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Olefin Detection

# Unexpected Effects of Terminal Olefins on a Cooperative Recognition System that Implicate Olefin–Olefin Interactions**

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To design receptors or building blocks that are useful for constructing supramolecular architectures, multiple noncovalent, relatively weak interactions are essential to realize flexible stimuli-responsive features. The systematic study of such weak but crucial interactions is of great importance in both synthetic and biological systems, but seem to be rather difficult to estimate because of their weakness or lability to the external environment. Among many approaches for understanding such weak interactions, Wilcox and co-workers introduced a smart method for the evaluation of CH–π interactions using a "molecular torsion balance", in which the rotational barrier between folded (with interaction) and unfolded (without interaction) states is used to calculate the force.[1] Diederich and co-workers applied a chemical double-mutant system[2] to the molecular torsion balance described by Wilcox for the measurement of CF–amide interactions, thus providing evidence that the stability is less than 4 kJ mol$^{-1}$.[3] In our recent study on the template synthesis of a pseudorotaxane complex facilitated by allosterism,[4] we noticed unexpectedly that the cooperative binding behavior of a host molecule bearing olefin substituents at the periphery of the binding sites are significantly different from those of a non-olefinic counterpart. As the structures are basically the same except for the presence or the absence of the terminal olefins, this difference in cooperativity (see below) seems to arise from the "interaction" among the olefin substituents. Herein, we report the influence of the terminal olefin substituents, which have been introduced into a series of host molecules, on their allosteric behavior. Based on the systematic investigation of the binding properties and the structural analysis of the olefinic host molecules, we have confirmed that the olefinic host molecules elicit a decrease in cooperativity and an increase in affinity for the first guest molecule. These findings clearly indicate that the weak interactions that exist between the olefin substituents can be detected using the allosteric recognition systems.

We first employed allosteric host molecules bearing four zincporphyrin units as recognition sites (**1a**–**1c**) to demonstrate the effect of terminal olefins on the recognition events (Scheme 1).These molecules have been previously reported to bind diamine molecules (**4**) with a 1:2 stoichiometry in an allosteric manner.[4,5] The binding of the first diamine molecule allows the recognition site for the second molecule to be predisposed to binding another diamine molecule because of the restriction of rotation around the butadiyne axis; as a result, **1a**–**1c** exhibit positive homotropic allosterism toward **4** (Figure 1 a).[6]

For the UV/Vis spectra of **1a**, the bathochromic shifts in the Q bands were observed upon successive addition of **4** in $CHCl_3$;[7] these changes arose from the formation of coordination bonds between zincporphyrins in **1** and amino groups in **4**. The degree of cooperativity can be analyzed by using the Hill equation: $\log(y/1-y) = n\log[\text{guest}] + \log K$, where the values for $n$ and $K$ are the Hill coefficient and the association constant, respectively.[8] It is known that a high $n$ value results from the increased cooperativity in a guest-binding process, and the maximum $n$ value is equal to the number of binding sites of a host molecule. We previously reported that the diamine binding to **1a** has the Hill coefficient $n = 1.9$,[5,7] thus indicating that two guest molecules are bound cooperatively. The $n$ values of **1b** and **1c**, bearing two and six pairs of terminal olefins, respectively, were slightly smaller than that of **1a**; $n = 1.8$ for **1b** and $n = 1.6$ for **1c**.[4,7] Although the observed difference in $n$ values is relatively small, the comparison of the first association constants ($K_1$), which was evaluated by a standard non-linear curve-fitting method, reveals the significant difference among them; $K_1 = 1.6 \times 10^5\,\text{M}^{-1}$ for **1a**, $K_1 = 4.7 \times 10^5\,\text{M}^{-1}$ for **1b**, and $K_1 = 8.3 \times 10^5\,\text{M}^{-1}$ for **1c**. Interestingly, the $n$ and $K_1$ values in the guest recognition correlate with the number of terminal olefins in the host molecules; that is, as the number of olefinic groups increases, the $n$ value decrease and the $K_1$ value increase.

