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Conformational control of flexible molecular tweezers by intramolecular CH/π interaction

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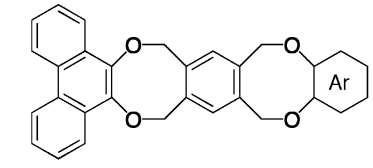
Abstract—The synthesis of new flexible molecular tweezers based on 3,4,8,10,11,13-hexahydro-1*H*,6*H*-2,5,9,12-tetraoxa-benzo[1,2:4,5]dicyclooctene bearing two naphthalenes is presented. Intramolecular CH/π interaction between the alkyl ring and the two terminal naphthalenes controls the conformation to give a self-quenched cleft form.

Non-covalent bonding interactions are important in controlling the shape of compounds and play an influential role in supramolecular chemistry. Recognition of planar molecules by the non-covalent interaction is an interesting topic in host guest chemistry in order to understand the effects of π–π stacking interactions. Molecular tweezers[1] are suitable receptors for planar π-electron guests, since they can hold the guest with the two aromatic arms through the π–π stacking interactions. In our previous works,[2] we have demonstrated that flexible molecular tweezers (**1**) can bind π-electron acceptors. The two terminal aromatic chromophores of the tweezers are different from each other. We could not prepare the tweezers having the same polycyclic rings as the terminal aromatic chromophore because of the solubility problem. Hence, we introduced alkyl chains into the tweezers. In this letter, we report that the introduced alkyl moiety controls the conformation of the tweezers.

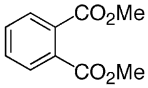
The immediate synthetic targets are compound **2**, which has two hexyloxy substituents and compound **3** carrying 1,14-dioxa-[14]paracyclophane structure in the central part of the tweezers. The synthesis of the targets is shown in Scheme 1. Intermolecular Williamson etherification of 2,3-dihydroxynaphtharene (**6**) with 1,2,4,5-tetrakis-bromomethyl-3,6-bis-hexyloxy-benzene (**4**)[3] by treatment with Cs_2CO_3 in acetone gives compound **2** in 62% yield. The yield of the corresponding coupling reaction of **5** and **6** is 56% yield. Both of the target compounds have good solubility in usual organic solvent.

The standard titration experiment between **2** and a guest molecule, tetracyanoquinodimethane (TCNQ), was

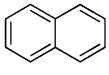


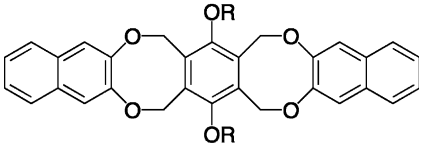
1a: Ar =

1b: Ar =



1c: Ar =





2: R = -CH_2-$(CH_2)_4$-CH_3
3: R = -CH_2-$(CH_2)_{10}$-CH_2-

Keywords: Molecular tweezers; Conformational control; CH/π interaction.
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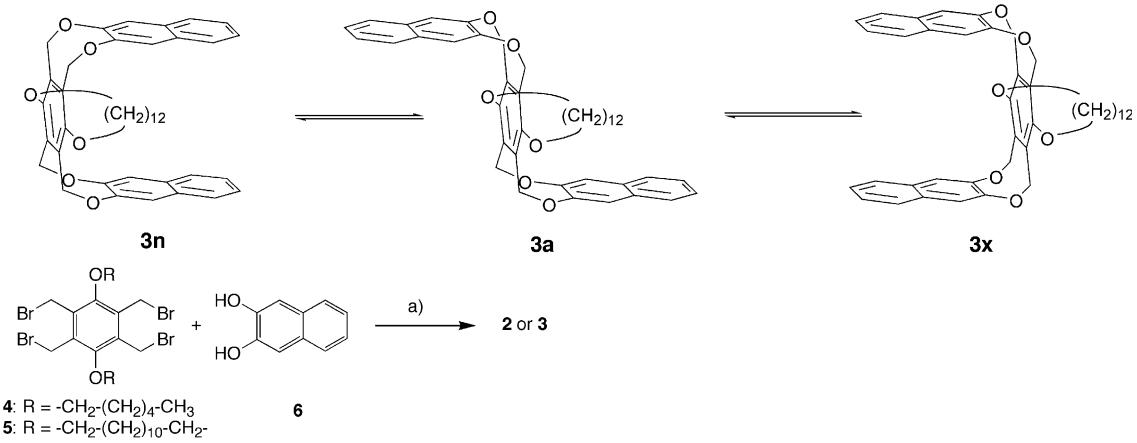
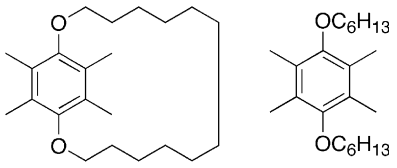


Scheme 1. Syntheses of molecular tweezers **2** and **3**. Reagents and conditions: (a) Cs_2CO_3, acetone, reflux.

carried out by ^{1}H NMR spectroscopy in $CDCl_3$, however, the binding constant was not estimated because the complexation induced shift of the guest proton is very small. The hexyloxy substituents on the central ring act as steric bulk to prevent the guest molecule coming into the cleft of **2**. To our surprise **3** did not show any propensity to bind TCNQ in $CDCl_3$,[4] although **3** can adopt an empty cleft conformation (**3x**) with alkyl bridge situated outside of it. This clearly indicated that the alkyl bridge of the paracyclophane moiety is an obstacle for the guest binding.



