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Conformational control of molecular tweezers containing a disulfide bond by redox reactions

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Abstract—Molecular tweezers **1b** having two alkyl thiol chains were prepared. Intramolecular cyclization of the thiols under oxidative conditions afforded tweezers **2b** containing a disulfide bond. X-ray crystal analysis and temperature dependent ^{1}H NMR spectra analysis revealed that the structure of **1b** has a stepped anti arrangement of the three aromatic rings, although that of **2b** adopted a cleft conformation because of the intramolecular interaction between the alkyl chain and the terminal naphthalene rings. The thiol–disulfide redox reaction proceeded smoothly and reversibly to control the conformation of the tweezers.

Non-covalent interactions are important in controlling the shapes of compounds and play an important role in supramolecular chemistry. A number of artificial receptors have been synthesized to study these interactions. Molecular tweezers,[1] which have two aromatic chromophores connected by a spacer, are suitable receptors for planar π-electron guests because the two aromatic arms can hold the guest through π–π stacking interactions. In our previous studies,[2] we reported the synthesis and conformation of a couple of molecular tweezers having alkyl moieties within the spacer. The structure of **2a** was found to have a self-quenched cleft conformation caused by intramolecular CH/π attractive interactions between the alkyl ring and the two naphthalenes (Fig. 1). In contrast, when the central C–C bond of the alkyl ring of **2a** was broken, the structure of the resultant compound (**1a**) was changed to a stepped anti arrangement of the three aromatic rings. Intramolecular interactions between the alkyl moieties and the terminal aromatic rings are found to play an important role in controlling the conformation of the tweezers.

Redox reactions are widely used in supramolecular chemistry, because they are chemically and electrically reversible, and useful for changing the conformations of molecules. Different types of conformational changes, such as rotation, bending, flipping, and shuttling, have been reported.[3] Molecules that can change their conformations in response to external chemical or electrical stimuli can be used to construct molecular machines or devices.[4] The thiol–disulfide exchange reaction can be controlled chemically and electrically. If we introduce disulfide into the alkyl ring of our molecular tweezers, the tweezers can respond to redox reactions with conformational changes from a stepped conformation in the dithiol state to a cleft conformation in the disulfide state. Here, we report the synthesis of molecular tweezers **1b** and **2b**, bearing two terminal alkyl thiols and a disulfide bond within an alkyl ring, respectively, and the conformational control between these molecular tweezers.

The tweezers (**1b**) were synthesized as shown in Scheme 1. Etherification of durohydroquinone (**3**)[5] with tosylate **4** by treatment with NaH in THF gives compound **5** in 52% yield. Bromination of each benzyl methyl group of **5** afforded the tetrakis-bromomethyl substituted compound **6** in quantitative yield. Intermolecular

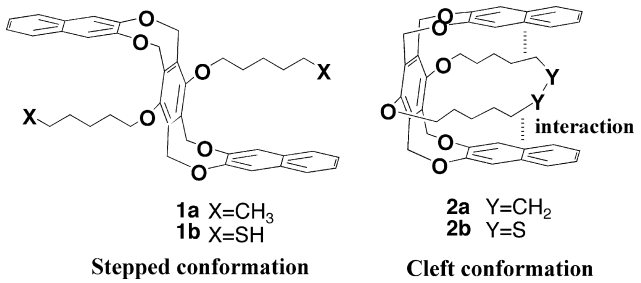

Figure 1.

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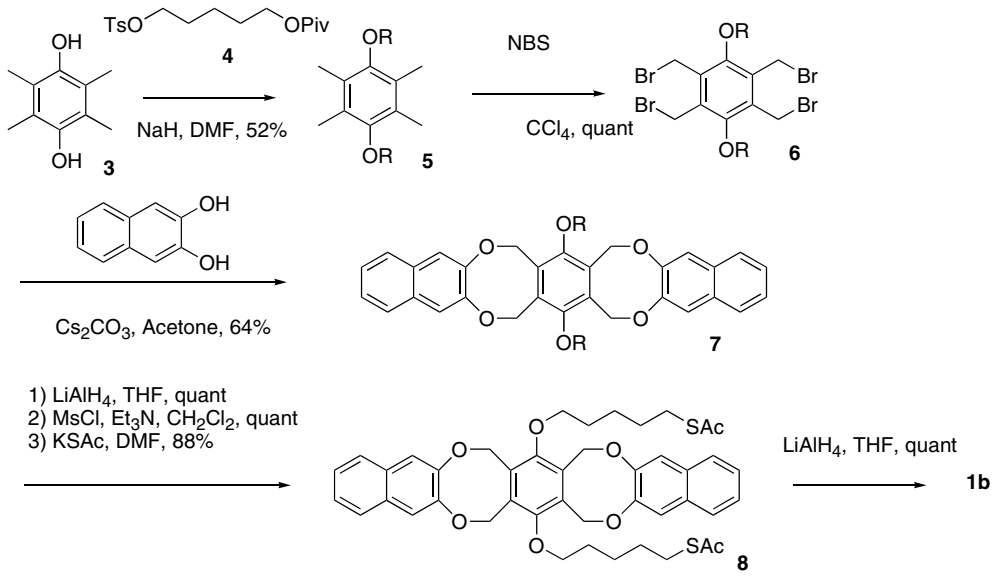