According to the Monod–Wyman–Changeux model for positive homotropic allosterism, a degree of cooperativity (the $n$ value) closely correlates with the $L$ value, where $L$ is defined as [$T$ (an unbound conformation)]/[$R$ (a bound conformation)].[9] In this model, the higher $L$ value results in a higher $n$ value, which supports the view that one can qualitatively assume the conformation of a host molecule without guest(s) from the $n$ value.[10] Our finding, which shows that the host molecules bearing terminal olefin substituents

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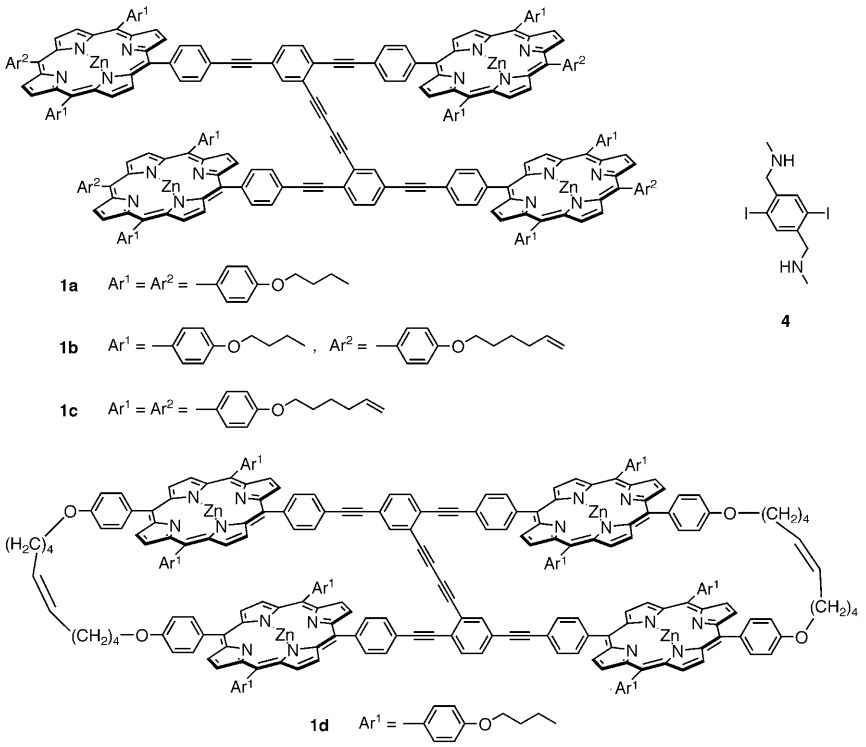



