (\text{DEB})_6$, by shifting the thermodynamic equilibrium in the four-component mixture $2_{3-n} \cdot 1b_n \cdot (\text{DEB})_6$ ($n = 0$ – 3) from an almost statistical composition (ca. 1:3:3:1) of all possible assemblies, towards a 1:1 mixture of the homomeric assemblies $1b_3 \cdot (\text{DEB})_6$ and $2_3 \cdot (\text{DEB})_6$.

In conclusion, we have described the guest-templated selection and amplification of the strongest binding receptor in a dynamic mixture of hydrogen-bonded assemblies. These noncovalent receptors are reminiscent of antibodies in the sense that they contain both a constant region, consisting of three functionalized calix[4]arenes dimelamines subunits held together in a noncovalent fashion, and a variable region generated by the introduction of a variety of substituents on the six melamine units.^[19] Current work in our group is aimed at the covalent capture of supramolecular libraries, a novel strategy to enable characterization by MALDI-TOF MS and HPLC.

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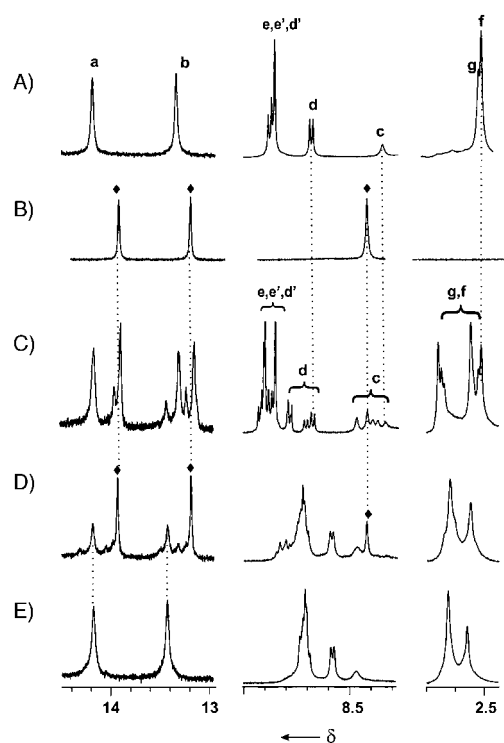


Figure 4. Parts of the ^1H NMR spectra of A) assembly $2_3 \cdot (\text{DEB})_6$; B) assembly $1b_3 \cdot (\text{DEB})_6$; C) 1:1 mixture of assemblies $1b_3 \cdot (\text{DEB})_6$ and $2_3 \cdot (\text{DEB})_6$; D) 1:1 mixture of assemblies $1b_3 \cdot (\text{DEB})_6$ and $2_3 \cdot (\text{DEB})_6$ after addition of two equivalents of **4**; E) assembly $2_3 \cdot (\text{DEB})_6$ plus two equivalents of **4**. All spectra were recorded at 300 MHz in CDCl_3 at room temperature. The signals marked with $\blacklozenge$ are from $1b_3 \cdot (\text{DEB})_6$ protons.

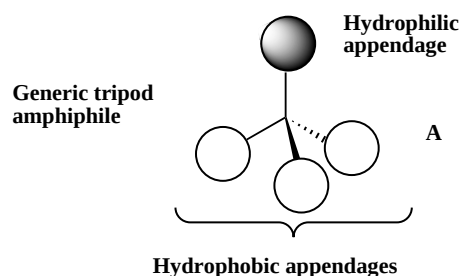
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- [16] The $\delta = 13$ –15 region of the ^1H NMR spectrum of the library is not very informative due to extensive overlap of signals for homomeric and heteromeric assemblies.
- [17] The experimental distribution was determined by integration of the proton signals in the $\delta = 2.5$ –2.7 region ($\text{H}_{\text{f,g}}$). The calculated distribution of 25/75% reflects the threefold higher probability for formation of the heteromeric assemblies.
- [18] The additional small signals present in spectrum 4D ($\delta = 13$ –15, around $\delta = 8.8$, and the two shoulders of the singlet at $\delta = 2.62$) are due to the presence of a slight excess of **4**, giving rise to the formation of small amounts of the heteromeric assembly $1\text{b}_2 \cdot 2 \cdot (\text{DEB})_6 \cdot 4_2$. Evidence for this comes from the fact that the intensity of these signals increases when **4** is present in larger excess.
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Rigid Amphiphiles for Membrane Protein Manipulation**

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The shape of an amphiphile strongly influences self-association in solution^[1] and in liquid crystalline phases,^[2] as well as interactions with self-assembled structures such as lipid bilayers.^[3] In recent years several groups have examined unusual amphiphile topologies.^[4,5] We and others, for example, have explored amphiphiles in which hydrophilic groups project on one side of an approximately planar hydrophobic unit (“contrafacial amphiphiles”).^[4] Here we introduce a related family of molecules based on a rigid quaternary carbon center, “tripod amphiphiles” (**A**), and present evidence that these amphiphiles can solubilize the two non-homologous membrane proteins bacteriorhodopsin (BR) and bovine rhodopsin (Rho) in a stable monomeric state.



Intrinsic membrane proteins perform many crucial functions, including transport, catalysis, photosynthesis, respiration, and signal transduction. The detailed study of membrane protein structure requires that the protein be isolated in a soluble native-like conformation, which in turn requires the use of a synthetic amphiphile (a detergent) to shield large

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