Enhancing the reactivity of 1,2,3-triazoles in "click" macrocycles by face-to-face dibenzylammonium ion binding†

Yi Liu,*[a] Xiyun Zhang,[b] Liana M. Klivansky[a] and Gayane Koshkakaryan[ac]

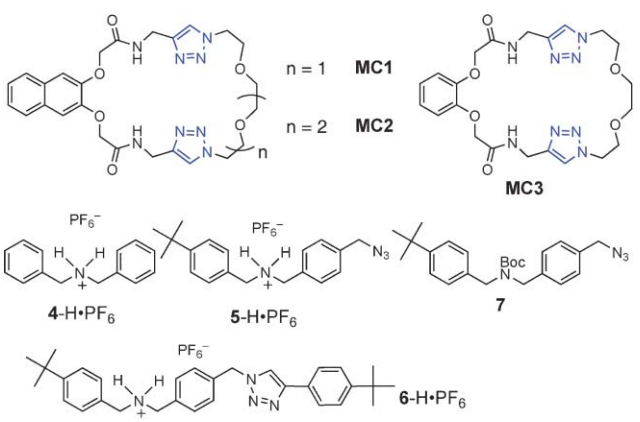
Received (in Austin, TX, USA) 30th July 2007, Accepted 15th October 2007
First published as an Advance Article on the web 23rd October 2007
DOI: 10.1039/b711505a

A face-to-face binding motif between dibenzylammonium ions and macrocycles containing 1,2,3-triazoles was established, which operates cooperatively to enhance the reactivity of 1,2,3-triazoles in an Arbuzov-type dealkylation reaction.

Crown ethers have been recognized[1] for their exceptional binding ability towards various types of cationic guests, including ammonium ions and primary alkylammonium ions (RNH_3^+).[2] Most RNH_3^+ ions complex with crown ethers in a face-to-face manner.[2] Recent studies on secondary dialkylammonium ions ($R_2NH_2^+$) and dibenzo[24]crown-8 (DB24C8) revealed[3] a threaded motif where the $R_2NH_2^+$ interpenetrates through the cavity of DB24C8 to give a [2]pseudorotaxane. Such discovery opens up the window for the construction of both discrete interlocked molecules[4] and more diverse functional interlocked molecular structures.[5] In the [2]pseudorotaxanes, collective [N^+–H···O] and [N^+C–H···O] hydrogen bondings are the major stabilizing noncovalent interactions, assisted by electrostatic interactions and macrocyclic effects.[6] Many variants of the macrocyclic hosts were synthesized and tested in terms of fine tuning the non-covalent binding interactions. It is shown that subtle structural changes to the crown structure can affect the binding ability significantly.[6b,7] Recently we have tested the Cu(I) catalyzed [3 + 2] cycloaddition — one of the supreme "click" reactions,[8] — in macrocycle synthesis. An appealing feature of such macrocycles is that the cycloaddition product, 1,2,3-triazole, can serve as ligands[9] to enhance host–guest interactions. Here we describe that "click" macrocycles **MC1–3**‡ (Scheme 1) can bind dibenzylammonium ions in a face-to-face manner rather than a threaded one.[10] Moreover, such noncovalent interaction acts cooperatively to enhance the receptor's reactivity in an Arbuzov-type[11] dealkylation reaction by placing the 1,2,3-triazole unit close to the reactive site.

The complexation between **MC3** and **4**-H·PF_6 was established by the ^{1}H NMR spectra (Fig. 1) of their equimolar mixture (5.0 mM) in CD_2Cl_2–CD_3CN (4 : 1). Both the NH_2^+ protons from **4**-H·PF_6 and the amide protons from **MC3** displayed noticeable downfield shifts, suggesting their involvement in hydrogen bondings. The benzyl protons in **4**-H·PF_6, originally resonating as a triplet at 4.35 ppm, now appeared as a singlet at slightly lower field. On the other hand, contrasting to the usual crown ether/ammonium complexes,[3a] very small shifts were observed for the ethylene glycol protons, implying that the ammonium center interacted weakly with the OCH_2CH_2 unit. The host–guest complexation underwent fast exchange on the ^{1}H NMR time scale as only one set of signals was observed. A binding constant (K_a) was measured to be 290 ± 20 M^{-1} in a mixed solvent system (CD_2Cl_2–CD_3CN 4 : 1) using a ^{1}H NMR titration method.[12] The host–guest complexation was highly solvent dependent. When CD_3CN was used as the solvent, no interaction could be seen between **MC3** and **4**-H·PF_6. The host–guest pair also existed in the gas phase as detected by electrospray ionization mass spectroscopy (ESI-MS). A peak at *m*/*z* 698 could be assigned to the molecular ion of the complex [**MC3**·**4**-H]$^+$. The same binding constant (290 ± 20 M^{-1}) was obtained for the **MC1**/**4**-H·PF_6 complexation, suggesting that increasing the π-surface from catechol to naphthanol did not affect the binding strength. In addition, increasing the ring size by including one extra CH_2CH_2O unit decreased the binding strength, as indicated by a smaller K_a (140 ± 30 M^{-1}) for the **MC2**/**4**-H^+ complexation, thus implying a diminished macrocyclic effect.[6b]