***Scheme 1.*** Allosteric hosts **1a–d** and guest molecule **4**.

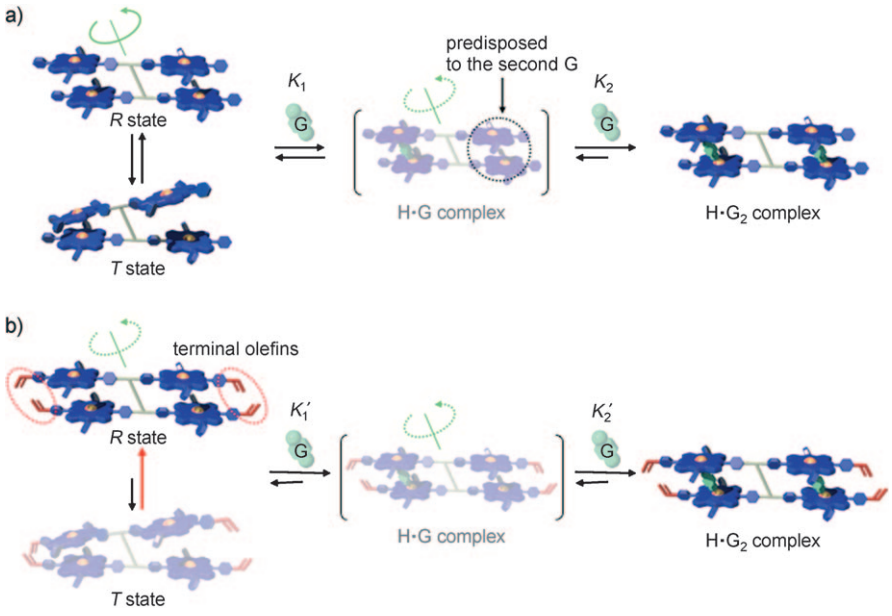
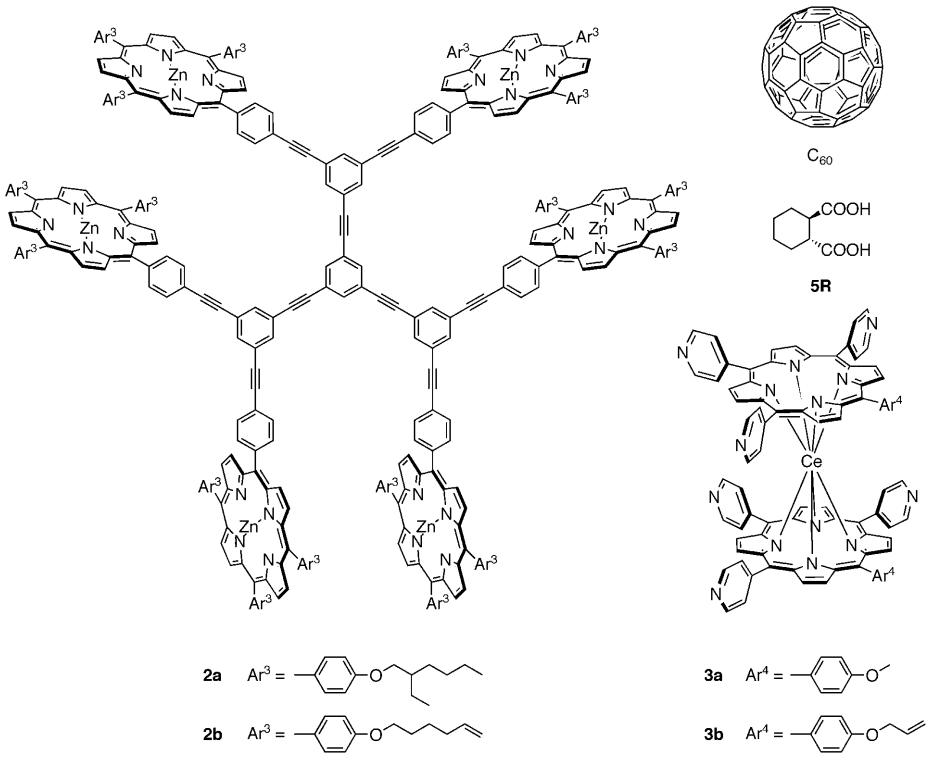



***Figure 1.*** Schematic representation of the binding behavior of the guest molecule with the allosteric host molecule a) without olefinic groups and b) with olefinic groups. The *R* state represents the guest-bound conformation and the *T* state represents the guest-unbound conformation.

