**Pseudocryptand-type [2]Pseudorotaxanes Based on Bis(meta-phenylene)-
32-Crown-10 Derivatives and Paraquats with Remarkably Improved
Association Constants**

Zhenbin Niu, Carla Slebodnick, Daniel Schoonover, Hugo Azurmendi, Kim Harich, and Harry
W. Gibson*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia,
24061

E-mail hwgibson@vt.edu

Contents

1. Materials and methods.....	S2
2. Synthesis of 1c	S2
3. Synthesis of 1d	S4
4. Synthesis of 1e	S6
5. ¹ H-NMR spectra: complexation of 1c and 2	S9
6. Stoichiometry of the complexation of 1c and 2	S9
7. Stoichiometry of the complexation of 1d and 2	S10
8. Determination of Δ_0 for 1a • 2	S10
9. Determination of Δ_0 of 1c • 2	S11
10. Determination of Δ_0 of 1d • 2	S11
11. Isothermal titration calorimetry (ITC) titration curve for 1e • 2	S12
12. Mass spectrum of 1c • 2	S12
13. Mass spectrum of 1d • 2	S13
14. Mass spectrum of 1e • 2	S13
15. 1D-NOESY study of 1c • 2	S14
16. 1D-NOESY study of 1d • 2	S15
17. 1D-NOESY study of 1e • 2	S16
18. Crystal structure of 1c	S17
19. Crystal structure of 1b • 2	S17
20. Crystal structure of 1c • 2	S17
21. Crystal structure of 1d • 2	S18
22. Crystal structure of 1e • 2	S18

1. Materials and methods

Picolinic acid, quinaldic acid, nahthyridine-2-carboxylic acid, 1-(3'-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 4-dimethylaminopyridine (DMAP) were reagent grade and used as received. Bis(*meta*-phenylene)-32-crown-10 (BMP32C10) diol (**1b**)¹ and dimethyl paraquat PF₆ (**2**)²⁻³ were prepared according to literature procedures. Solvents were either used as purchased or dried according to literature procedures. ¹H-NMR spectra were obtained on a JEOL ECLIPSE-500 spectrometer and an INOVA-400 spectrometer with internal standard TMS. ¹³C-NMR spectra were collected on a JEOL ECLIPSE-500 spectrometer at 125 MHz and an INOVA-400 spectrometer at 101 MHz. HR-MS were obtained by employing an Agilent LC-ESI-TOF and an Applied Biosystems 4800 MALDI TOF/TOF. Isothermal titration calorimetry was performed on a Microcal MCS instrument; raw isotherm data were collected using the Microcal Observer software. Integration and fitting of the isothermal data (*K_a* and ΔH) were accomplished using Origin software with a one set of sites algorithm.

2. Synthesis of **1c**

Scheme S1. Synthesis of dipicolinate BMP32C10 ester **1c** via EDCI/DMAP coupling.

BMP32C10 diol (410 mg, 0.69 mmol), picolinic acid (340 mg, 2.77 mmol), EDCI (265 mg, 1.38 mmol) and DMAP (169 mg, 1.38 mmol) were dissolved in dichloromethane (DCM, anhydrous, 50 mL). The solution was stirred under N₂ for 2 days at room temperature. The reaction mixture was washed with DI water (3 times) and a brown oil was obtained, which was dried in a vacuum oven with P₂O₅ overnight. The crude product was purified via a silica gel column by employing gradient elution (DCM to DCM : methanol = 96 : 4) to afford **1c** as a white solid (523 mg, 94%), mp 82.0-83.3 °C. ¹H-NMR (CDCl₃/CD₃CN = 1/1 <v/v>, 500 MHz) (Figure S1): δ (ppm): 8.71 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 2H), 8.11-8.05 (dt, *J* = 7.9, 1.0 Hz, 2H), 7.87 (td, *J* = 7.7, 1.8 Hz, 2H), 7.53-7.50 (m, 2H), 6.56 (d, *J* = 2.3 Hz, 4H), 6.39 (t, *J* = 2.3 Hz, 2H), 5.28 (s, 4H), 4.03-4.01 (m, 8H), 3.77-3.74 (m, 8H), 3.63-3.58 (m, 17H). ¹³C-NMR (CDCl₃, 101 MHz) (Figure S2): δ (ppm): 164.86, 160.02, 149.92, 147.89, 137.69, 136.97, 126.93, 125.29, 107.14, 101.32, 70.85, 70.81, 69.59, 67.57, 67.30. HR-ESIMS (Figure S3): calcd. for [M + H]⁺: 807.0855, found: *m/z*, 807.0876 [M + H]⁺, error: -2.60 ppm.

