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Control of binding affinity to paraquat by novel macrocyclic systems responding to redox reactions

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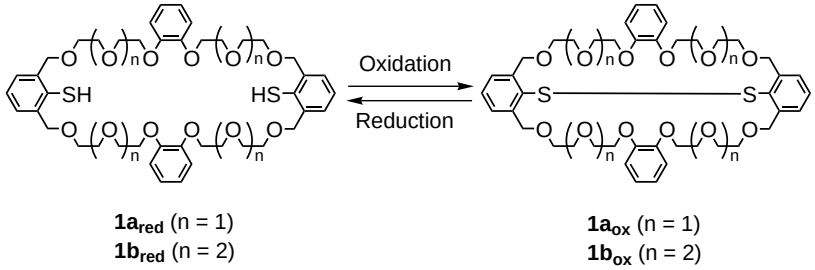
Abstract—Interconvertible crown ethers bearing two thiol groups or a disulfide moiety by redox reactions have been prepared. The binding affinity to paraquat is controlled by using these redox active molecular systems. Efficient contribution of charge transfer interaction between the thiol hosts and the guest was suggested by UV–vis spectroscopy.

Structural conversion of molecules by redox reactions is extremely interesting and useful for controlling molecular functions in biological[1] and artificial systems.[2] In particular, redox reactions between thiols and disulfides are known to regulate enzymatic activity[1] and ion recognition of artificial hosts.[3] We have reported macrocyclic hosts with a redox gate responding to the redox reactions.[3d] This system exhibits all-or-none switching of ion recognition via opening and closing of the binding cavity. This strategy can be extended to the control of binding to much larger cationic guests than metal ions. Here we report preparation and binding behavior of hosts **1**, which possess two thiol groups and one disulfide bond in the cavity of the reduced ($\mathbf{1}_{red}$) and oxidized ($\mathbf{1}_{ox}$) forms, respectively (Fig. 1). The electron-rich aromatic rings at the center of the polyetherchains would interact with a guest bearing electron-deficient aromatic rings. We have achieved regulation of paraquat recognition with the highly interconvertible hosts $\mathbf{1b}_{red}$ and $\mathbf{1b}_{ox}$ by utilizing the charge transfer (CT) interaction.

Synthesis of the crown ethers **1a**,**b** is shown in Scheme 1.[4] Diols **3** were treated with tribromide **4** in the presence of NaH under high dilution conditions to give cyclic dibromides **5** in 50% yield. Lithiation of **5** followed by addition of S_8 afforded the dithiol hosts ($\mathbf{1a}_{red}$ in 70% and $\mathbf{1b}_{red}$ in 43%). The disulfide hosts $\mathbf{1a}_{ox}$ and $\mathbf{1b}_{ox}$ were obtained by oxidation of $\mathbf{1a}_{red}$ and $\mathbf{1b}_{red}$ with H_2O_2 in 96% and 91%, respectively. Reduction of $\mathbf{1a}_{ox}$ and $\mathbf{1b}_{ox}$ produced $\mathbf{1a}_{red}$ (86%) and $\mathbf{1b}_{red}$ (83%).

Paraquat affinity of the hosts **1a** and **1b** was examined by ^{1}H NMR titration. The binding constants ($CDCl_3$:CD_3CN = 1:1) were obtained from the binding isotherms by using a non-linear least-squares method (Table 1). Job plot by ^{1}H NMR spectroscopy supports the 1:1 complexation between $\mathbf{1b}_{red}$ and paraquat.[5] Both of the thiol hosts showed a higher affinity than the corresponding oxidized hosts. $\mathbf{1b}_{red}$ binds paraquat three times as strong (K_a = 490 M^{-1}) as the corresponding disulfide host $\mathbf{1b}_{ox}$ (K_a = 150 M^{-1}). Paraquat affinity of $\mathbf{1a}_{red}$ (K_a = 160 M^{-1}) and $\mathbf{1a}_{ox}$ is much smaller than



$\mathbf{1a}_{red}$ (n = 1)
$\mathbf{1b}_{red}$ (n = 2)

$\mathbf{1a}_{ox}$ (n = 1)
$\mathbf{1b}_{ox}$ (n = 2)

Figure 1. Interconvertible crown ethers **1** responding to redox reactions between thiol and disulfide.

