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Tetrahedron Letters 49 (2008) 3449–3452
Tetrahedron Letters

Dynamic covalent chemistry of a boronylammonium ion and a crown ether: formation of a C_3-symmetric [4]rotaxane

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Received 23 January 2008; revised 15 March 2008; accepted 21 March 2008
Available online 28 March 2008

Abstract

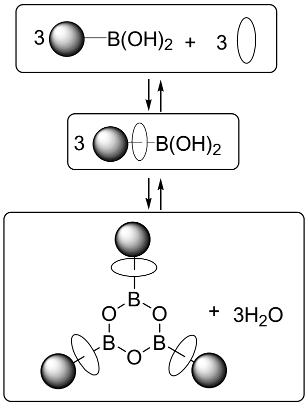
This Letter describes an efficient method for constructing a C_3-symmetric [4]rotaxane through hydrogen bond-guided self-assembly and boroxine formation. The reactions proceed under mild conditions in solution, with entropically driven forces promoting the formation of the [4]rotaxane.

Keywords: Dynamic covalent chemistry; Rotaxane; Hydrogen bonding; Boroxine

Dynamic covalent chemistry is a powerful method for synthesizing thermodynamically stable products selectively from among a set of potential products.[1] In particular, it is very effective for constructing and functionalizing mechanically interlocked molecules, such as catenanes and rotaxanes, through bond dissociation/recombination processes. Various reactions leading to covalent connection between reactants have been demonstrated, including olefin metathesis,[2] imine[3] and hydrazone[4] formation, thiol–disulfide interchange,[5] transacetalation,[6] tritylation of thioethers,[7] and coordinative bond formation.[8]

Boroxines are six-membered-ring inorganic heterocycles; their attractive C_3-symmetric tripodal structures are readily prepared through the dehydration of corresponding boronic acids. Recently, we reported the reversible condensation of different boronic acids at room temperature to give their corresponding boroxines; the trimerization of pairs of these boronic acids allowed us to prepare a unique dynamic combinational library.[9] In this present study, we used two reversible processes—hydrogen bond-guided self-assembly ([2]pseudorotaxane formation) and boroxine formation ([4]rotaxane construction)—to synthesize a C_3-symmetric [4]rotaxane containing a boroxine core (Scheme 1), and used ^{1}H NMR spectroscopy to determine this interlocked molecule's thermodynamic stability.

The preparation of the key secondary dialkylammonium salt $\mathbf{1}\cdot PF_6$ was initiated through the condensation of 4-formylphenylboronic acid with 3,5-dimethylbenzylamine to afford the corresponding imine. Reduction of this imine,



Scheme 1.

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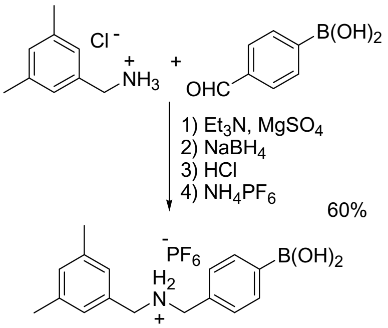
doi:10.1016/j.tetlet.2008.03.106



1·PF$_6$

Scheme 2.

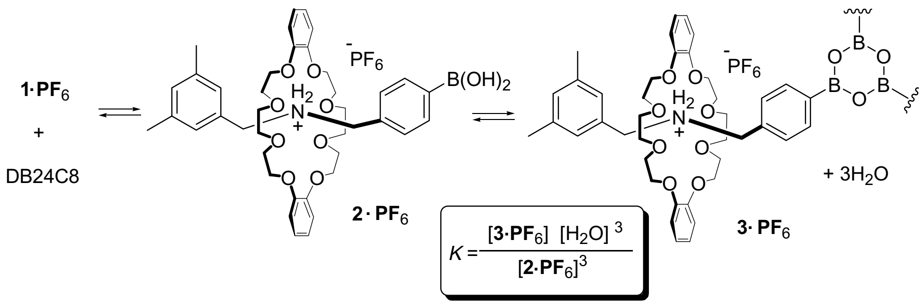
followed by protonation and counterion exchange, produced the ammonium salt **1**·PF$_6$, which possessed a bulky aryl group at one end and a boronyl group at the other (Scheme 2).