7 **8**

The failure of the guest binding for **3** suggested that the alkyl bridge should be situated above the naphthalene ring(s) so that there is no room for the electron acceptor guest in the cavity. This was supported by the ^{1}H NMR chemical shift of the alkyl bridge. The chemical shifts of the methylene protons of the alkyl bridge are shifted up-field when compared to the corresponding values of the reference compound, 16,17,19,20-tetramethyl-1,14-dioxa-[14]paracyclophane (**7**) (−0.31, β; −0.23, γ; −0.51, δ; −1.10, ε; −0.91 ppm for ξ methylene from the ether oxygen). Up-field shift of the methylene protons clearly suggested that a conformation in which the alkyl ring of the paracyclophane moiety is situated above the naphthalene ring(s) is significantly populating in the dynamic conformational equilibrium of **3**. In such a conformation, the alkyl ring moiety does act as the obstacle for the guest binding.

A self-quenched conformation[5] of **3** was suggested from the temperature dependent ^{1}H NMR spectra. In order to examine the preferred conformation of **3**, the ^{1}H NMR at low temperature was examined. The signals of the alkyl ring of the paracyclophane moiety were shifted further to the higher magnetic field when lower the temperature (Fig. 1). Especially prominent is the shift of the ε methylene. The chemical shift difference from 25 to −80 °C is −0.56 ppm. Hence, the chemical shift difference of the methylene protons reaches to −1.66 ppm from that of **7**. The chemical shifts of the individual methylene proton are summarized in Table 1. Up-field shift of each methylene protons clearly suggested that the conformation in which the alkyl ring of the paracyclophane moiety is nested within the cleft of the two naphthalene rings became predominant, when lower the temperature.

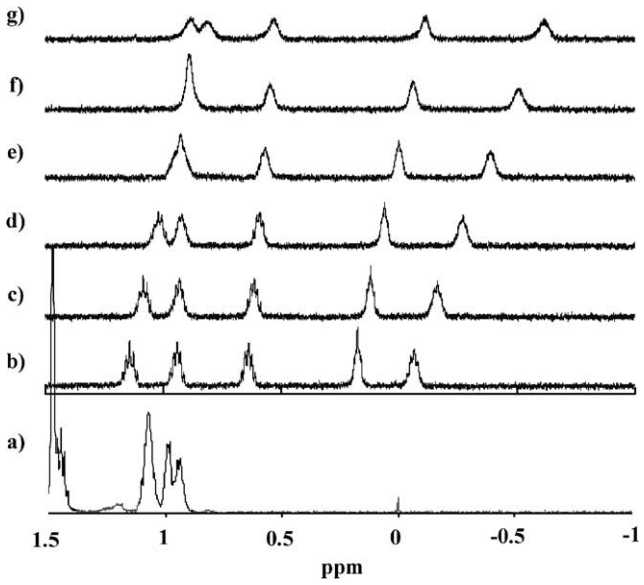


Figure 1. Partial ^{1}H NMR spectra (500 MHz) at various temperatures of (a) **7** at 25 °C, (b) **3** at 25 °C, (c) 0 °C, (d) −20 °C, (e) −40 °C, (f) −60 °C, and (g) −80 °C.

Table 1. ^{1}H NMR chemical shift of **3** and **7** at various temperatures

Compound	Temperature (°C)	Chemical shift (ppm)				
		β	γ	δ	ε	ξ
3	−80	0.79	0.86	0.50	−0.65	−0.14
	25	1.21	0.92	0.62	−0.09	0.15
7	25	1.52	1.15	1.13	1.01	1.06

The cleft conformation of **3** in which the alkyl ring moiety is nested is further supported by the molecular structure in crystalline **3** (Fig. 2).[6] As can be clearly seen, the two naphthalene rings of **3** have face-to-face arrangement and the alkyl ring of the paracyclophane moiety is situated within the cleft of the two naphthalene rings. The CH/π attractive interaction[7] between the alkyl moiety and the terminal naphthalene rings plays an important role in stabilizing this conformation.