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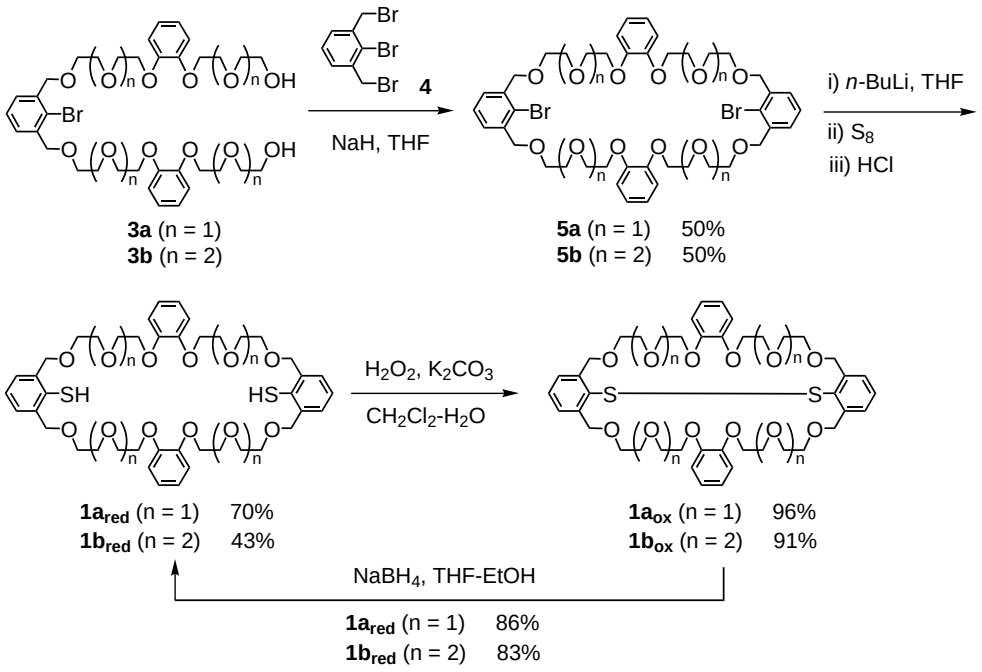
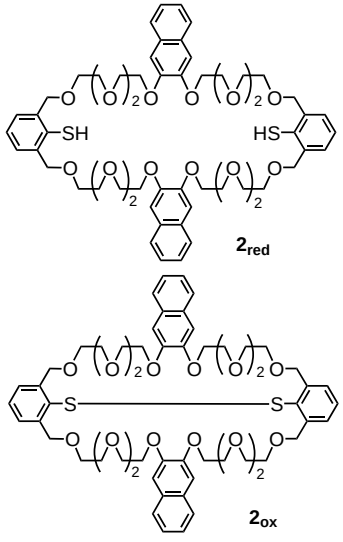


Scheme 1. Synthesis of crown ethers **1**.

