Graphical Abstract

Pseudocryptand-Type Complexes of Heterocyclic Derivatives of Bis(*meta*-phenylene)-32-Crown-10 with Diquat

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ABSTRACT

The readily prepared dipicolinate, diquinaldate and dinaphthyridate ester derivatives **1c-1e** of bis(*m*-phenylene)-32-crown-10 (BMP32C10) diol **1b** demonstrated improved association constants with diquat (**3**) compared with BMP32C10 itself (**1a**). Importantly, the association constant of dinaphthyridyl BMP32C10 (**1e**) with diquat is even higher than some BMP32C10-based cryptands, which are synthetically difficult to obtain. An unusual pseudocryptand-type alternating poly[2]pseudorotaxane was formed between **1e** and diquat in the solid state.

Keywords: Crown ether; pseudocryptand; diquat; inclusion complex; poly[2]pseudorotaxane.

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1. Introduction

Since Pedersen's first reports of crown ether/alkali metal ion complex systems,¹ crown ethers (such as **1**) have become an important class of hosts that bind metal ions and other cationic species well, leading to the formation of pseudorotaxanes² - mechanically interlocked molecular architectures constructed from linear molecular components ("guests") encircled by macrocyclic components ("hosts"). N,N'-Dialkyl-4,4'-bipyridinium salts (**2**)³ and N,N'-dialkyl-2,2'-bipyridinium salts (e. g., **3**), known as paraquat and diquat salts, respectively, are commonly used as guests for crown ether hosts.⁴ Since stable pseudorotaxanes are necessary building units for many advanced supramolecular species, such as rotaxanes, catenanes, polypseudorotaxanes, polyrotaxanes, polycatenanes and supramolecular polymers,⁵ design and efficient preparation of new and easily accessible pseudorotaxane systems with high association constants are important. Crown ether-based cryptands (such as **4**, **5** and **6**) have proved to be much better hosts for paraquat and diquat derivatives than crown ethers due to preorganization and introduction of more binding sites,⁶ but their lower synthetic accessibility limits their applications in building advanced supramolecular species. Recently, we reported the BMP32C10 diesters **1c-e**^{7a} synthetically easily accessible from diol **1b**;^{7b} these hosts displayed high association constants (K_a) with paraquats (**2**),^{7a} comparable to cryptands due to the formation of novel pseudocryptand structures.⁸ Inspired by these exciting results, we studied the complexation between **1c-e** and another important model guest, diquat (**3**), whose molecular width is greater than that of paraquat (**2a**) and commonly demonstrates different complexation behaviour.^{6c,6f}

2. Results & Discussion

BMP32C10 derivatives **1c-1e** and diquat salt **3** (Figure 1) were prepared via reported procedures.^{7,9} The individual solutions of dipicolinate **1c** and **3** in (CD₃)₂CO were colorless. In contrast, the mixed solutions of **1c** and **3** in (CD₃)₂CO were yellow due to the charge-transfer interaction between the electron-rich aromatic rings of **1c** and the electron-poor pyridinium rings of diquat **3**. ¹H-NMR spectra of the mixed solutions of **1c** and **3** displayed only one set of peaks, demonstrating fast exchange complexation behaviour (Figure 2). Upon complexation, peaks corresponding to H₃, H₄, H₅, H₆, H₇ and H₈ of **1c** and H_{d2}, H_{d4} and H_{d5} of **3** moved upfield, while H₁, H₂, H₁₀ and H₁₁ of **1c** moved downfield.

The stoichiometry between **1c** and **3** was determined to be 1:1 in (CD₃)₂CO by the Job plot method¹⁰ based on ¹H-NMR analysis (Figure 3), which was confirmed by Electrospray Ionization Mass Spectrometry (ESI-MS): m/z 1135.34 [**1c**·**3**-PF₆]⁺ (theory 1135.39), 990.22 [**1c**·**3**-2PF₆]⁺ (theory 990.43), 495.29 [**1c**·**3**-2PF₆]²⁺ (theory 495.22). The association constant (*K_a*) between **1c** and **3** was determined to be 774 ± 66 M⁻¹ based on ¹H-NMR experiments,¹¹ much higher than that of the unfunctionalized crown/diquat system - **1a**·**3**, 390 M⁻¹ in the same solvent.^{3a}

Figure 1. Structures of BMP32C10 (**1a**) and its derivatives **1b-e**, paraquat derivatives **2**, diquat (**3**) and cryptands **4-6**.