In order to ascertain whether such an attractive interaction between the naphthalene and the alkyl chain is effective enough for the conformational control of the tweezers, the conformation of **2** was examined. This compound has the same number of carbon atoms as **3**, though the two termini of the alkyl chain were not connected to each other. The chemical shifts of the methylene and methyl protons of the alkyl chain showed small down-field shift when compared to the corresponding values of the reference compound, 1,4-bis-hexyloxy-2,3,5,6-tetramethylbenzene (**8**) (0.07, β; 0.05, γ; 0.05, δ; 0.05 ppm for ε methylene from the ether oxygen, and 0.04 ppm for methyl protons). The signals of alkyl chains did not prominently shift to the higher magnetic field even when the temperature was lowered (the maximum shift was shown in the ε methylene, the chemical shift difference is -0.08 ppm: $\delta_{-80\,^{\circ}C} - \delta_{25\,^{\circ}C}$).

The molecular structure of **2** in the crystalline state[8] has a stepped anti arrangement of the three aromatic rings (Fig. 3). Due to the intramolecular alkyl–arene interaction, many examples of folded chain conformation[9] have been reported, however, the hexyloxy chains do not adopt a folded conformation in this case. The conformations of the two chains are slightly different from each other, but they are essentially extended form in the crystalline state. This clearly shows that the intramolecular CH/π attractive interaction between the alkyl chain and the terminal naphthalene rings is not operative effectively in this molecule. The entropic cost to fix the chain into a folded conformation suitable for the alkyl–arene interaction is higher than the energy gain due to the attractive interaction between the folded alkyl chain and the terminal naphthalene rings.

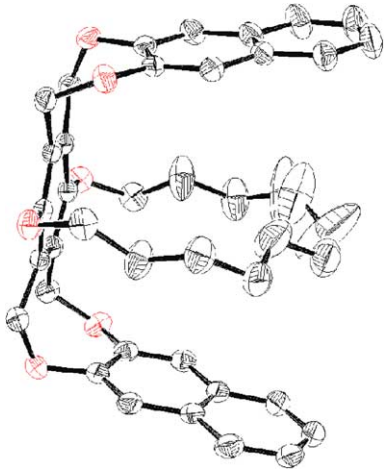


Figure 2. X-ray crystal structure of **3**. Hydrogen atoms are omitted for clarity.

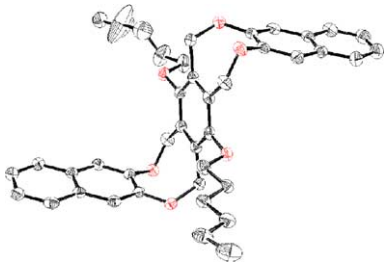


Figure 3. X-ray crystal structure of **2**. Hydrogen atoms are omitted for clarity.

In conclusion, the structure of **3** was found to have a self-quenched cleft conformation by the intramolecular CH/π attractive interaction between the alkyl ring and the two naphthalenes. The intramolecular interaction is so strong that the molecule cannot adopt the empty cleft conformation to have a donor–acceptor–donor type sandwich arrangement by the intermolecular charge transfer interaction even in the presence of a large excess amount of an electron acceptors such as TCNQ. In contrast, when the central C–C bond of the alkyl ring of **3** was broken, the structure was changed to have the stepped anti arrangement of the three aromatic rings.

Acknowledgements

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6. The crystal data for **3** are as follows; **3**; $C_{42}H_{44}O_6$, FW = 644.81, monoclinic, space group $P2_1/n$ with $a = 17.759(5)$, $b = 9.554(5)$, $c = 19.879(5)$ Å, $\beta = 90.221(5)°$, $V = 3373(2)$ Å^3, and $Z = 4$. The measurement was performed with Mac Science MXC18 at ambient temperature; radiation Mo Kα ($\lambda = 0.71073$); unique reflections 7817, observed 4963 with $|F_o| > 4.0\sigma|F_o|$. The structures were solved by the direct method (SHELXL-97). Full-matrix least squares refinements converged to a conventional R factor of 0.096, $wR = 0.237$ ($I > 2\sigma(I)$). The crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 245021. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk.
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8. The crystal data for **2** are as follows; **2**; $C_{42}H_{46}O_6$, FW = 646.82, monoclinic, space group $P2_1/a$ with $a = 9.032(5)$, $b = 25.435(5)$, $c = 15.214(5)$ Å, $\beta = 97.447(5)°$, $V = 3466(2)$ Å^3, and $Z = 4$. The measurement was performed with Mac Science MXC18 at 200 K; radiation Mo Kα ($\lambda = 0.71073$); unique reflections 7232, observed 4864 with $|F_o| > 4.0\sigma|F_o|$. The structures were solved by the direct method (SHELXL-97). Full-matrix least squares refinements converged to a conventional R factor of 0.122, $wR = 0.289$ ($I > 2\sigma(I)$). The crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 245022.
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