It is difficult to conclude from the ^{1}H NMR spectra whether the ammonium center threads through the macrocycles to form a [2]pseudorotaxane or binds the macrocycles face-to-face. To identify if [2]pseudorotaxane complexes formed in solution, we attempted the stoppering reaction by installing bulky groups to the ammonium salt in the presence of **MC3**. A mild "click" reaction condition was employed where **MC3**, azide-functionalized ammonium salt **5**-H·PF_6, 4-*tert*-butylphenylacetylene, $CuPF_6$·4MeCN



Scheme 1 The molecular structures of 1,2,3-triazole-containing macrocycles **MC1–3** and the dibenzylammonium salts **4**-H·PF_6, **5**-H·PF_6 and **6**-H·PF_6, and the azide **7**.

[a]*The Molecular Foundry, Lawrence Berkeley National Laboratory, One Cyclotron Road, MS 67R6110, Berkeley, CA, 94720, USA. E-mail: yliu@lbl.gov; Fax: 01 510 4867413; Tel: 01 510 4866287*
[b]*Codexis Inc., 200 Penobsco, Redwood City, CA, 94063, USA*
[c]*University of California, Berkeley, CA, 94720, USA*

† Electronic supplementary information (ESI) available: Experimental procedures for the syntheses of all the new compounds and their characterization data. Details on binding constant measurements using ^{1}H NMR spectroscopic method. See DOI: 10.1039/b711505a

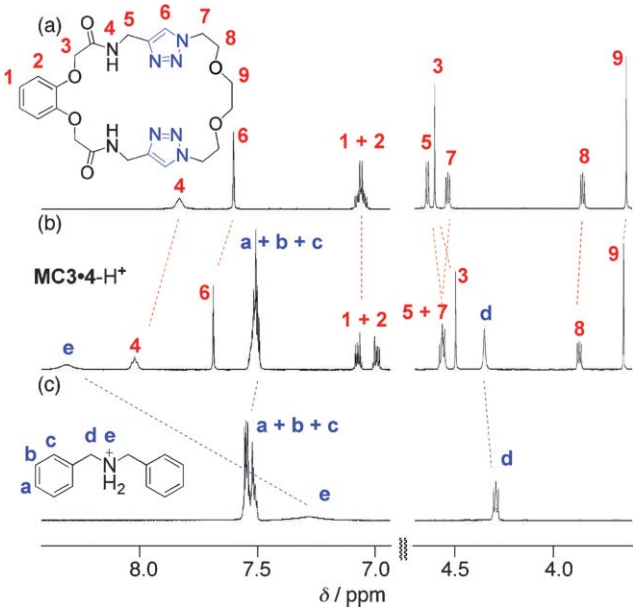


Fig. 1 Partial ^{1}H NMR spectra (500 MHz, CD_2Cl_2–CD_3CN 4 : 1, 298 K) of (a) **MC3**, (b) an equimolar mixture of **MC3** and **4**-H·PF_6, and (c) **4**-H·PF_6.