Figure 2. Partial proton NMR spectra (400 MHz, (CD₃)₂CO, 25°C) of: (a) **1c**; (b) **1c** and **3** ([**1c**] = [**3**] = 1.1 mM); (c) **3**.

X-ray analysis of a single crystal revealed that **1c·3** assumed a pseudocryptand-type [2]pseudorotaxane structure in the solid state (Figure 4). In the complex the host molecule **1c** is folded and the two pyridyl rings of the host interact with each other via bonds between the hydrogens of one pyridyl ring and the nitrogen atom and the ether oxygen linkage of the other pyridyl ring. The diquat molecule threads through the central cavity of the folded host **1c**, stabilized by bonds between the oxygen atoms of **1c** and hydrogen atoms of **3** and off-set face-to-face π -stacking between the phenylene rings of **1c** and the pyridinium rings of **3**. Surprisingly unlike the situation with guest **2a** neither of the pyridyl nitrogen atoms of host **1c** interacts with the guest.

Similar to **1c·3**, mixed solutions of diquinaldate ester **1d** and **3** are yellow due to charge transfer interactions and display 1:1 stoichiometry in (CD₃)₂CO based on ¹H-NMR data, as confirmed by ESI-MS: m/z 1235.36 [**1d·3**-PF₆]⁺ (theory 1235.42), 1090.62 [**1d·3**-2PF₆]⁺ (theory 1090.46), 545.21 [**1d·3**-2PF₆]²⁺ (theory 545.23). K_a was determined to be 574 ± 35 M⁻¹ based on ¹H-NMR analysis¹¹ and 564 ± 37 M⁻¹ by Isothermal Titration Calorimetry (ITC) in acetone, higher than that of **1a·3**, 390 M⁻¹ in the same solvent.^{3a} Unexpectedly, the K_a of **1d·3** is lower than that of **1c·3**, unlike the paraquat complexes, in which the K_a of **1d·2a** is four-fold higher

than that of **1c·2a**, presumably due to stronger face-to-face π -stacking between the quinolyl rings and the extra hydrogen bonds introduced.^{7a}

X-ray analysis of a single crystal of **1d·3** revealed a pseudocryptand-type poly[2]pseudorotaxane (Figure 5). In the repeating unit the central part of the crown ether is folded into a “taco”-shape and the diquat guest is threaded through the central cavity. One quinolyl ring points to the guest **3** and interacts with it via bonds between the hydrogen atoms of **3** and oxygen/nitrogen atoms of the arm, and, as a result, closes the open-end of the “taco” structure. At the same time, the nitrogen atom of the other quinolyl ring arm points to the diquat **3** in the adjacent repeating unit and interacts by hydrogen bonds (*o*, *m* and *n* in Figure 4). In addition, the two quinoline rings interact by CH- π interactions. Thus a pseudocryptand type polymeric inclusion complex was formed. Fewer hydrogen bonds exist in **1d·3** than in **1c·3** (12 vs. 14 hydrogen bonds), consistent with the lower K_a of the former.

Based on ^1H -NMR data, a Job plot indicated that the stoichiometry of the complex of dinaphthylidate ester **1e** and **3** was 1:1 in $(\text{CD}_3)_2\text{CO}$, as confirmed by ESI-MS: m/z 1237.38 [**1e·3**-

$\text{PF}_6]^+$ (theory 1237.41), 1092.35 [**1e·3**-2 $\text{PF}_6]^+$ (theory 1092.45), 546.22 [**1e·3**-2 $\text{PF}_6]^{2+}$ (theory 546.22). K_a was determined to be $3.2 \pm 0.1 \times 10^4 \text{ M}^{-1}$ in acetone by ITC analysis, a value about 82 times higher than that of **1d·3** and even higher than some complexes with BMP32C10-based

cryptands, which are synthetically more difficult to obtain: $7.4 \pm 0.7 \times 10^3 \text{ M}^{-1}$ for **4**·**3**, $1.7 \pm 0.2 \times 10^3 \text{ M}^{-1}$ for **5**·**3** and $9.3 \pm 0.9 \times 10^2 \text{ M}^{-1}$ for **6**·**3**.¹²