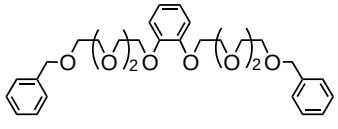
that of $\mathbf{1b_{red}}$ and $\mathbf{1b_{ox}}$, probably because the more flexible framework of $\mathbf{1b_{red}}$ is suitable for induced-fit-type binding to paraquat. $\mathbf{1b_{red}}$ binds paraquat more strongly in $CDCl_3$:CD_3CN = 1:1 (K_a = 490 M^{-1}) than in CD_3CN (K_a = 110 M^{-1}). Namely, increase of solvent polarity is unfavorable for this host–guest interaction. Host **2** bearing 2,3-dioxonaphthalene units binds paraquat 1.8 times as strong (K_a = 890 M^{-1} in $CDCl_3$:CD_3CN = 1:1) as $\mathbf{1b_{red}}$ (K_a = 490 M^{-1}), probably due to the more electron-donating property than that of the 1,2-dioxophenyl units in $\mathbf{1b_{red}}$. These results suggest that the CT interactions between the electron-rich rings of the hosts and the electron-deficient pyridinium rings of paraquat play a very important role for this recognition. Furthermore, UV–vis spectra of an equimolar mixture of each thiol host and paraquat ([host] = [paraquat] = 2.0 mM, $CDCl_3$:CD_3CN = 1:1) clearly indicate the CT interaction, because a new broad absorption above 470 nm ascribed to the CT complex appeared (Fig. 2). The more significant spectral change observed in $\mathbf{1_{red}}$ than that of $\mathbf{1_{ox}}$ suggests that the higher affinity of the thiol hosts than the corresponding disulfide hosts is caused by the CT interaction. Linear polyether **6** did not exhibit detectable UV–vis spectroscopic change in the presence of paraquat. We assume a sandwich mode for the recognition of the $\mathbf{1b_{red}}$ toward paraquat (Fig. 3), because similar binding modes between electron-deficient and electron-rich aromatic rings have been reported.[6]

Table 1. Association constants between hosts (**1** and **2**) and paraquat·$2PF_6^-$



Host	K_a (M^{-1})[a]	
	Thiol form (red)	Disulfide form (ox)
1a	160 ± 40	–[b]
1b	490 ± 60	160 ± 30
1b	110 ± 10 (in CD_3CN)	–
2	890 ± 130	150 ± 20

[a] Determined by ^1H NMR spectroscopy (400 MHz, $CDCl_3$:CD_3CN = 1:1, [host] = 2.0 mM).
[b] Not determined due to small changes in chemical shifts.



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In conclusion, we have achieved regulation of paraquat recognition by the redox active hosts. The strategy

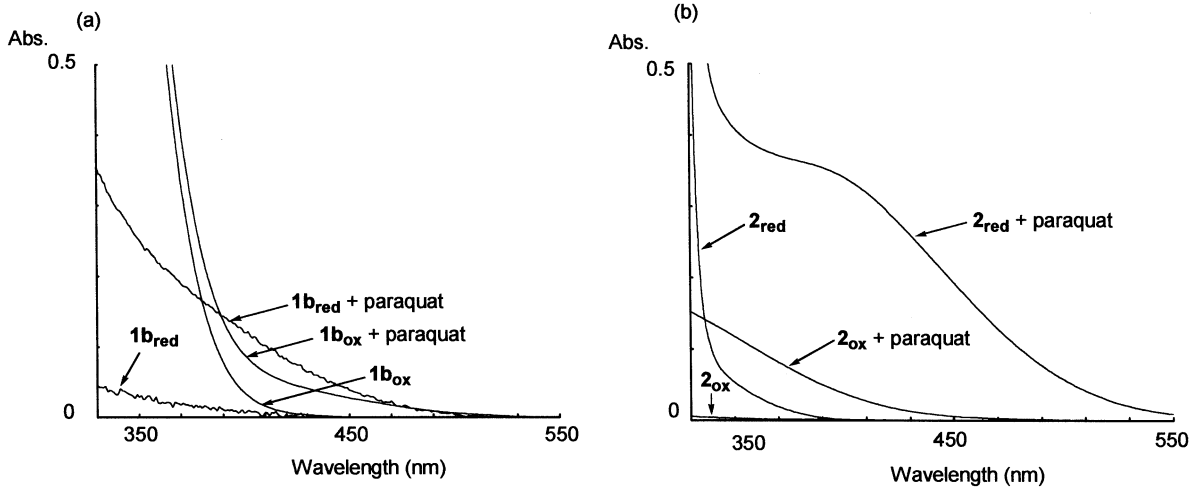

Figure 2. UV–vis spectroscopic changes of (a) **1** and (b) **2** by the addition of 1.0 equiv. of paraquat ([host] = 2.0 mM, $CDCl_3$:CD_3CN = 1:1).

