Allosteric function facilitates template assisted olefin metathesis†

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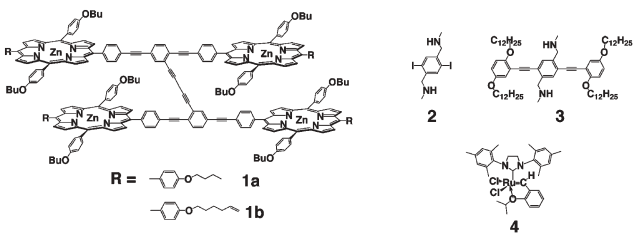
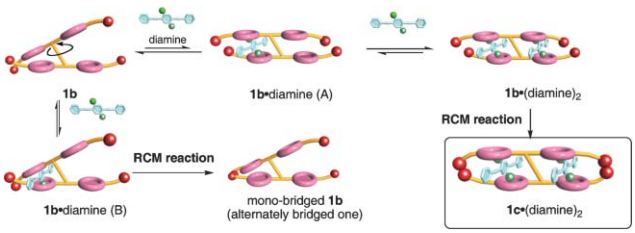
Template assisted olefin metathesis of an allosteric host 1b to give the corresponding bicyclic compound 1c was achieved and 1c can allosterically bind the template guest diamines, 2 and 3 with different affinity and cooperativity.

The design of artificial allosteric systems is of great significance to regulate the complexation ability or the catalytic activity of artificial receptors in a nonlinear fashion.[1,2] Among them, positive homotropic allosterism is the most attractive but most difficult one because the guest binding information in a subunit should be passed to other all subunits in unison.[3,4] We recently designed a zinc porphyrin tetramer **1a** with a butadiyne axle moiety, where two pairs of cofacial zinc porphyrin tweezers can bind two diamines in an allosteric manner and the rotational angle of a butadiynyl axis can adjust the cleft size to a variety of guest molecules.[5] This cooperativity is ascribed to the favoured spacing and orientation of the second binding site for the second guest molecule. In other words, the cofacial zinc porpyrin tweezers in **1a**·(diamine)$_2$ complex are arranged at the specific spatial position by guest diamines. It occurred to us that in **1b** the ring closing olefin metathesis (RCM) reaction to produce new bicyclic host molecules would efficiently take place in the presence of guest diamines with the aid of the allosteric function.[6,7]



Here we describe the synthesis, guest-binding properties, and template assisted olefin metathesis of a porphyrin tetramer **1b** bearing olefinic groups at the peripheral positions. Four zinc porphyrins are arranged around a butadiynyl rotational axis and two pairs of cofacial zinc porpyrin clefts are expected to bind two equivalents of diamine derivatives in an allosteric manner (Scheme 1).[5] Once **1b** binds two diamines in its porphyrin clefts cooperatively, the peripheral two pairs of olefinic moieties, which are separated by 5.3 nm from one another, are preorganized and aligned by guest diamines whereby the RCM reaction would occur efficiently to produce a bicyclic host molecule (**1c**) (Scheme 1). Mono-complexed species (A) and (B) were estimated to have the same stabilities by a computational method (Insight II, Discover) as shown in Scheme 1 and Fig. S1 (ESI†); without the aid of the allosteric effect, the unfavorable reaction to produce mono-bridged **1b** should also proceed. Compound **1c** would show different affinity and cooperativity to guest diamines from those of **1b**.



Scheme 1

Compound **1b** was synthesized according to Scheme 2 and identified by ^{1}H NMR, MALDI TOF MS spectroscopic evidence and elemental analysis.‡