Similarly to **1d**·**3**, the crystal structure of **1e**·**3** revealed a polypseudorotaxane structure in the solid state. However, unlike **1d**·**3**, each repeating unit of **1e**·**3** contains two stereoisomeric [2]pseudorotaxane units, as shown in Figure 6. The two [2]pseudorotaxane units assume different conformations, stabilized by hydrogen bonds, off-set face-to-face π -stacking and CH- π interactions between host and guest. In both **1e**·**3** isomers, the guest is threaded through the central part of the folded host. The nitrogen atom of one naphthyridyl ring points to the guest and interacts via hydrogen bonds. The nitrogen atom of the other naphthyridyl ring points to the next diquat in the adjacent repeat unit and interacts by hydrogen bonding. In addition, the two naphthyridyl rings interact with each other by hydrogen bonds. Unlike an earlier “polymeric” solid state complex of **1a** and a paraquat¹³ the PF_6 counterions do not participate. Thus, a pseudocryptand-type alternating poly[2]pseudorotaxane is formed. To the best of our knowledge, it is the first example of this type of solid state structure.

In summary, the complexations between pyridyl, quinolyl and naphthyridyl-based BMP32C10 derivatives **1c-e** and diquat **3** were demonstrated to exceed that with the parent BMP32C10 (**1a**).

Moreover, the association constant of naphthyridyl BMP32C10 diester **1e** with diquat is even higher than some cryptands, which are synthetically difficult to obtain. Interestingly, the first example of a pseudocryptand-type poly[2]pseudorotaxane was formed between **1e** and **3** in the solid state. The present protocol provides a facile method to prepare inclusion complexes of diquat with relatively high association constants.

References

- (1) (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017-7036. (b) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495-2496. (c) Pedersen, C. J. *J. Org. Chem.* **1971**, *36*, 254-257.
- (2) (a) Gibson, H. W. In *Large Ring Molecules*; Semlyen, J. A., ed.; John Wiley & Sons: New York, 1996; pp. 191-262; (b) Raymo, F. M.; Stoddart, J. F. *Chem. Rev.* **1999**, *99*, 1643-1664. (c) Harada, A. *Acc. Chem. Res.* **2001**, *34*, 456-464; (d) Hernandez, J. V.; Kay, E. R.; Leigh, D. A. *Science* **2004**, *306*, 1532-1537. (e) Vickers, M. S.; Beer, P. D. *Chem. Soc. Rev.* **2007**, *36*, 211-225. (f) Zhang, M.; Zhu, K.; Huang, F. *Chem. Commun.* **2010**, 8131-8141. (g) Ogoshi, T.; Yamagishi, T. *Chem. Commun.* **2014**, *50*, 4776-4787. (h) Xue, M.; Yang, Y.; Chi, X.; Yan, X.; Huang, F. *Chem. Rev.* **2015**, *115*, 7398-7501.
- (3) (a) Allwood, B. L.; Spencer, N.; Shahriari-Zavareh, H.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1058-1061. (b) Shen, Y. X.; Engen, P. T.; Berg, M. A. G.; Merola, J. S.; Gibson, H. W. *Macromolecules* **1992**, *25*, 2786-2788.
- (4) (a) Huang, F.; Nagvekar, D. S.; Zhou, X. C.; Gibson, H. W. *Macromolecules* **2007**, *40*, 3561-3567. (b) Wang, F.; Han, C.; He, C.; Zhou, Q.; Zhang, J.; Wang, C.; Li, N.; Huang, F. *J. Am. Chem. Soc.* **2008**, *130*, 11254-11255. (c) Wang, C.; Olson, M. A.; Fang, L.; Benítez, D.; Tkatchouk, E.; Basu, S.; Basuray, A. N.; Zhang, D.; Zhu, D.; Goddard, W. A.; Stoddart, J. F. *Proc. Nat. Acad. Sci. USA* **2010**, *107*, 13991-13996. (d) Trabolsi, A.; Fahrenbach, A. C.; Dey, S. K.; Share, A. I.; Friedman, D. C.; Basu, S.; Gasa, T. B.; Khashab, N. M.; Saha, S.; Aprahamian, I.; Khatib, H. A.; Flood, A. H.; Stoddart, J. F. *Chem. Commun.* **2010**, 46, 871-873. (e) Jiang, Y.; Cao, J.; Zhao, J.-M.; Xiang, J.-F.; Chen, C.-F. *J. Org. Chem.* **2010**, *75*, 1767-1770. (f) Deska, M.; Kozłowska, J.; Sliwa, W. *ARKIVOC* **2013**, 294-332. (g) Dong, S.; Zheng, B.; Wang, F.; Huang, F. *Acc. Chem. Res.* **2014**, *47*, 1982-1994.
- (5) (a) De Greef, T. F. A.; Smulders, M. M. J.; Wolffs, M.; Schenning, A. P. H. J.; Sijbesma, R. P.; Meijer, E. W. *Chem. Rev.* **2009**, *109*, 5687-5754. (b) Harada, A.; Hashidzume, A.; Yamaguchi, H.; Takashima, Y. *Chem. Rev.* **2009**, *109*, 5974-6023. (c) Niu, Z.; Gibson, H. W. *Chem. Rev.* **2009**, *109*, 6024-6046. (d) Fang, L.; Olson, M. A.; Benítez, D.; Tkatchouk, E.; Goddard, W. A. III; Stoddart, J. F. *Chem. Soc. Rev.* **2010**, *39*, 17-29. (e) Hanni, K. D.; Leigh, D. A. *Chem. Soc. Rev.* **2010**, *39*, 1240-1251. (f) Lee, M.; Moore, R. B.; Gibson, H. W. *Macromolecules* **2011**, *44*, 5987-5993. (g) Niu, Z.; Huang, F.; Gibson, H. W. *J. Am. Chem. Soc.* **2011**, *133*, 2836-2839. (h) Arunachalam, M.; Gibson, H. W. *Progr. Polym. Sci.*, **2014**, *39*, 1043-1073. (i) Zhang, Z.; Luo, Y.; Chen, J.;