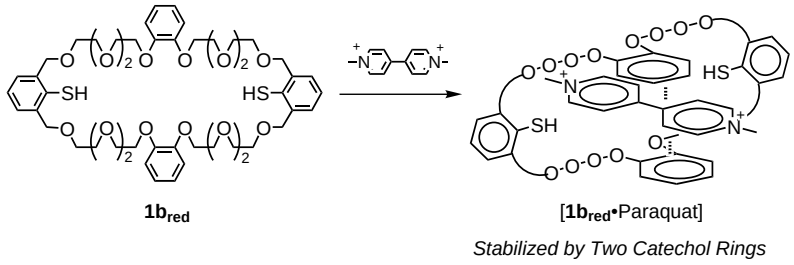

Figure 3. Plausible interaction mode between $\mathbf{1b}_{red}$ and paraquat.

achieved here provides a new useful way to construct rotaxanes and catenanes,[7] because paraquat and its analogues can be easily introduced to various host–guest systems. Thus, the regulation of paraquat affinity is expected to lead to the production of more sophisticated molecules such as a molecular shuttle and a motor.[8]

Acknowledgements

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4. The detailed synthetic procedures for **1** and **2** will be published elsewhere.
Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 4H, J = 7.8 Hz), 7.24 (t, 2H, J = 7.8 Hz), 6.91 (s, 8H), 4.57 (s, 8H), 4.17 (t, 8H, J = 4.8 Hz), 3.88 (t, 8H, J = 4.8 Hz), 3.78 (t, 8H, J = 4.6 Hz), 3.68 (t, 8H, J = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0 (s), 137.9 (s), 127.9 (d), 127.2 (d), 122.6 (s), 121.6 (d), 114.7 (d), 72.7 (t), 70.8 (t), 70.2 (t), 69.9 (t), 69.1 (t); Anal. calcd for $C_{44}H_{54}Br_2O_{12}$: C, 56.54;

H, 5.82. Found: C, 56.36; H, 5.92; mp: 106.5–108.5°C; ESI MS: $[M+Na]^+$ calcd for $C_{44}H_{54}O_{12}Br_2Na^+$: 955.2. Found: 955.2.

Compound **5b**: ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, 4H, $J=8.0$ Hz), 7.26 (t, 2H, $J=6.4$ Hz), 6.89 (s, 8H), 4.61 (s, 8H), 4.15 (t, 8H, $J=4.8$ Hz), 3.86 (t, 8H, $J=5.0$ Hz), 3.67–3.76 (m, 32H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0 (s), 137.9 (s), 127.9 (d), 127.2 (d), 122.6 (s), 121.6 (d), 114.8 (d), 72.7 (t), 70.9 (t), 70.8 (t), 70.6 (t), 70.2 (t), 69.8 (t), 69.0 (t); Anal. calcd for $C_{52}H_{70}Br_2O_{16}$: C, 56.22; H, 6.35. Found: C, 56.30; H, 6.44; mp: 84.0–85.5°C; ESI MS: $[M+Na]^+$ calcd. for $C_{52}H_{70}O_{16}Br_2Na^+$: 1131.3. Found: 1131.5.