give the lower cooperativity (smaller $n$ value), indicates that the initial conformation of the unbound olefinic host molecules is more or less inclined toward the guest-complexed conformation (*R* state). In such a conformation, the peripheral olefin substituents must exist in close proximity to each other (Figure 1 b). We infer that this phenomenon is caused by a weak but significant interaction operating between the peripheral olefins; the interaction could influence the initial conformation of the host molecules and alter their allosteric behavior.[11] To see if the changes observed in their allosteric behavior resulted from the initial conformation of the host molecules we used **1d**, which was derived from **1b** by a metathesis reaction.[4] Since the rotational movement around the central axis is totally inhibited in **1d**, the cleft structure constructed between porphyrins is thoroughly predisposed for **4**. The binding parameters of the **1d**·**4**$_2$ complex were estimated to be $n = 1.4$ and $K_1 = 2.2 \times 10^6\,\text{M}^{-1}$,[7] which led us to conclude that **1d** is an extreme case of preorganization along the $n$ order of **1c** < **1b** < **1a** for the recognition of **4**. These findings support the view that some weak interaction is operating between the terminal olefins.

We further investigated host molecules bearing six zincporphyrins (**2a** and **2b**) and double-decker cerium(IV) bisporphyrinates (**3a** and **3b**) to amplify this weak interaction (Scheme 2). It is already known that **2a** forms 1:3 host–guest complexes with **4**[5] or $C_{60}$,[12] and **3a** forms 1:3 host–guest complexes with **5R**[13] both in an allosteric manner. The binding parameters obtained from the UV/Vis spectra and the circular dichroism (CD) spectroscopic titrations are summarized in Table 1.[14–17] For all cases, we have confirmed that the terminal olefins in host molecules show similar trends in their guest-binding parameters, even when we used different host–guest combinations and conditions. Comparison of the Hill parameters for **2b** with **2a** reveals that the preorganization tendency (i.e., the decrease in $n$ and the increase in $K_1$ values) is further intensified by the "interaction" of nine pairs of terminal olefins.[18]

Finally, $^1$H NMR measurements were acquired to obtain spectroscopic evidence for the difference in the initial conformation of the host molecules. In the $^1$H NMR spectra of **1a–c** in $CDCl_3$, little difference was observed among them at both 298 K and 253 K (see the Supporting Information). This outcome indicates that the difference in the conformation is negligibly small (if any), and it is difficult to detect by means of the $^1$H NMR spectroscopy. In contrast,




***Scheme 2.*** Allosteric hosts **2** and **3** and guest molecules.

***Table 1:*** Selected binding parameters of the guest recognition by porphyrinatozinc tetramers **1a–d**, hexamers **2a** and **2b**, and double-decker porphyrin complexes **3a** and **3b**.[14]

| Host | Guest | Number of olefins | $n$ | $K_1\,10^{-5}$ [$M^{-1}$] | log $K_{tot}$ | $\Delta G$ [kJmol$^{-1}$] |
|---|---|---|---|---|---|---|
| **1a** | **4** | 0 | 1.9 | 1.6 | 10.69 | −60.96 |
| **1b** | **4** | 4 (2 pairs) | 1.8 | 4.7 | 11.23 | −64.08 |
| **1c** | **4** | 12 (6 pairs) | 1.6 | 8.3 | 11.83 | −67.48 |
| **1d** | **4** | – | 1.4 | 22 | 12.30 | −70.11 |
| **2a** | **4** | 0 | 2.8 | 8.8 | 18.59 | −106.06 |
| **2b** | **4** | 18 (9 pairs) | 1.8 | 15 | 18.91 | −107.88 |
| **2a** | $C_{60}$ | 0 | 2.8 | –[a] | 8.15 | −46.47 |
| **2b** | $C_{60}$ | 18 (9 pairs) | 1.6 | $5.6\times10^{-3}$ | 8.43 | −48.12 |
| **3a** | **5R** | 0 | 3.0 | –[a] | 8.35 | −47.64 |
| **3b** | **5R** | 2 (1 pair) | 1.8 | $7.7\times10^{-3}$ | 8.73 | −49.81 |

[a] The binding process is highly cooperative.

two porphyrin planes in double-decker cerium(IV) bisporphyrinates feature the relatively slow rotation rate around the central cerium ion, and the rotation is slow enough to be followed by variable temperature NMR analysis.[19] The exchange between rotational isomers is often estimated by monitoring the chemical shifts of the β-pyrrole protons.[19] The $^1$H NMR spectra of **3a** and **3b** at 233 K gave complicated patterns in the β-pyrrole region (8.36–8.51 ppm), however, one can recognize the difference between **3a** and **3b** (see the Supporting Information). The spectrum of **3b** is somewhat simpler than that of **3a**, and similar to the pattern of $A_3B$-type porphyrins. These results suggest that **3b** tends to adopt the more defined conformation, which would arise from the interaction between the terminal olefins.

