Pergamon

Tetrahedron Letters 42 (2001) 7435–7438

TETRAHEDRON LETTERS

A porphyrin tetramer for a positive homotropic allosteric recognition system: efficient binding information transduction through butadiynyl axis rotation

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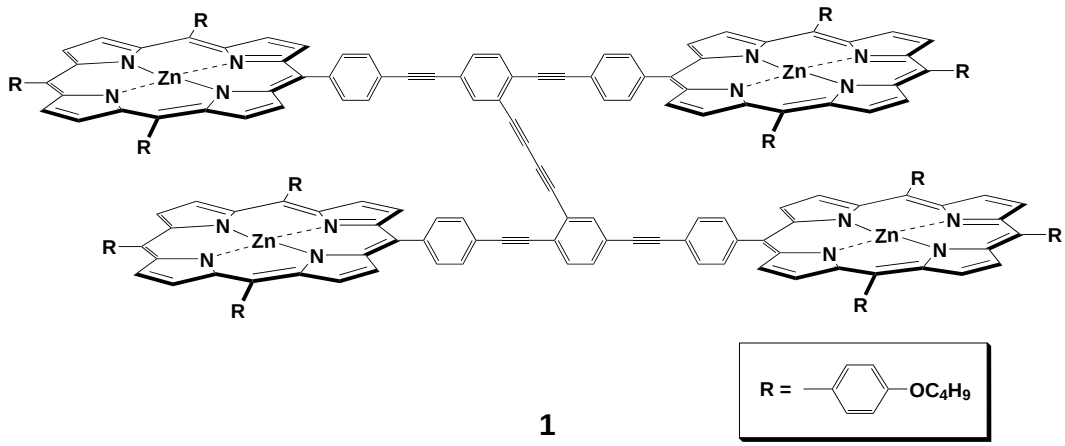
Received 17 July 2001; revised 15 August 2001; accepted 17 August 2001

Abstract—A porphyrin tetramer **1** was newly designed and synthesized to construct a novel allosteric guest-binding system. Compound **1** has a butadiynyl rotational axis, which is expected to act as a guest-binding information transducer. In chloroform, **1** can bind bidentate amines, such as 1,3-di(4-piperidyl)propane (DPP), in an allosteric manner to produce a 1:2 **1**/diamine complex with a Hill coefficient of 1.9. © 2001 Elsevier Science Ltd. All rights reserved.

The biomimetic design of allosteric systems is of great significance in order to regulate the complexation ability or the catalytic activity of artificial receptors in a nonlinear fashion.[1] Although both positive and negative allosteric systems are ubiquitously seen in nature, the reproduction of homotropic allosterism is particularly difficult in an artificial system, where the initial binding of a guest species has a different effect on that of the subsequent interactions between the same host and guest. Especially, in the positive homotropic one, one may consider the design scheme of host molecules in which the guest binding information in a subunit would be passed to other all subunits *in unison* (a binding information transduction process).[2]

How can we design and reproduce 'positive homotropic allosterism' in an artificial molecular system? Some allosteric proteins are supposed to have a contrivance of the allosteric transition occurring via subunit(s) rotation about its own symmetry axis without dissociation of the oligosubunits.[3] With this scheme in mind, we recently designed dimeric porphyrin systems potentially capable of achieving positive homotropic allosterism, namely bis[porphyrinato]cerium(IV) double-decker complexes[4] and *meso–meso*-linked porphyrin.[5] In these systems, the two porphyrins can rotate (or oscillate) relative to each other like two wheels with the central metal ion or bridging C–C bond acting as an axle as well as a binding information transducer.[6]



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Keywords: porphyrin; cooperativity; allosterism; molecular recognition; rotational axis.