Compound $\mathbf{1a_{red}}$: ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, 4H, $J=7.2$ Hz), 7.09 (t, 2H, $J=7.4$ Hz), 6.90 (s, 8H), 4.58 (s, 8H), 4.52 (s, 2H), 4.15 (t, 8H, $J=4.6$ Hz), 3.84 (t, 8H, $J=4.8$ Hz), 3.73 (t, 8H, $J=4.8$ Hz), 3.62 (t, 8H, $J=4.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (s), 136.9 (s), 132.4 (s), 129.2 (d), 125.1 (d), 121.6 (d), 114.9 (d), 72.5 (t), 70.7 (t), 69.8 (t), 69.5 (t), 69.1 (t); IR (NaCl): 2537 cm^{-1}; Anal. calcd for $C_{52}H_{70}Br_2O_{16}\cdot 0.5H_2O$: C, 62.17; H, 6.76. Found: C, 61.90; H, 6.64; ESI MS: $[M+Na]^+$ calcd for $C_{44}H_{56}O_{12}S_2Na^+$: 863.3. Found: 863.5.

Compound $\mathbf{1b_{red}}$: ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.27 (m, 4H), 7.09 (t, 2H, $J=7.6$ Hz), 4.60 (s, 8H), 4.15 (t, 8H, $J=5.0$ Hz), 3.85 (t, 8H, $J=5.2$ Hz), 3.60–3.80 (m, 32H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2 (s), 137.1 (s), 132.7 (s), 129.5 (d), 125.3 (d), 121.8 (d), 115.0 (d), 72.8 (t), 71.1 (t), 71.0 (t), 70.7 (t), 70.0 (t), 69.8 (t), 69.1 (t); IR (NaCl): 2530 cm^{-1}; Anal. calcd for $C_{52}H_{70}Br_2O_{16}\cdot 0.5H_2O$: C, 60.86; H, 7.17. Found: C, 60.69; H, 7.09; ESI MS: $[M+Na]^+$ calcd for $C_{52}H_{72}O_{16}S_2Na^+$: 1039.4. Found: 1039.4.

Compound $\mathbf{1a_{ox}}$: ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (brs, 4H), 7.32 (t, 2H, $J=7.6$ Hz), 6.90 (s, 8H), 4.44 (brs, 8H), 4.17 (t, 8H, $J=4.6$ Hz), 3.90 (t, 8H, $J=4.2$ Hz), 3.78 (brs, 8H), 3.59 (brs, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (s), 143.1 (s), 131.8 (s), 130.2 (d), 127.6 (d), 121.5 (d), 114.2 (d), 70.9 (t), 70.6 (t), 70.2 (t), 69.7 (t), 69.2 (t); Anal. calcd for $C_{52}H_{70}S_2O_{16}\cdot 0.25H_2O$: C, 62.65; H, 6.51. Found: C, 62.64. H, 6.56; ESI MS: $[M+Na]^+$ calcd for $C_{44}H_{54}O_{12}S_2Na^+$: 861.3. Found: 861.4.

Compound $\mathbf{1b_{ox}}$: ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.43 (m, 6H), 6.90 (s, 8H), 4.46 (brs, 8H), 4.17 (t, 8H, $J=4.7$ Hz), 3.91 (t, 8H, $J=4.8$ Hz), 3.79 (t, 8H, $J=4.7$ Hz), 3.62–3.70 (m, 16H), 3.52 (brs, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0 (s), 143.1 (s), 131.5 (s), 130.2 (d), 127.2 (d), 121.6 (d), 114.6 (d), 71.0 (t), 70.8 (t), 70.8 (t), 70.5 (t), 70.0 (t), 69.9 (t), 69.2 (t); Anal. calcd for $C_{52}H_{70}S_2O_{16}$: C, 61.52; H, 6.95. Found: C, 61.36; H, 7.11; ESI MS: $[M+Na]^+$ calcd for $C_{52}H_{70}O_{16}S_2Na^+$: 1037.4. Found: 1037.5.

5. The Job plot for complexation between $\mathbf{1b_{red}}$ and paraquat was carried out by using chemical shift changes of the benzylic methylene protons of $\mathbf{1b_{red}}$ ($[\mathbf{1b_{red}}]$+[paraquat]= 4.0 mM in $CDCl_3$:CD_3CN = 1:1).

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