Figure S1. ^1H -NMR ($\text{CDCl}_3/\text{CD}_3\text{CN} = 1/1$ <v/v>, 500 MHz, room temperature) of dipicolinate BMP32C10 ester **1c**.

— 164.86
 — 160.02
 ~ 149.92
 ~ 147.89
 ~ 137.69
 ~ 136.97
 ~ 126.93
 ~ 125.29
 — 107.14
 — 101.32
 70.85
 70.81
 69.59
 67.57
 67.30

Figure S2. ^{13}C -NMR (CDCl_3 , 101 MHz, room temperature) of dipicolinate BMP32C10 ester **1c**.

Figure S3. Electrospray ionization mass spectrum of dipicolinate BMP32C10 ester **1c**.

3. Synthesis of **1d**

Scheme S2. Synthesis of diquinaldate BMP32C10 ester **1d** via EDCI/DMAP coupling.

BMP32C10 diol (216 mg, 0.36 mmol), quinaldic acid (256 mg, 1.45 mmol), EDCI (139 mg, 0.72 mmol) and DMAP (88.7 mg, 0.72 mmol) were dissolved in dichloromethane (DCM, anhydrous, 10 mL). The solution was stirred under N₂ for 2 days at room temperature. The reaction mixture was washed with DI water (3 times) and a dark oil was obtained, which was dried in a vacuum oven with P₂O₅ overnight. The crude product was pre-separated via a short silica gel column (DCM : methanol = 97 : 3). Then further purification was performed on another silica gel column (ethyl acetate first, then DCM to DCM : methanol = 96 : 4) and **1d** was obtained as a colorless oil. The oil was recrystallized in hexane/dichloromethane and a white solid was obtained, 319 mg (98%), mp 110.8 – 112.2°C. ¹H-NMR (CDCl₃, 500 MHz) (Figure S4): δ (ppm): 8.28 (m, 4 H), 8.15 (d, J = 8.5 Hz, 2 H), 7.86 (d, J = 8.2 Hz, 2 H), 7.79-7.75 (m, 2 H), 7.65-7.61 (m, 2 H), 6.64 (d, J = 2.2 Hz, 4 H), 6.44 (t, J = 2.2 Hz, 2 H), 5.40 (s, 4 H), 4.08-4.04 (m, 8 H), 3.83-3.79 (m, 8 H), 3.71-3.64 (m, 17 H). ¹³C-NMR (CDCl₃, 101 MHz) (Figure S5): δ (ppm): 165.06, 160.04, 147.86, 147.64, 137.75, 137.22, 130.81, 130.21, 129.29, 128.58, 127.50, 121.12, 107.10, 101.32, 70.86, 70.82, 69.60, 67.58, 67.48. HR-ESIMS (Figure S6): calcd. for [M + H]⁺: 907.3648, found: m/z, 907.3694 [M + H]⁺, error: 5.15 ppm.

Figure S4. ¹H-NMR (CDCl₃, 500 MHz, room temperature) of diquinaldate BMP32C10 ester **1d**.

-164.86
 -160.02
 ~149.92
 ~147.89
 ~137.69
 ~136.97
 ~126.93
 ~125.29
 -107.14
 -101.32
 70.85
 70.81
 69.59
 67.57
 67.30

Figure S5. ¹³C-NMR (CDCl₃, 101 MHz, room temperature) of diquinaldate BMP32C10 ester **1d**.

Figure S6. Electrospray ionization mass spectrum of diquinaldate BMP32C10 ester **1d**.

4. Synthesis of **1e**

Scheme S3. Synthesis of dinaphthyridate BMP32C10 ester **1e**.