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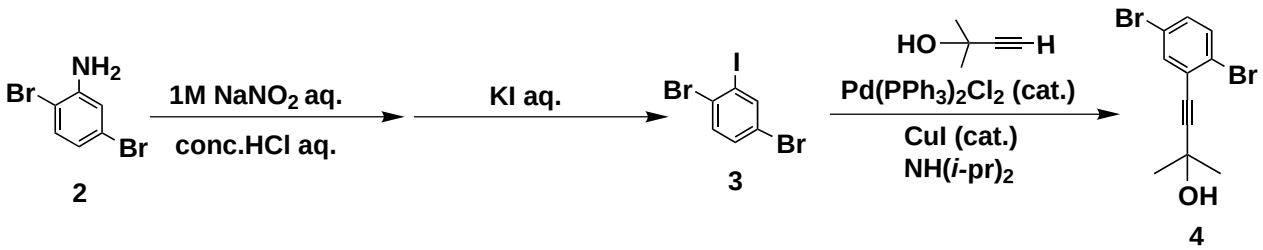
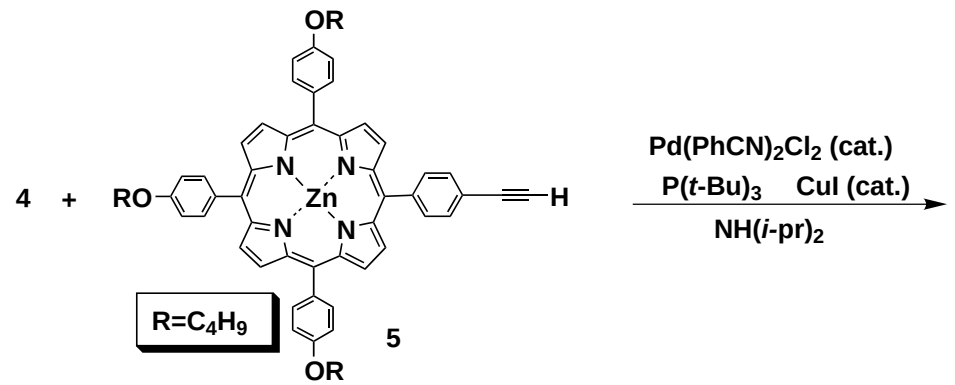
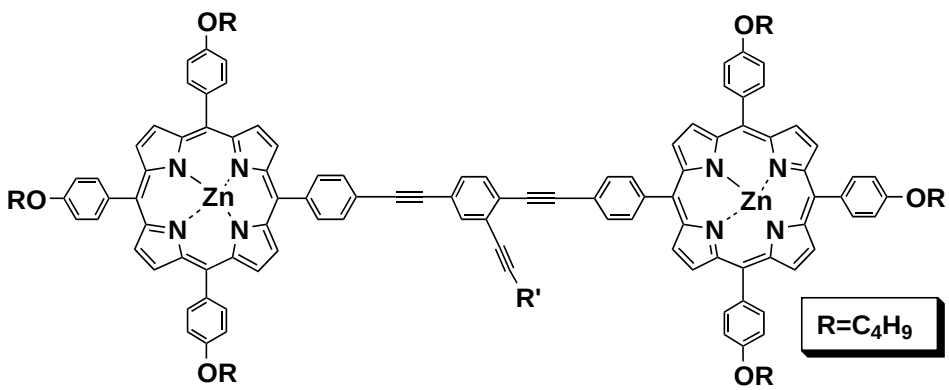
PII: S0040-4039(01)01546-5

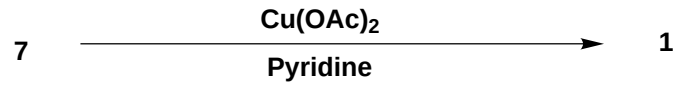
Here we describe synthesis and binding properties of a novel porphyrin tetramer **1** where four porphyrins are arranged around a butadiynyl rotational axis[7] and the butadiynyl axis should act as an efficient binding information transducer. Two pairs of co-facial zinc porphyrin tweezers[8] in **1** are expected to bind 2 equiv. of bidentate base, such as diamine derivatives, in an allosteric manner.

Compound **1** has been synthesized according to Scheme 1. 2,5-Dibromoaniline **2** was converted to the iodo derivative **3** (65%) and modified with 3-methyl-1-butyn-









Scheme 1.

3-ol by Sonogashira coupling to yield **4** (89%). Reaction of **4** with 5,10,15-tris(4-*n*-buthoxyphenyl)-20-(4-ethynylphenyl)porphyrinatozinc **5** afforded **6** in 37% yield according to the method reported recently by Fu and Buchwald.[9] After deprotection of the ethynyl group in **6** by NaOH (68%), compound **7** was treated with $Cu(OAc)_2$ in pyridine to yield compound **1** in 20% yield. Each compound was identified by ^1H NMR, ^1H–^1H COSY, IR, and MALDI-TOF MS spectroscopic evidence, and elemental analysis.[10]