In an initial experiment using chloroform as the solvent, we validated the feasibility of forming the boroxine from the [2]pseudorotaxane formed from the dialkylammonium ion **1**·PF$_6$ and dibenzo[24]crown-8 (DB24C8). We suspected that [2]pseudorotaxane **2**·PF$_6$ formed in solution because the dialkylammonium salt **1**·PF$_6$ is insoluble in chloroform in the absence of the crown ether; that is, **1**·PF$_6$ was solubilised upon complexation with DB24C8. The cyclotrimerization of [2]pseudorotaxane **2**·PF$_6$ proceeded (Scheme 3) while sonicating a mixture of **1**·PF$_6$ and an excess of DB24C8 in $CDCl_3$ for four hours until a disappearance of the solid. We confirmed the structures of **2**·PF$_6$ and **3**·PF$_6$ from spectroscopic and analytical data. Figure 1a displays the ^{1}H NMR spectrum of a mixture of **1**·PF$_6$ and DB24C8. By comparing the spectrum of DB24C8 with that of the mixture, we observe two sets of resonances, which we assigned to the [2]pseudorotaxane **2**·PF$_6$ and [4]rotaxane **3**·PF$_6$. The CH_2N protons of the dumbbell-shaped units appear at 4.36 and 4.63 ppm for [2]pseudorotaxane **2**·PF$_6$ and at 4.48 and 4.75 ppm for [4]rotaxane **3**·PF$_6$, with the corresponding aromatic protons at 7.39 and 7.76 ppm for **2**·PF$_6$ and 7.59 and 8.14 ppm for **3**·PF$_6$. The resonances of the aliphatic and aromatic protons of the DB24C8 components appear at 3.30–3.67 and 6.50–6.68 ppm, respectively. These chemical shift assignments are consistent with those reported previously for structurally similar systems.[2d,e,3c,5b,c,7] To assign specific resonances to the protons of [2]pseudorotaxane **2**·PF$_6$ and [4]rotaxane **3**·PF$_6$, we recorded a ^{1}H NMR spectrum of the mixture in the presence of an excess of D_2O (Fig. 1c), which hydrolyzed the boroxine. The ESI mass spectrum of a mixture of **1**·PF$_6$ and DB24C8 in dichloromethane confirmed the presence of the [2]pseudorotaxane and [4]rotaxane structures, which were represented by peaks for their $[M{-}PF_6^{-}]^+$ ions at *m*/*z* 718 and 2391, respectively.[10]

Next, we calculated the equilibrium constant (K_{eq}) for boroxine formation ($3 \times \mathbf{2}{\cdot}PF_6 \leftrightarrows \mathbf{3}{\cdot}PF_6 + 3H_2O$)[11] through the integration of the signals for **2**·PF$_6$, **3**·PF$_6$, water, and an internal standard (trimethyl 1,3,5-benzenetricarboxylate) in ^{1}H NMR spectra recorded at 10–35 °C. A plot of ΔG versus temperature for the equilibria (boroxine formation) yielded a straight line (Fig. 2), from which we determined the enthalpic ($\Delta H = 2.53 \pm 0.63$ kJ/mol) and entropic ($\Delta S = 132 \pm 2$ J/mol K) parameters. Consistent with the findings reported previously, the formation of this boroxine is an entropically driven process because of the release of three free water molecules into the bulk solvent.[9,12,13]

It has been reported that the presence of an electron-donating group in the *para* position of the phenyl ring increases the thermodynamic stability of triphenylboroxine derivatives toward hydrolysis;[9] computational studies support this empirical finding.[11,14] The equilibrium constant (K_{eq}: 1.32 ± 0.33 M) for the formation of **3**·PF$_6$ from **2**·PF$_6$ is, however, similar to that for the cyclotrimerization of *p*-methoxyphenylboronic acid, which possesses such an electron-donating group (for examples of K_{eq} value, *p*-methoxyphenylboronic acid: 1.40 M, *p*-tolylboronic acid: 0.45 M).[15] We suspect that several factors are responsible for this phenomenon: (1) the benzene rings of the DB24C8 and dumbbell-shaped units interact to enhance the electron density of the aromatic rings connected to the boroxine core; (2) hydrogen bonds to the crown ether unit weaken the electron-withdrawing properties of the $CH_2NH_2^+$ moieties; (3) the DB24C8 units provide steric stabilization against the hydrolysis of the boroxine.

In summary, we have constructed a C_3-symmetric [4]rotaxane **3**·PF$_6$ using two reversible processes: [2]pseudo-



Scheme 3.