As shown here, the weak but significant influence of the terminal olefins at the periphery of binding sites exists, and is detectable as characteristic parameters for the allosteric recognition processes; that is, the decrease in cooperativity and the increase in affinity. Moreover, the phenomena we have demonstrated here are not affected by the difference in the structures of both host and guest species. These results consistently imply the presence of a weak interaction between the terminal olefin substituents. In other words, this approach may be considered to be a new method to demonstrate the weak attractive forces operating in, for example, π–π, CH–π, and cation–π interactions. There are three key points in the present system: 1) a periaxial rotation, which does not change the molecular structure significantly, is used to induce a conformational change; 2) the allosteric system used here is sensitive enough to be readily influenced by the external or internal environment; 3) combination with the host–guest system provides an advantage to make the stimulus transduction process clear. Our new approach, which incorporates the weak interaction in synthetic allosteric receptors, will become a complementary tool for the detection or the confirmation of weak interactions. Also possible is the structural control of the higher-order architectures using terminal olefins, not only in artificial systems but also in biological systems.

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[10] We recently demonstrated that an unconventional enantioselective recognition system for **5R** can be designed using an allosteric double-decker host molecule. Since the allosteric host is predisposed for memorized **5R** (*R* state) but it is sterically biased for the unmemorized *S* enantiomer (*T* state), the host molecule can differentiate between two enantiomers with extremely high selectivity; that is, the host molecule binds the *R* enantiomer ($n = 1.6$ and $K_1 = 1.3 \times 10^3\,\text{M}^{-1}$) with low cooperativity whereas it binds the *S* enantiomer ($n = 2.9$ and $K_1 = 5.0\,\text{M}^{-1}$) with high cooperativity. This result implies that the original conformation of a host molecule exerts a strong effect on the cooperativity in the binding of guest molecules, see: T. Ikeda, O. Hirata, M. Takeuchi, S. Shinkai, *J. Am. Chem. Soc.* **2006**, *128*, 16008 – 16009.
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[14] The cooperative guest-binding process was analyzed according to the Hill equation and a nonlinear least-squares method. The $K_{tot}$ values were obtained by the multiplication of each sequential binding constant or by the Hill equation for **2a** with $C_{60}$ and **3a** with **5R**, which showed the maximum cooperativity. The Gibbs free energy change ($\Delta G$) was calculated by the equation: $\Delta G = -RT\ln K_{tot}$, where *R* and *T* are the gas constant and temperature, respectively.
[15] See the Supporting Information for details of UV/Vis spectroscopic titration of **2a**–**2b** with **4** in $CHCl_3$ (Figures S6–S8).
[16] See the Supporting Information for details of UV/Vis spectroscopic titration of **2b** with $C_{60}$ in toluene (Figures S9 and S10).
[17] See the Supporting Information for details of circular dichroism spectroscopic titration of **3a**–**3b** with **5R** in $CH_2Cl_2$/AcOEt = 30:1 (v/v; Figures S11–S13).
[18] Host molecules **1a–c** show the higher effects on the energy difference in $\Delta G$ between olefinic and non-olefinic hosts compared to those of **2**. This energy difference probably arises from the shorter distance between olefin substituents within **1b** and **1c**, and/or to the less rotational freedom of **1** than that of **2**; host molecules **1** have only one rotational axis within the structure whereas the receptors **2** have as many as three axes.
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