The face-to-face distance between porphyrins in a parallel geometry was evaluated to be ca. 11 Å and the distance between a pair of porphyrins can vary in the range of 7–17 Å through butadiynyl axis rotation. We thus chose 1,3-di(4-piperidyl)propane (DPP) as a guest molecule (the N–N distance is estimated to be ca. 10 Å). Upon addition of DPP to the solution of **1** (1.00 μM) in chloroform at 25°C, the Soret band of **1** shifted from 428.5 nm to longer wavelength (433.5 nm) with clear isosbestic points (Fig. 1A). The fluorescence maximum of **1** ($\lambda_{ex}=470$ nm) shifted from 607 to 620 nm and the intensity increased with increasing [DPP] (Fig. 1B), suggesting that one DPP bridges two porphyrins, resulting in a more rigid structure, **1**·$(DPP)_2$.[11] To obtain insights into the binding mode, the stoichiometry between **1** and DPP was estimated by a mole ratio plot, which clearly showed 1:2 **1**·$(DPP)_2$ complex formation. Importantly, plots of absorbance at the Soret band (433.5 nm) versus [DPP] featured a sigmoidal curvature, indicating that the binding of DPP to **1** occurs cooperatively (i.e. according to positive, homotropic allosterism) (Fig. 2A). This cooperative guest binding was analyzed with the Hill equation:[12]

$$\log(y/(1-y)) = n\ \log[\text{guest}] + \log K$$

where K and n are the association constant and Hill coefficient, respectively, and $y=K/([\text{guest}]^{-n}+K)$. From the slope and the intercept of the linear plot, we obtained $\log K=12.0$ (1:2 **1**/DPP complex) and $n=1.9$. We further utilized Scatchard plots[12] to characterize the binding mode. In these plots Hill coefficients (n) are correlated with the maximum values (y_{max}) with $n=1/(1-y_{max})$, and positive and negative allosterisms are expressed by the upward and downward curvatures, respectively.[12] Consistently, the y_{max} values revealed a maximum at 0.5 with an upward curvature.

We measured ^1H NMR spectra for mixtures of **1** and 2 equiv. of DPP in $CDCl_3$ ([**1**]=0.52 mM). Proton signals assignable to DPP shifted to higher magnetic field (–2.71, –2.57, –1.05, –0.92, –0.62, and –0.37 ppm), indicating that DPP lies between the porphyrin planes in **1**.

To demonstrate the selectivity of **1** to DPP, we examined the influence of a second coexisting monoamine (piperidine) on the fluorescence spectrum of the **1**·$(DPP)_2$ complex.[13] The fluorescence spectrum of **1**·$(DPP)_2$ ([**1**]=1.00 μM, [DPP]=10.0 μM) was essentially unaffected by added piperidine up to 0.20 mM. From this study the affinity of **1** for DPP is estimated to be at least 400 times higher than that for piperidine. It is likely, therefore, that both the allosterism and the complementarity to **1** contribute to achieve the high DPP selectivity.

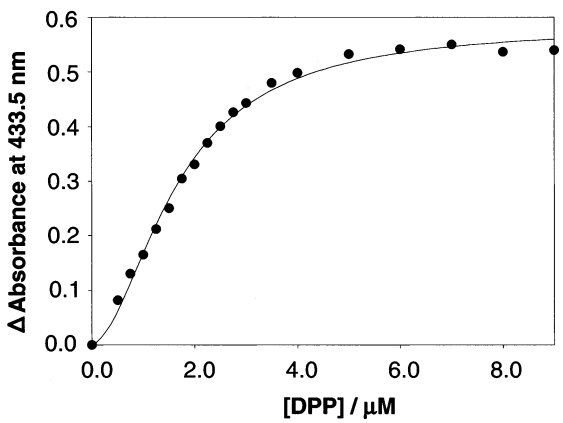


Figure 2. Plots of absorbance change at 433.5 nm for **1** versus [DPP]. The solid lines represent theoretical curves for complex formation. The measurement conditions are the same as those in Fig. 1.