Scheme 1. Synthesis of molecular tweezers **1b**.

Williamson etherification of 2,3-naphtharenediol with **6** by treatment with Cs_2CO_3 in acetone gives compound **7** in 64% yield. Deprotection of the pivaroyl groups of **7** in reductive conditions ($LiAlH_4$, THF), followed by mesylation (MsCl, Et_3N, CH_2Cl_2) gave the corresponding mesylate; its substitution with KSAc in DMF furnished compound **8**. Deprotection of acetyl groups was performed with $LiAlH_4$ in THF to afford **1b** in quantitative yield.[6]

Formation of the intramolecular disulfide bond was accomplished under oxidative conditions:[7] treatment of **1b** with iodine and pyridine in CH_2Cl_2, to give **2b** in 45% yield.[8,9]

Under oxidative conditions (5 equiv I_2, 5 equiv pyridine), the NMR signals of **1b** were disappeared and the signals of **2b** were observed (Fig. 2). Prominent changes were seen on the methylene protons of the 8-membered ring of 5,8-dihydro-[1,4]dioxocine moieties. While the methylene protons of **1b** are seen as a singlet, those of **2b** appear as two doublets at 5.64 and 5.54 ppm

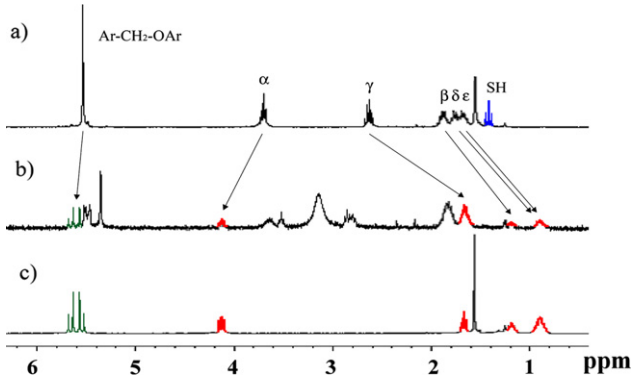


Figure 2. Partial ^1H NMR spectra (500 MHz) of (a) **1b**, (b) **1b** with added I_2 and pyridine, (c) **2b**.

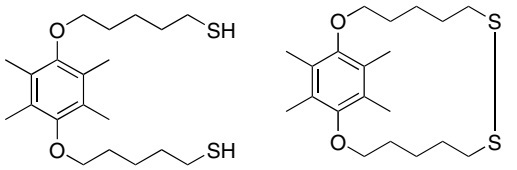
because the disulfide ring formation makes them enantiotopic to each other.

To know the conformation of the molecular tweezers **1b** and **2b** in solution, NMR analysis was carried out. Table 1 shows the ^1H NMR chemical shifts of **1b** and **2b**, together with those of the corresponding reference compounds (Fig. 3). The chemical shifts of the methylene protons of the alkyl bridge are shifted to the upfield when compared to the corresponding values of the reference compound, 16,17,19,20-tetramethyl-1,14-dioxa-7,8-dithia-[14]paracyclophane (**11**) (−0.330, β; −0.286, γ; −0.520, δ; −0.798 ppm for ε methylene from the ether oxygen). The signals of the alkyl ring of the paracyclophane moiety were shifted further to the higher magnetic field at lower temperatures. The upfield shift of the methylene protons clearly suggested that conformations in those of which the alkyl ring of the paracyclophane moiety is situated above the naphthalene ring(s) are present in significant amounts in the dynamic conformational equilibrium of **2b**. On the other hand, the chemical shifts of the methylene protons of the alkyl thiol chain of **1b** showed a small downfield shift when compared to the corresponding values of the reference compound, 1,4-bis-(4-mercapto-pentyloxy)-2,3,5,6-tetramethylbenzene (**10**) (0.039, β; 0.033, γ; 0.022, δ; 0.025 ppm for ε methylene from the ether oxygen). The signals of the alkyl chains did not prominently shift to the higher magnetic field even when the temperature was lowered (the maximum shift was shown in the δ methylene, the chemical shift difference is −0.057 ppm: $\delta_{-80\,^\circ C} - \delta_{20\,^\circ C}$). These results suggest that **1b** mainly adopts conformations in which the alkyl chains are not affected by a ring current effect of the naphthalenes.