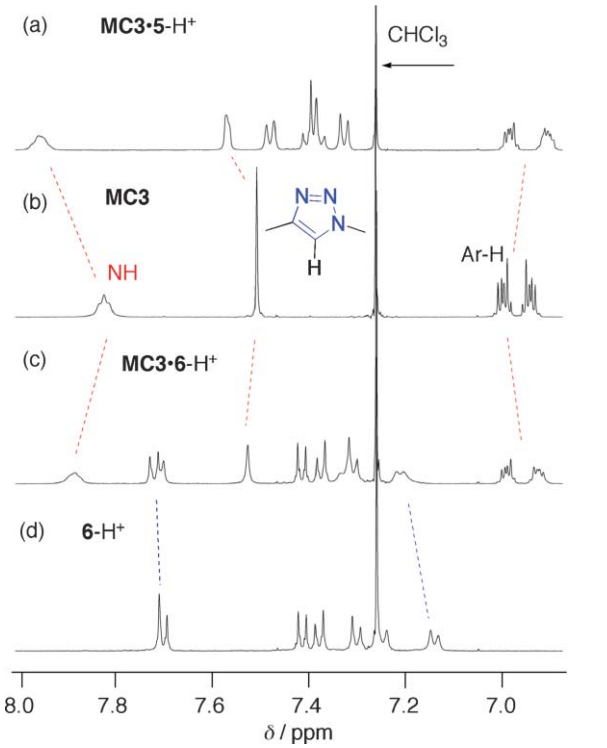


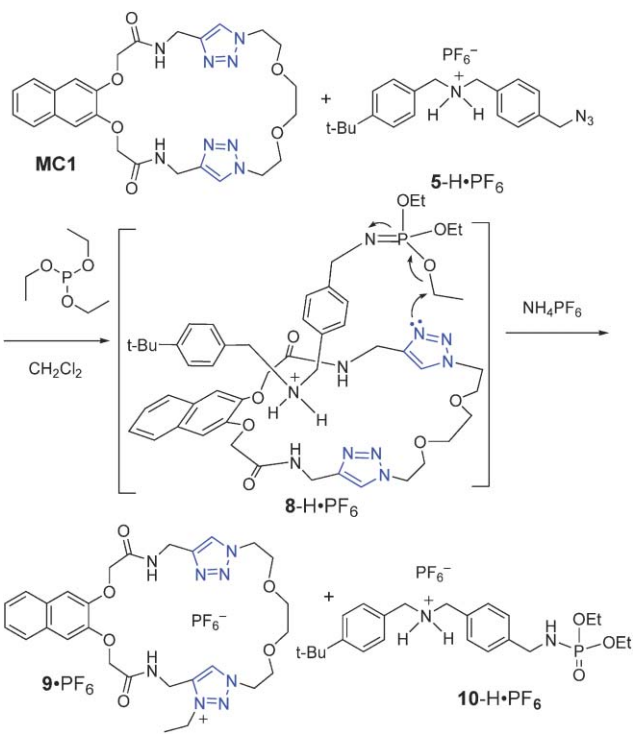
Fig. 2 The aromatic region of ^{1}H NMR spectra (500 MHz, $CDCl_3$, 298 K) of (a) an equimolar mixture of **MC3** and the azide-containing ammonium salt **5**-H·PF_6, (b) **MC3**, (c) an equimolar mixture of **MC3** and the stoppered ammonium salt **6**-H·PF_6, and (d) **6**-H·PF_6.

(cat.) and diisopropylethylamine (cat.) were mixed in a CH_2Cl_2–MeCN (4 : 1) solution under N_2 atmosphere. From the reaction mixture only the stoppered ammonium salt **6**-H·PF_6 was isolated in 92% yield and no rotaxane could be identified. The lack of [2]rotaxane formation is a good indication of the absence of [2]pseudorotaxane in solution.

We then mixed the stoppered ammonium ion **6**-H·PF_6 with **MC3** in $CDCl_3$ and followed the chemical shifts using ^{1}H NMR spectroscopy. The formation of [2]pseudorotaxane should be excluded on account of the sterically demanding threading process.[6b] As indicated in Fig. 2(b), the resonances of the mixture of **MC3** and **6**-H·PF_6 displayed chemical shifts that were similar to those observed in the mixture of **MC3** and the azido ammonium salt **5**-H·PF_6 (Fig. 2(a)). Such results confirmed that the complexation between the macrocycle and the dibenzylammonium ion, although weaker,[13] was still present in the solution, and it had to be a face-to-face one.

The origin of face-to-face binding might be understood from the relatively rigid nature of the macrocycles on account of the 1,4-disubstituted triazole units. The arrangement of oxygen atoms on the oligo-ethylene glycol unit is disrupted to the extent where [N^+–H···O] and [C–H···O] interactions, the major driving forces for the formation of [2]pseudorotaxanes,[6] are significantly weakened.