- Dong, S.; Yu, Y.; Ma, Z.; Huang, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1397-1401. (j) Dong, S.; Luo, Y.; Yan, X.; Zheng, B.; Ding, X.; Yu, Y.; Ma, Z.; Zhou, Q.; Huang, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1905-1909. (k) Bruns, C. J.; Stoddart, J. F. *Acc. Chem. Res.* **2014**, *47*, 2186-2199. (l) Neal, E. A.; Goldup, S. M. *Chem. Comm.* **2014**, *50*, 5128-5142. (m) Ogawa, T.; Nakazono, K.; Aoki, D.; Uchida, S.; Takata, T. *ACS Macro Lett.* **2015**, *4*, 343-347. (n) Sawada, J.; Aoki, D.; Uchida, S.; Otsuka, H.; Takata, T. *ACS Macro Lett.* **2015**, *4*, 598-601. (o) Kali, G.; Eisenbarth, H.; Wenz, G. *Macromolecular Rapid Comm.* **2015**, Ahead of Print.
- (6) (a) Huang, F.; Zhou, L.; Jones, J. W.; Gibson, H. W.; Ashraf-Khorassani, M. *Chem. Commun.* **2004**, 2670-2671. (b) Huang, F.; Switek, K. A.; Gibson, H. W. *Chem. Commun.* **2005**, 3655-3657. (c) Huang, F.; Slebodnick, C.; Switek, K. A.; Gibson, H. W. *Chem. Commun.* **2006**, 1929-1931 (d) Gibson, H. W.; Wang, H.; Slebodnick, C.; Merola, J.; Kassel, S.; Rheingold, A. L. *J. Org. Chem.* **2007**, *72*, 3381-3393. (e) Pederson, A. M.-P.; Vctor, R. C.; Rouser, M. A.; Huang, F.; Slebodnick, C.; Schoonover, D. S.; Gibson, H. W. *J. Org. Chem.* **2008**, *73*, 5570-5573. (f) Pederson, A. M.-P.; Ward, E.; Schoonover, D. S.; Slebodnick, C. S.; Gibson, H. W. *J. Org. Chem.* **2008**, *73*, 9094-9101. (g) Niu, Z.; Huang, F.; Gibson, H. W. *J. Am. Chem. Soc.* **2011**, *133*, 2836-2839. (h) Zhang, M.; Yan, X.; Huang, F.; Niu, Z.; Gibson, H. W. *Acc. Chem. Res.* **2014**, *47*, 1995-2005. (i) Han, Y.; Jiang, Y.; Chen, C.-F. *Tetrahedron* **2015**, *71*, 503-522.
- (7) (a) Niu, Z.; Slebodnick, C.; Schoonover, D.; Azurmendi, H.; Harich, K.; Gibson, H. W. *Org. Lett.* **2011**, *13*, 3992-3995. (b) Gibson, H. W.; Nagvekar, D. S. *Can. J. Chem.* **1997**, *75*, 1375-1384.
- (8) For a discussion of pseudocryptands, see: (a) Nabeshima, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 969-991; (b) Jones, J. W.; Zakharov, L. N.; Rheingold, A. L.; Gibson, H. W. *J. Am. Chem. Soc.* **2002**, *124*, 13378-13379; (c) Huang, F.; Zhakarov, L.; Rheingold, A. L.; Jones, J. W.; Gibson, H. W. *Chem. Commun.* **2003**, 2122-2123.
- (9) Xiao, Y.; Chu, L.; Sanakis, Y.; Liu, P. *J. Am. Chem. Soc.* **2009**, *131*, 9931-9933.
- (10) (a) Job, P. *Ann. Chim. Appl.* **1928**, 113-203. (b) Hirose, K. *J. Incl. Phenom. Macrocyc. Chem.* **2001**, *39*, 193-209.