The cleft conformation of **2b** with its nested alkyl ring moiety is further supported by the molecular structure in crystalline **2b**[10] (Fig. 4). As can be clearly seen, the two naphthalene rings of **2b** have a face-to-face arrangement and the alkyl ring of the paracyclophane moiety is

Table 1. ^{1}H NMR Chemical shift of **3** and **7** in CD_2Cl_2

Compound	Temperature (°C)	Chemical shift (ppm)			
		β	γ	δ	ε
2b	20	1.213	0.898	0.956	1.699
2b	−80	0.987	0.783	0.841	1.511
11	20	1.543	1.184	1.476	2.497
$\Delta\delta_{\mathbf{2b-11}}$	20	−0.33	−0.286	−0.52	−0.798
1b	20	1.928	1.721	1.798	2.664
1b	−80	1.874	1.680	1.741	2.614
10	20	1.889	1.688	1.776	2.639
$\Delta\delta_{\mathbf{1b-10}}$	20	0.039	0.033	0.022	0.025



10 **11**

Figure 3. Reference compounds **10** and **11**.

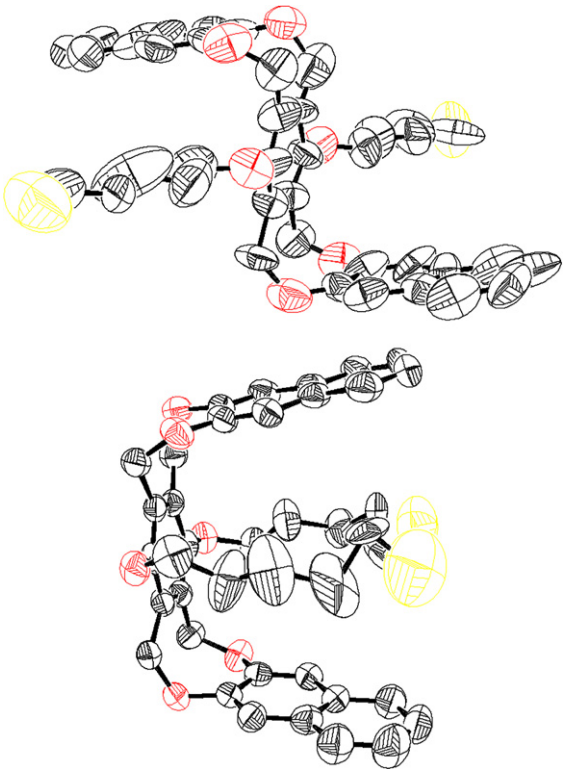


Figure 4. X-ray crystal structure of **1b** (upper) and **2b** (lower). Hydrogen atoms are omitted for clarity.

situated within the cleft of the two naphthalene rings. In contrast, an X-ray crystallographic analysis revealed that the structure of **1b**[11] has a stepped anti arrangement of the three aromatic rings. These results are consistent with previous results, in which **1a** and **2a** have different conformations from each other. The attractive interaction[12] between the disulfide containing alkyl ring moiety and the terminal naphthalene rings plays an important role in stabilizing the cleft conformation.

Finally, we found that reductive cleavage of the disulfide bond of **2b** with tri-*n*-butylphospine quantitatively gave **1b**, which was reoxidized to **2b**.[13] These redox thiol–disulfide reactions can give the large conformational changes of molecular tweezers.

In conclusion, the structure of **2b** was found to have a self-quenched cleft conformation caused by the intramolecular CH/π attractive interaction between the alkyl ring and the two naphthalenes. In contrast, when the S–S bond of **2b** was broken, the structure of product **1b** was changed to have the stepped anti arrangement of the three aromatic rings. These two compounds can be interchangeable with each other. In our tweezers, the exchange reactions cause the large conformational changes of the tweezers. Thus, our system would be applicable to a molecular device. We are now continuing further investigation toward this goal.