The binding of guest diamines, 2,5-diiodo-1,4-bis(*N*-methylaminomethyl)benzene (**2**) and its bis(2,5-didodecyloxyphenylethynyl) derivative (**3**), to **1b** was confirmed by UV-vis spectroscopy. Upon addition of **2** to the solution of **1b** (2.00 μM) in chloroform at 25 °C, the Soret band and Q bands of **1b** shifted from 429.0, 556.5 and 599.0 nm to longer wavelengths, 432.5, 564.5 and 607.0 nm, respectively, with clear isosbestic points (Fig. 1). Addition of compound **3** also resulted in the similar bathochromic shift of the Soret band and Q bands of **1b**. To obtain insights into the binding mode, the stoichiometry between **1b** and guest molecules (**2** and **3**) was estimated by a molar ratio method, which clearly supported formation of 1:2 **1b**·(**2**)$_2$ and **1b**·(**3**)$_2$ complex. The plots of absorbance against [diamine] were firstly analyzed with the Hill equation (Figs. S2 and S3, ESI†).[8] The Hill plots for **2** and **3** provided evidence for the cooperativity as shown by n (Hill coefficient) = 1.8 and 1.3, respectively. It is undoubted, therefore, that the binding to **1b** is taking place cooperatively, although the cooperativity for the binding of **2** is somewhat higher than that for the binding of **3**. We thus analyzed the binding isotherm with a nonlinear least-squares method assuming the stepwise formation of 1:1 and 1:2 complexes. The association constants thus obtained are $K_1 = 4.7 \times 10^5$ M^{-1} and $K_2 = 3.6 \times 10^5$ M^{-1} for **2** and $K_1 = 1.4 \times 10^5$ M^{-1} and $K_2 = 3.9 \times 10^4$ M^{-1} for **3**, which satisfy the prerequisite for positive homotropic allosterism, $K_2 > 0.25K_1$.[8] These association constants and Hill coefficients n obtained for **2** and **3** are sufficiently high to apply this system to the template assisted olefin metathesis.

A chloroform solution of **1b** (0.25 mM) was treated with Hoveyda–Grubbs catalyst **4** (40 mol% with respect to **1b**) at 40 °C under an Ar atmosphere with and without diamines. It was

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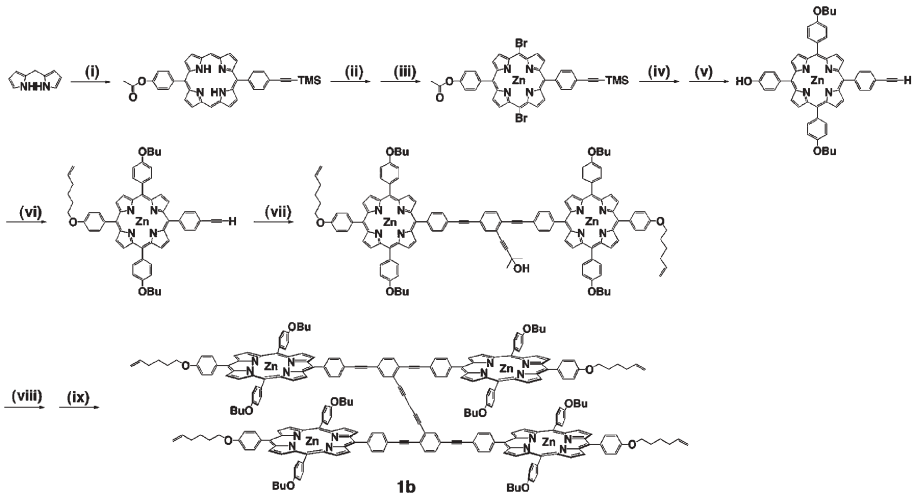

Scheme 2 *Reagents and conditions*: (i) 4-acetoxybenzaldehyde, 4-trimethylsilylethynylbenzaldehyde, TFA, DDQ, CH_2Cl_2, r.t., 4.5 h (19%); (ii) NBS, pyridine, $CHCl_3$, 0 °C, 40 min (89%); (iii) $Zn(OAc)_2{\cdot}2H_2O$, $CHCl_3$, MeOH, r.t., 35 min (99%); (iv) 4-butoxyphenylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, THF, reflux, 24 h (40%); (v) CsF, THF, EtOH, r.t., 26 h (99%); (vi) 6-bromo-1-hexene, K_2CO_3, KI, DMF, 65 °C, 2 h (76%); (vii) 1-(2,5-diiodophenyl)-1-butyn-3-methyl-3-ol, $Pd(PPh_3)_4$, CuI, THF, *i*-Pr_2NH, r.t., 4.5 h (50%); (viii) NaOH, toluene, reflux, 7 h (70%); (ix) $Cu(OAc)_2$, pyridine, 80 °C, 9.5 h (31%).