Another stoppering reaction under mild conditions was tested by reacting the azide containing **5**-H·PF_6 with triethyl phosphite to give a phosphoramidate.[14] $P(OEt)_3$ was added to a solution of **MC1** and **5**-H·PF_6 in CH_2Cl_2 (Scheme 2). No rotaxane product was detected, again supported the absence of [2]pseudorotaxane. Interestingly, a macrocyclic triazolium **9**·PF_6 was obtained in 45% yield with one of the 1,2,3-triazoles in **MC1** being alkylated, resulting a low-symmetry ^{1}H NMR spectrum compared to the parent macrocycle **MC1**. The protons of the newly introduced ethyl group could be identified at around δ 4.9 ppm and 1.7 ppm. The formation of **9**·PF_6 indicated that one of the 1,2,3-triazoles



Scheme 2 The reaction pathway illustrating the participation of 1,2,3-triazole in the Arbuzov-type dealkylation process.

participated in the dealkylation step during the formation of phosphoramidate **10**-H·PF_6.[15] Similar monoalkylated product was obtained when the catechol-based **MC3** was used.[16] To understand

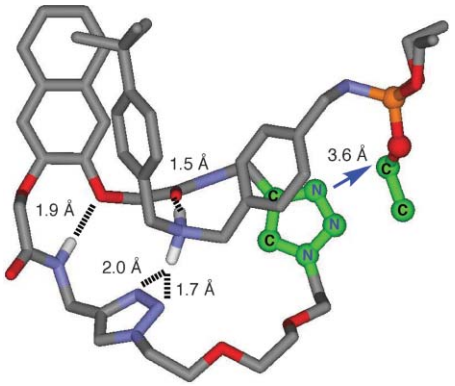


Fig. 3 Optimized structure of the intermediate **8**-H·PF_6. The reaction center is highlighted with green ball-and-stick model. The blue arrow indicates the bond to be formed between triazole N atom and ethoxy C atom. All the hydrogen atoms were omitted for clarity except for those involved in hydrogen bonding.

better the role of hydrogen bonding in such reactions, a couple of control experiments were conducted. When the *N*-Boc protected azide **7** was used instead of **5**-H·PF_6 and subjected to the same reaction conditions, no alkylated product was detected. In another experiment where MeCN was used to suppress hydrogen bonding interactions, no triazolium **9**·PF_6 was formed either. These results clearly indicated that the 1,2,3-triazole was not reactive when hydrogen bonding was unavailable, thus proving the key role of hydrogen bonding in order for the triazole alkylation to happen.

Based on these results, a proposed reaction pathway was depicted in Scheme 2. The face-to-face hydrogen bonding interactions between **MC1** and the ammonium salt **5**-H·PF_6 brings the triazole and the ethoxy unit in phosphorimidate to close proximity. Such spatial arrangement facilitates a nucleophilic attack of the long pair of the triazole N atom towards the ethyl group to furnish an alkylated product while generating a phosphoramidate as the leaving group.

The proposed reaction pathway of the triazolium formation was also supported by molecular modeling results (Fig. 3). The intermediate **8**-H·PF_6 was constructed using MOE2006[17] and optimized with MMFF94x force field implemented in MOE. The resulting structure suggested that intermolecular [N^+–H···N] hydrogen bondings could be formed between one of the triazole units and the ammonium center. [N^+–H···O] interaction was also seen between the ammonium center and one of the amide carbonyl groups on the macrocycle.[18] Meanwhile, N^3 of another triazole unit could be placed in an appropriate position where S_N2 attack of the electron deficient ethoxy carbon atom on the phosphorimidate was ready to occur.

In summary, macrocycles containing 1,2,3-triazoles were shown to recognize secondary dibenzylammonium ions in a face-to-face manner rather than a threaded one. Moreover, such supramolecular interactions were shown to be responsible for the enhanced reactivity of one of the 1,2,3-triazole units in the macrocyclic host. To the best of our knowledge, covalent modification of the host modulated by noncovalent interactions was not seen before in the related classical crown ether/ammonium host–guest systems, and is reminiscent of the enzymatic action in biological processes. Such findings may have an impact on the application of the popular click reaction in many areas, such as the design of novel supramolecular and biomimetic systems.

This work was performed at the Molecular Foundry, Lawrence Berkeley National Laboratory, and was supported by the Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under contract No. DE-AC02-05 CH11231. We thank Prof. K. Barry Sharpless and Prof. Valery V. Fokin for their support of the early work.

Notes and references

‡ For the synthetic details of **MC1–3**, please see the Electronic Supplementary Information (ESI†).