- (11) ¹H-NMR characterizations were done on solutions with constant [1] and varied [3]. Based on these data, Δ_o , the difference in δ values for proton H₅ of **1c** in the uncomplexed and fully complexed species, was determined to be 0.540 ppm as the y-intercept of a plot of $\Delta = \delta - \delta_a$ vs. $1/[3]_0$ in the high initial concentration range of **3**. K_a was calculated from $K_a = (\Delta/\Delta_o)/\{[1-(\Delta/\Delta_o)]/[3]_0 - (\Delta/\Delta_o)[1c]_0\}$ for several (5-10) different combinations of concentrations of the two components with 20-80% complexation of the hosts, as required by the "Weber rule" (Weber, G. *Molecular Biophysics*; Pullman, B., Weissbluth, M., eds.; Academic Press: New York, 1965; pp 369-397), and the average and standard deviation are reported. For **1d-3**, the Δ_o of H₅ was determined to be 0.570 ppm and K_a was estimated analogously. This is the stepwise process associated with the classical Benesi-Hildebrand method (Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703-2710; Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inone, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. *Comprehensive Supramolecular Chemistry*, Vol. 6, Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., eds.; Pergamon: Oxford, 1996; pp. 425-482). This approach avoids hidden issues that may arise from "black box" curve fitting methods. One such issue involves cases of non-ion paired complexes of salts which by themselves are ion paired in solution; this necessitates evaluation of the ion pair dissociation constant of the salt and the binding constant for the free cation with the host; the current method reveals this quite clearly in that the inappropriately defined K_a changes by up to an order of magnitude at various concentrations; for examples see: Huang, F.; Jones, J. W.; Gibson, H. W. *J. Am. Chem. Soc.* **2003**, *125*,

- 14458-14464; Gibson, H. W.; Wang, H.; Bonrad, K.; Jones, J. W.; Slebodnick, C.; Habenicht, B.; Lobue, P. *Org. Biomol. Chem.* **2005**, *3*, 2114-2121; Huang, F.; Jones, J. W.; Gibson, H. W. *J. Org. Chem.* **2007**, *72*, 6573-6576; Gibson, H. W.; Jones, J. W.; Zakharov, L. N.; Rheingold, A. L.; Slebodnick, C. *Chem. Eur. J.* **2011**, *17*, 3192-3206.
- (12) Huang, F.; Slebodnick, C.; Switek, K. A.; Gibson, H. W. *Tetrahedron* **2007**, *63*, 2829-2839.
- (13) Huang, F.; Fronczek, F. R. Gibson, H. W. *Chem. Commun.* **2003**, 1480-1481.