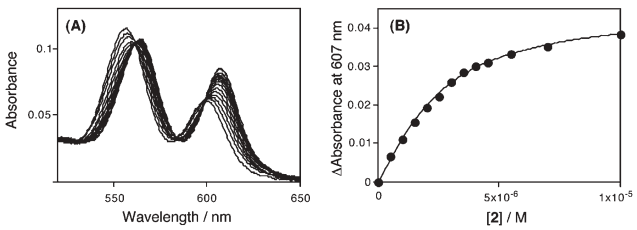

Fig. 1 (A) UV-vis spectral change of **1b** (2.00 μM) upon addition of **2** and (B) plot of absorbance change at 607 nm for **1b** *vs.* [**2**]. The solid line in (B) represents a theoretical curve for 1:2 complex formation.

confirmed by a ^1H NMR method that in chloroform-d_1 no decomposition of **4** is induced by added **2**. In addition, it was also confirmed by UV-vis spectroscopy that **1b**·(diamine)$_2$ complex is formed quantitatively under the reaction conditions. The time course of the reaction was monitored by MALDI TOF MS. During the reaction, a mass peak of *m*/*z* 3973.42 ($[M + H]^+$) decreased gradually, while a new mass peak of *m*/*z* 3945.41 ($[M + H]^+ - 28$) appeared, followed by another mass peak *m*/*z* 3917.55 ($[M + H]^+ - 56$) (Fig. S4, ESI†). The stepwise loss of *m*/*z* 28 (ethylene) from **1b** ($[M + H]^+ = 3973.42$) shows that an intramolecular RCM reaction took place to afford a bicyclic host molecule **1c**. The reaction was terminated after 24 h and the reaction mixture was analyzed and separated by GPC (JAIGEL 2H-40 and JAIGEL 1H-40, chloroform: Fig. 2). The bicyclic compound **1c** (25%, retention time 51.5 min) as a mixture of *E* and *Z* isomers (*E*/*Z* = 1:3), mono-bridged **1b** along with a small amount of unreacted **1b** (49.5 min), and inseparable mixtures (45.5 min) were isolated by this GPC method. The difference in retention time of 2.0 min between **1c** and **1b** was probably due to the smaller exclusion volume of **1c**. Further addition of **4** to a reaction mixture did not cause any change in the ratio of mono-bridged **1b** and **1c**, indicating that the remaining mono-bridged **1b** should be an alternately bridged compound, in which the second ring closure is sterically impossible (Scheme 1). In the presence of the template molecule **2** (1.1 and 2.4 equivalents with respect to **1**),

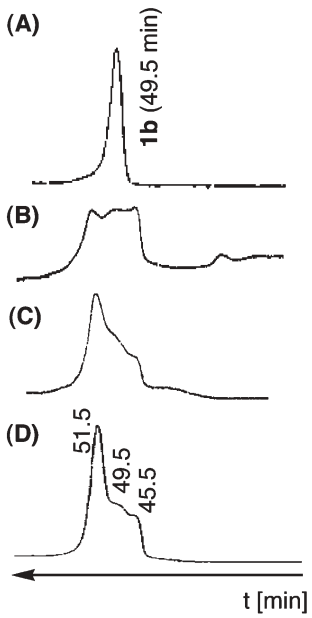

Fig. 2 GPC chromatograms for (A) **1b** and for the reaction mixture of the RCM reaction under the conditions of (B) **1b** without **2**, (C) **1b** + 1.1 equivalent of **2**, (D) **1b** + 2.4 equivalents of **2**.

as we expected, the percentage of a main product **1c** significantly increased up to *ca.* 50% (with 1.1 equivalent of **2**) and *ca.* 70% yield (with 2.4 equivalents of **2**) as estimated by the area ratio in GPC chromatogram (Fig. 2(C) and (D)).