1 (*a*) C. J. Pedersen, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1021–1027; (*b*) G. W. Gokel, W. M. Leevy and M. E. Weber, *Chem. Rev.*, 2004, **104**, 2723–2750.
2 (*a*) C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017–2036; (*b*) R. C. Helgeson, J. M. Timko and D. J. Cram, *J. Am. Chem. Soc.*, 1973, **95**, 3023–3025; (*c*) *Crown Ethers and Analogous Compounds*, ed. M. Hiraoka, Elsevier, Amsterdam, The Netherlands, 1992.
3 (*a*) P. R. Ashton, P. J. Campbell, E. J. T. Chrystal, P. T. Glink, S. Menzer, D. Philp, N. Spencer, J. F. Stoddart, P. A. Tasker and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1865–1869; (*b*) A. G. Kolchinski, D. H. Busch and N. W. Alcock, *J. Chem. Soc., Chem. Commun.*, 1995, 1289–1291.
4 (*a*) P. R. Ashton, P. T. Glink, J. F. Stoddart, P. A. Tasker, A. J. P. White and D. J. Williams, *Chem.–Eur. J.*, 1996, **2**, 729–736; (*b*) S. J. Cantrill, S. J. Rowan and J. F. Stoddart, *Org. Lett.*, 1999, **1**, 1363–1366; (*c*) S.-H. Chiu, S. J. Rowan, S. J. Cantrill, J. F. Stoddart, A. J. P. White and D. J. Williams, *Chem.–Eur. J.*, 2002, **8**, 5170–5183.
5 (*a*) J.-P. Collin, C. Dietrich-Buchecker, P. Gavina, M. C. Jimenez-Molero and J.-P. Sauvage, *Acc. Chem. Res.*, 2001, **34**, 477–487; (*b*) J. D. Badjic, V. Balzani, A. Credi and J. F. Stoddart, *Science*, 2004, **303**, 1845–1849; (*c*) E. R. Kay, D. A. Leigh and F. Zerbetto, *Angew. Chem., Int. Ed.*, 2007, **46**, 72–191.
6 (*a*) W. S. Bryant, I. A. Guzei, A. L. Rheingold, J. S. Merola and H. W. Gibson, *J. Org. Chem.*, 1998, **63**, 7634–7639; (*b*) P.-N. Cheng, P.-Y. Huang, W.-S. Li, S.-H. Ueng, W.-C. Hung, Y.-H. Liu, C.-C. Lai, Y. Wang, S.-M. Peng, I. Chao and S.-H. Chiu, *J. Org. Chem.*, 2006, **71**, 2372–2383.
7 S. J. Cantrill, D. A. Fulton, A. M. Heiss, A. R. Pease, J. F. Stoddart, A. J. P. White and D. J. Williams, *Chem.–Eur. J.*, 2000, **6**, 2274–2287.
8 (*a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (*b*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599.
9 (*a*) T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Folkin, *Org. Lett.*, 2004, **6**, 2853–2587; (*b*) Y. Li, J. C. Huffman and A. H. Flood, *Chem. Commun.*, 2007, 2692–2694.
10 Crown ethers having less than 24 atoms in their macrorings were reported to form complexes with secondary dialkylammonium ions in a face-to-face manner. See: (*a*) J. C. Metcalfe, J. F. Stoddart and G. Jones, *J. Am. Chem. Soc.*, 1977, **99**, 8317–8319; (*b*) S. S. Abed-Ali, B. J. Brisdon and R. England, *J. Chem. Soc., Chem. Commun.*, 1987, 1565–1566.
11 B. A. Arbuzov, *Pure Appl. Chem.*, 1964, **9**, 307–335.
12 The binding constant was determined using WinEQNMR program. For a discussion of its application in determining binding constant, see: M. J. Hayes, *J. Chem. Soc., Dalton Trans.*, 1993, 311–312.
13 The binding constants were measured to be 50 $\pm$ 20 M^{-1} and 120 $\pm$ 80 M^{-1} for **MC3/6**-H·PF_6 and **MC3/5**-H·PF_6, respectively.
14 W.-C. Huang, K.-S. Liao, Y.-H. Liu, S.-M. Peng and S.-H. Chiu, *Org. Lett.*, 2004, **6**, 4183–4186.
15 **10**-H·PF_6 could not be isolated from the reaction mixture although its presence was clearly confirmed by a prominent *m/z* peak at 419.2 in electrospray ionization mass spectrometry, corresponding to $[M - PF_6]^+$. The spectrum was included in ESI†.
16 See ESI† for the synthetic details and characterization data.
17 MOE2006 is a product of Chemical Computing Group, Montreal, Canada.
18 Intramolecular [N–H···O] interaction was also seen between one of the amide NH groups and a naphthanolic oxygen in the macrocycle.