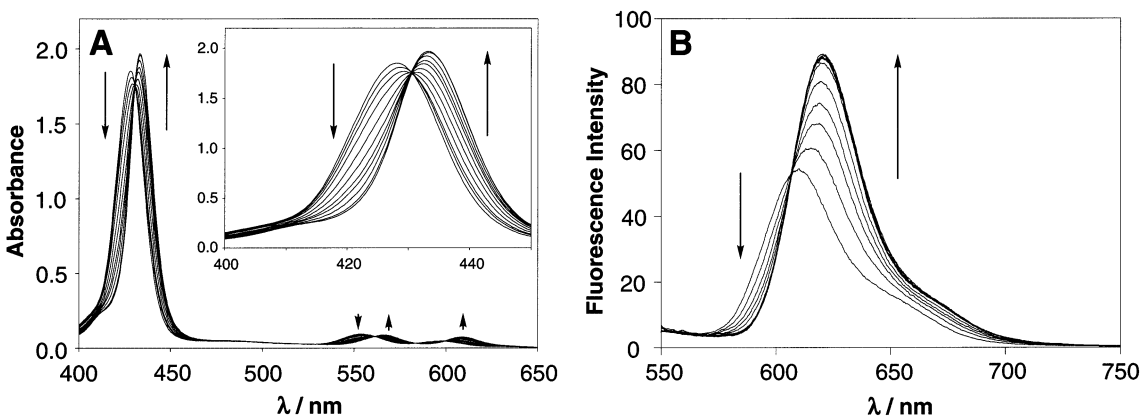
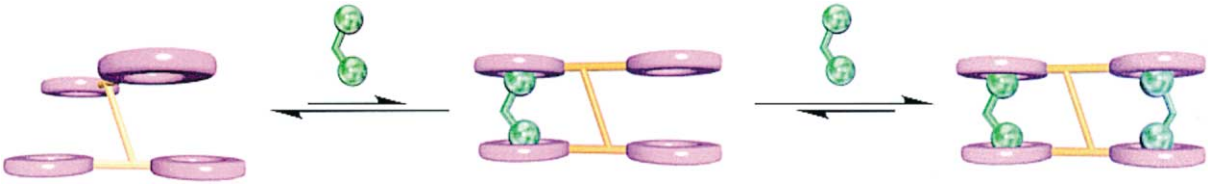


Figure 1. Concentration dependence of (A) UV–vis spectra ([**1**]=1.00 μM, [DPP]=0.5–10 μM, chloroform at 25°C) and (B) fluorescence spectra ([**1**]=0.60 μM, [DPP]=0.5–10 μM, chloroform at 25°C).



Scheme 2.

These findings clearly show that once the first pair of porphyrins binds the first DPP in their cleft, the second pair of porphyrins enhances its affinity toward the second DPP. This is due to preorganization and alignment of the second binding site, i.e. a butadiynyl rotational axis in **1** can act as an efficient transducer of the binding information (Scheme 2).

In conclusion, we have demonstrated that **1** is a novel scaffold for the design of a positive homotropic allosteric systems with a Hill coefficient of 1.9. Additionally, the subunits for guest binding, which are rationally arranged around the rotational axis such as metal ions or butadiynylene, would work cooperatively to bind guest molecules in a nonlinear fashion. One can readily apply this system to more complex oligomeric or polymeric binding-site systems, e.g. for constructing highly sensitive and selective sensory materials. These studies are now in progress in our group.

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10. Compound **1**: mp >300°C; MALDI-TOF MS (dithranol) m/z 3867.91 ($[M+H]^+ = 3868.41$); ^1H NMR (600 MHz, $CDCl_3$, TMS, 25°C): δ/ppm 0.98 (t, 12H), 1.10 (m, 24H), 1.48 (m, 8H), 1.65 (m, 16H), 1.75 (m, 8H), 1.97 (m, 16H), 3.95 (t, $J=6.0$, 8H), 4.16 (t, $J=6.2$, 4H), 4.24 (t, $J=6.0$, 8H), 4.28 (t, $J=6.3$, 4H), 7.04 (d, $J=7.9$, 8H), 7.08 (d, $J=6.0$, 4H), 7.24 (m, 8H), 7.28 (m, 4H), 7.60 (d, $J=7.7$, 2H), 7.66 (m, 6H), 7.86 (s, 4H), 7.91 (s, 4H), 7.98 (s, 2H), 7.99 (d, $J=7.3$, 8H), 8.07 (d, $J=7.6$, 8H), 8.11 (d, $J=7.3$, 4H), 8.14 (d, $J=7.4$, 4H), 8.31 (d, $J=7.1$, 4H) and 8.74–8.98 (m, 32H). Anal. calcd for $C_{248}H_{218}N_{16}O_{12}Zn_4 \cdot 0.5CHCl_3$: C, 75.83; H, 5.60; N, 5.69. Found: C, 75.48; H, 5.61; N, 5.53%.
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13. We have found that piperidine binding to **1** results in a fluorescence maximum shift (from 608 to 617 nm) and the intensity decreases. This is the reason why we chose piperidine as a competing monoamine guest.