When compound **3** (4.0 equivalents with respect to **1b**) was used as a template molecule, the RCM reaction of **1b** would proceed straightforward to produce a double-pseudorotaxane **1c**·(**3**)$_2$ due to the four bulky dodecyl groups. After 48 h, the reaction mixture was monitored by UV-vis spectroscopy and MALDI TOF MS. It was found that 80% of porphyrinatozinc in **1c** was still complexed with **3** by UV-vis spectroscopy. We tried to isolate **1c**·(**3**)$_2$ complex by size exclusion chromatography (SEC; Bio-beads

SX-1, chloroform). The first fraction, which was identified to be **1c**·(**3**)$_2$, was isolated by SEC. The UV-vis spectrum indicated that this fraction contains **1c** and **3** in a ratio of 1.0:1.8, whereas the second and the third fractions contains **1c** and **3**, respectively. The emission spectrum (λ_{ex} = 390 nm) of the first fraction showed that the emission from **3** (λ_{em} = 429 nm) was quenched by **1c** due to efficient energy transfer from **3** to **1c** within the complex, because the emission wavelength of **3** considerably overlaps with the Soret band of **1c**.

The resulting bicyclic compound **1c** possessing preorganized and aligned two cavities should be the host molecule possessing different affinities with **2** and with **3**. Compound **1c** was titrated with **2** and **3** in chloroform by UV-vis spectroscopy. The same bathochromic shifts in the Soret and Q bands were observed as those for **1b** with **2** or **3**. The association constants for **1c** with **2** and **3** were estimated by a nonlinear least-squares method to be $K_1 = 2.2 \times 10^6$ M^{-1} and $K_2 = 9.0 \times 10^5$ M^{-1} for **2** and $K_1 = 6.2 \times 10^4$ M^{-1} and $K_2 = 1.8 \times 10^4$ M^{-1} for **3**, respectively (Figs. S5 and S6, ESI†). Furthermore, Hill coefficients n obtained for **2** and **3** with **1c** were both 1.4, indicating that **1c** can cooperatively bind diamines, although a degree of cooperativity is not so high. The loss of the rotational freedom in the butadynyl axis from **1b** by the RCM reaction resulted in higher affinities with smaller n in the case of **2** and in lower affinities with almost the same n in the case of **3**. It is known in the MWC model for positive homotropic allosterism that a degree of cooperativity n is correlated with L value, where L is [T (an unbound conformation)]/[R (a bound conformation)] and a higher L value results in a higher n value.[3c] The lower n for **1c** with **2** would be ascribed to the lower L value because the binding sites in **1c** are already preorganized.

In conclusion, we have demonstrated that allosteric function of **1b** facilitates template assisted olefin metathesis and the resulting **1c** can still cooperatively bind the template guest diamines, **2** and **3**. Additionally, the guest molecule **2**, which is rationally arranged around the rotational axis in **1c** (2.5 nm apart from each other), would act as a monomer for polymerization to produce polyrotaxanes. These studies are now in progress in our group.

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Notes and references

‡ ^{1}H NMR (600 MHz, $CDCl_3$, δ/ppm, J/Hz); δ 0.98 (t, J = 7.3 Hz, 12H), 1.10 (t, J = 7.4 Hz, 12H), 1.50 (m, 8H), 1.66 (m, 8H), 1.75 (m, 16H), 1.97 (m, 12H), 2.02 (m, 4H), 2.26 (m, 8H), 3.96 (t, J = 6.2, 8H), 4.15 (t, J = 6.2, 4H), 4.24 (t, J = 6.3, 8H), 4.28 (t, J = 6.3, 4H), 5.06 (d, J = 5.7, 4H), 5.13 (dd, J = 16.7, 6.7, 4H), 5.94 (m, 4H), 7.04 (d, J = 8.3, 8H), 7.07 (d, J = 7.9, 4H), 7.24 (d, 8H), 7.28 (d, J = 8.5, 4H), 7.59 (d, J = 7.6, 2H), 7.65 (d, J = 9.3, 2H), 7.66 (d, J = 8.0, 4H), 7.86 (d, 4H), 7.91 (d, 4H), 7.97 (s, 2H), 8.00 (d, J = 7.9, 8H), 8.07 (d, J = 7.9, 8H), 8.11 (d, J = 8.0, 4H), 8.14 (d, J = 7.7, 4H), 8.31 (d, J = 7.2, 4H), 8.74–8.98 (m, 32H). MALDI TOF MS [dithranol] m/z calc. for $[M + H]^+$ = 3973.14, found 3973.42. Anal. Calc. for $C_{256}H_{218}N_{16}O_{12}Zn_4 \cdot 2H_2O$: C, 76.71; H, 5.58; N, 5.59. Found: C, 76.40; H, 5.72; N, 5.45%.

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