Acknowledgments

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6. Compound **1b**; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.64 (m, 4H), 7.37 (s, 4H), 7.31 (m, 4H), 5.53 (s, 8H), 3.70 (t, $J = 6.6$ Hz, 4H), 2.64 (dt, $J = 7.14$, 7.41 Hz, 4H), 1.87 (m, 4H), 1.63–1.79 (m, 8H), 1.42 (t, $J = 7.7$ Hz, 2H). ^{13}C NMR (75 MHz, acetone-d_6) δ 151.7, 149.6, 130.8, 130.7, 126.7, 124.8, 118.1, 75.6, 68.5, 33.8, 29.5, 24.8, 24.5. HRMS (EI$^{(+)}$) Calcd for $C_{40}H_{42}O_6S_2$: 682.2423. Found: 682.2402. Elemental Anal. Calcd for $C_{40}H_{42}O_6S_2$ with acetone: C, 69.70; H, 6.53; S, 8.66. Found: C, 69.44; H, 6.31; S, 8.65. IR (KBr, cm^{-1}) 2931, 2853, 2571, 1503, 1469, 1258, 1247, 1000, 746.
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8. Compound **2b**; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.62 (m, 4H), 7.38 (s, 4H), 7.30 (m, 4H), 5.66 (dAB, $J = 13.2$ Hz, 4H), 5.54 (dAB, $J = 13.5$ Hz, 4H), 4.13 (t, $J = 7.5$ Hz, 4H), 1.19 (t, $J = 7.5$ Hz, 4H), 1.87 (m), 0.95–0.84 (m, 8H). ^{13}C NMR (75 MHz, acetone-d_6) δ 150.6, 149.3, 130.7, 130.6, 126.7, 125.0, 118.3, 75.2, 69.3, 38.3, 27.8, 27.5, 23.7. Elemental Anal. Calcd for $C_{40}H_{40}O_6S_2$ with acetone: C, 69.89; H, 6.27; S, 8.68. Found: C, 69.66; H, 5.90; S, 8.72. IR (KBr, cm^{-1}) 2931, 2857, 1504, 1470, 1266, 1251, 1030, 744. HRMS (FAB$^{(+)}$, NBA matrix) Calcd for $C_{40}H_{40}O_6S_2$: 680.2266. Found 680.2285.
9. By-products, such as dimer (12%) and oligomeric compounds, were produced at the same time.
10. The crystal data for **2b** are as follows: **2b**; $C_{40}H_{40}O_6S_2$, FW = 680.89. Monoclinic, space group $P2_1/n$ with $a = 17.764(13)$, $b = 9.538(7)$, $c = 19.956(15)$ Å, $\beta = 90.324(17)°$, $V = 3381(4)$ Å^3, and $Z = 4$. The measurement was performed with a Bruker SMART-APEX three-circle diffractometer, equipped with a CCD area detector; graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å); unique reflections 4861, observed 1699 with $|F_o| > 4.0\sigma|F_o|$. The structures were solved by the direct method and refined by full-matrix least squares refinements on F^2 of all data using SHELXL-97 software (Sheldrick, G. M. Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen, Germany, 1997). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed using AFIX instructions. The structure converged with $R = 0.0857$, $wR = 0.2444$. Crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 662264.
11. The crystal data for **1b** are as follows: **1b**; $C_{40}H_{42}O_6S_2$, FW = 682.24. Monoclinic, space group $P2_1$ with $a = 7.456(1)$, $b = 14.873(2)$, $c = 16.181(3)$ Å, $\beta = 93.738(3)°$, $V = 1790.6(5)$ Å^3, and $Z = 4$. The measurement was performed with a Bruker SMART-APEX three-circle diffractometer, equipped with a CCD area detector; graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å); unique reflections 5023, observed 1045 with $|F_o| > 4.0\sigma|F_o|$. The structures were solved by the direct method and refined by full-matrix least squares refinements on F^2 of all data using SHELXL-97 software (Sheldrick, G. M. Program for the Refinement of Crystal Structures, University of Göttingen, Göttingen, Germany, 1997). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed using AFIX instructions. The structure converged with $R = 0.0398$, $wR = 0.0762$. Crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 662265.
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