BMP32C10 diol (194 mg, 0.33 mmol), naphthyridine-2-carboxylic acid (227 mg, 1.32 mmol), EDCI (504 mg, 2.64 mmol) and DMAP (322 mg, 2.64 mmol) were dissolved in DCM (anhydrous). The reaction mixture was stirred at room temperature under N₂ for 3 days. The organic phase was washed with DI water (5 times) and a brown oil was obtained after solvent was removed. The brown oil was dried in a vacuum oven with P₂O₅ overnight. The crude product was purified by employing a silica gel column (DCM to DCM/MeOH = 95/5) and a pale-yellow solid was obtained (334 mg, 93%), mp 163.6-165.0 °C. ¹H-NMR (CDCl₃, 500 MHz) (Figure S7): δ (ppm): 9.21 (dd, J = 4.2, 2.0 Hz, 2 H), 8.34 (d, J = 8.4 Hz, 2 H), 8.30 – 8.21 (m, 4 H), 7.57 (dd, J = 8.2, 4.2 Hz, 2 H), 6.64 (d, J = 2.2 Hz, 4 H), 6.43 (t, J = 2.2 Hz, 2 H), 5.39 (s, 4 H), 4.07 – 4.03 (m, 8 H), 3.82 – 3.79 (m, 8 H), 3.70 – 3.65 (m, 16 H). ¹³C-NMR (CDCl₃, 101 MHz) (Figure S8): δ (ppm): 164.82, 160.02, 155.25, 154.79, 150.92, 138.58, 137.58, 136.78, 124.27, 123.64, 122.15, 107.27, 101.44, 70.86, 70.81, 69.60, 67.68, 67.60. HR-ESIMS (Figure S8): calcd. for [M + H]⁺: 909.3958, found: m/z, 909.3979 [M + H]⁺, error: -2.3 ppm.

Figure S7. ^1H -NMR (CDCl_3 , 500 MHz, room temperature) of dinaphthyridate BMP32C10 ester **1e**.

Figure S8. ^{13}C -NMR (CDCl_3 , 101 MHz, room temperature) of dinaphthyridate BMP32C10 ester **1e**.

Figure S9. Electrospray ionization mass spectrum of dinaphthyridate BMP32C10 ester **1e**.

5. ^1H -NMR spectra for complexation of **1c** and **2**

Figure S10. Partial proton NMR spectra (500 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN} = 1/1$ $\langle v/v \rangle$, 25°C) of: (a): **1c**; (b): **1c** and **2** ($[\text{1c}] = [\text{2}] = 1.0$ mM); (c): **2**.

6. Stoichiometry of complexation of **1c** and **2**

Figure S11. Job plot showing the 1:1 stoichiometry of the complex between **1c** and **2** in $\text{CDCl}_3/\text{CD}_3\text{CN} = 1/1$ $\langle v/v \rangle$. $[\text{1c}]_0 + [\text{2}]_0 = 2.00$ mM.

7. Stoichiometry of complexation of **1d** and **2**

Figure S12. Job plot showing the 1:1 stoichiometry of the complex between **1d** and **2** in $CDCl_3/CD_3CN = 1/1$ $\langle v/v \rangle$.
 $[1d]_0 + [2]_0 = 1.22$ mM.

8. Determination of Δ_0 for **1a**·**2**

Figure S13. Determination of Δ_0 of **1a**·**2** in $CDCl_3/CD_3CN = 1/1$ $\langle v/v \rangle$. $[1a]_0 = 0.198$ mM.

9. Determination of Δ_0 for **1c**·2

Figure S14. Determination of Δ_0 of **1c**·2 in CDCl₃/CD₃CN = 1/1 <v/v>. [**1c**]₀ = 0.200 mM.

10. Determination of Δ_0 for **1d**·2

Figure S15. Determination of Δ_0 of **1d**·2 in CDCl₃/CD₃CN = 1/1 <v/v>. [**1d**]₀ = 0.225 mM.

11. Isothermal titration calorimetry (ITC) titration curve of **1e**·**2**

Figure S16. ITC curve of **1e**·**2** in $\text{CHCl}_3/\text{CH}_3\text{CN} = 1/1$ $\langle v/v \rangle$. The host (**1e**) concentration (cell) was 0.211 mM. The guest (**2**) concentration (syringe) was 5.12 mM. The guest solution was titrated into the host solution (cell) at 25°C.

12. Mass spectrum of **1c**·**2**

Figure S17. Electrospray ionization (ESI) mass spectrum of **1c**·**2**.

13. Mass spectrum of **1d**·2

Figure S18. Matrix-assisted laser desorption/ionisation-time of flight (MALDI-TOF) mass spectrum of **1d**·2.

14. Mass spectrum of **1e**·2

Figure S19. Electrospray ionization (ESI) mass spectrum of **1e**·2.

15. 1D-NOESY study of **1c·2**

Figure S20. 1D-NOESY NMR spectrum (500 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN} = 1/1$ $\langle v/v \rangle$, 25°C) of **1c·2**. Based on the crystal structure of **1c·2** (Figure 2), 1D-NOESY experiments were performed by selective irradiation of H_{11} on **1c**. The $\text{H}_{11} \cdots \text{H}_a$ shortest distances ($\text{\AA}$) obtained from crystal structures: $a = \text{p1}$, 3.212; $a = \text{p2}$, 3.507; $a = 6$, 2.676; $a = 7$, 3.070. The correlations between H_{11} and H_{p1} , H_{p2} , H_6 and H_7 are clearly observed, which is consistent with results obtained from the crystal structure of **1c·2** and indicate the formation of pseudocryptand-type [2]pseudorotaxane structure in solution.

16. 1D-NOESY study of **1d·2**

Figure S21. 1D-NOESY NMR spectrum (500 MHz, $CDCl_3/CD_3CN = 1/1$ $\langle v/v \rangle$, 25°C) of **1d·2**. Based on the crystal structure of **1d·2** (Figure 2), 1D-NOESY experiments were performed by selective irradiation of H_{p2} on **1c**. The $H_{p2} \cdots H_{17}$ shortest distances (Å) obtained from the crystal structure was 3.093. The correlation between H_{p2} and H_{17} is consistent with the crystal structure.

17. 1D-NOESY study of **1e·2**

Figure S22. 1D-NOESY NMR spectrum (500 MHz, CDCl₃/CD₃CN = 1/1 <v/v>, 25°C) of **1e·2**. Based on crystal structure of **1e·2** (Figure 2), 1D-NOESY experiments were performed by selective irradiation of H₂₃ on **1e**. The H₂₃-H₆ shortest distance (Å) obtained from the crystal structure was 2.669. The observed correlation between H₂₃ and H₆ is consistent with the crystal structure, while no correlation between H₂₃ and H₆ was observed from a solution of **1e** in the same solvent.

18. Crystal structure of **1c**

Figure S23. Two views of the X-ray structure of **1c**. Oxygen atoms are red. Carbon atoms are black. Nitrogen atoms are purple. Hydrogen atoms are green.

19. Crystal structure of **1b·2**

Figure S24. X-ray structure of “taco”-shaped **1b·2**. Disordered solvent molecules (water and acetone, which share a site) and counterions omitted for clarity, except for a fluorine atom of one PF₆, represented by the gray circle). Both positions of the disordered oxygen atom of the hydroxymethyl group, denoted by **, are shown treated as half populated. H-bond distances in Å: **a**) 2.44, **b**) 2.83, **c**) 2.34, **d**) 2.42, **e**) 2.72. H-bond angles (C-H...O, C-H...F, or O-H...O) in degrees: **a**) 144, **b**) 130, **c**) 168, **d**) 144, **e**) 156. The figure was reproduced with permission from ref 4.

20. Crystal structure of **1c·2**

Figure S25. The other view of the X-ray structure of **1c·2**. overlapped hydrogen bonds are omitted for clarity.

21. Crystal structure of **1d**·**2**

Figure S26. The other view of the X-ray structure of **1d**·**2**. overlapped hydrogen bonds are omitted for clarity.

22. Crystal structure of **1e**·**2**

Figure S27. The other view of the X-ray structure of **1e**·**2**. overlapped hydrogen bonds are omitted for clarity.

References:

- (1) Gibson, H. W.; Nagvekar, D. S. *Can. J. Chem.* **1997**, 75, 1375-1384.
- (2) Allwood, B. L.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *Chem. Commun.* **1987**, 1058-1061.
- (3) Asakawa, M.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Bělohradský, M.; Gandolfi, M. T.; Kocian, O.; Prodi, L.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1997**, 119, 302-310.
- (4) (a) Bryant, W. S.; Jones, J. W.; Mason, P. E.; Guzei, I.; Rheingold, A. L.; Fronczek, F. R.; Nagvekar, D. S.; Gibson, H. W. *Org. Lett.* **1999**, 1, 1001-1004.