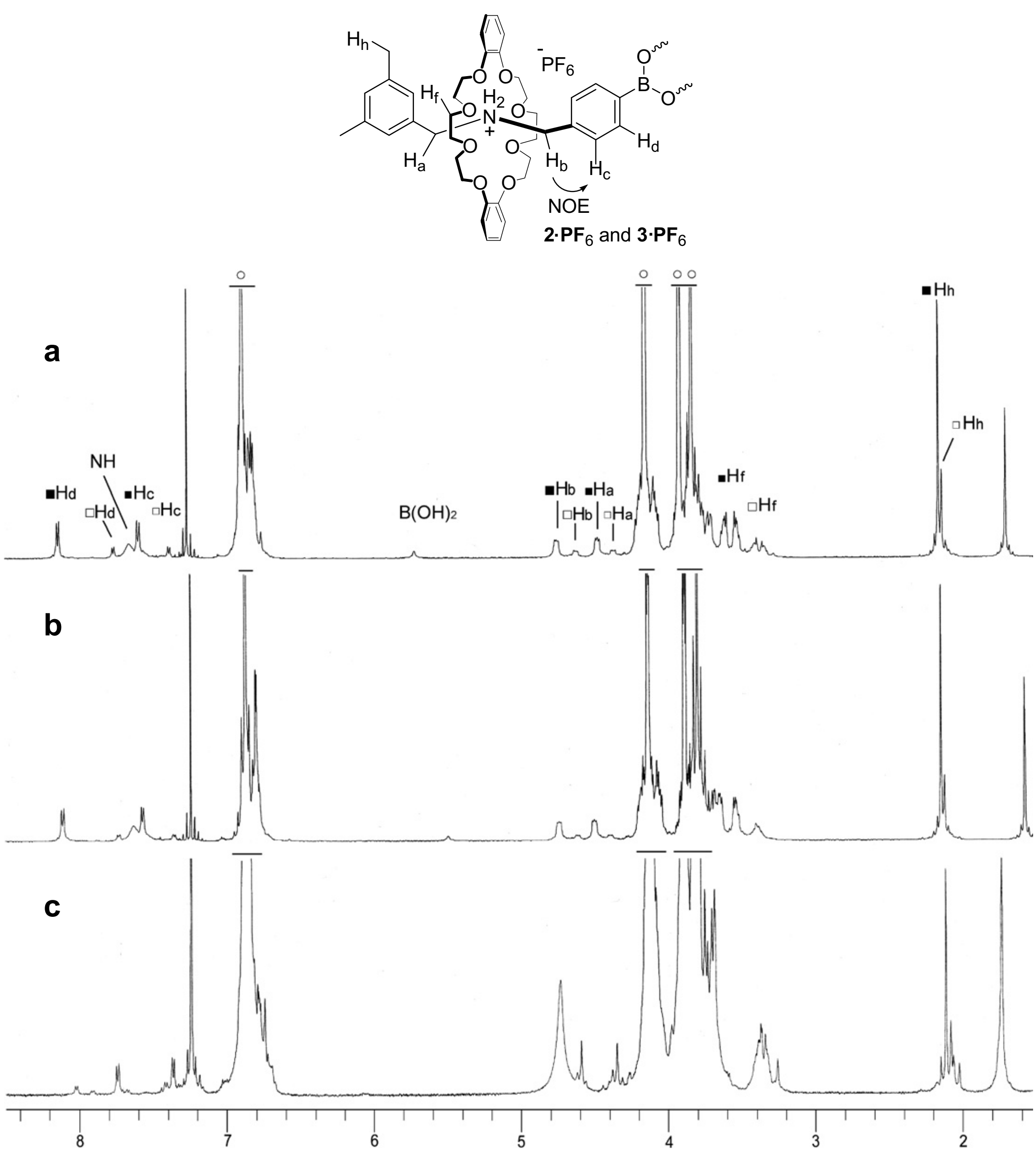


Fig. 1. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of a mixture of the boronic acid **1**·PF$_6$ (10 mM) and DB24C8 (30 mM) at (a) 25 and (b) 45 °C and (c) in the presence of an excess of D_2O at 25 °C. ■: [4]rotaxane **3**·PF$_6$; □: [2]pseudorotaxane **2**·PF$_6$; ○: DB24C8.

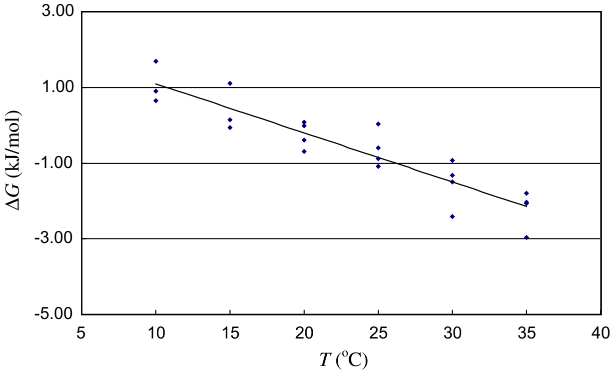


Fig. 2. Plots of ΔG versus temperature for boroxine formation. The experiments were performed four times. Concentration data were obtained from integration of the appropriate signals for **2**·PF$_6$, **3**·PF$_6$, water, and the internal standard (trimethyl 1,3,5-benzenetricarboxylate) in the ^{1}H NMR spectra recorded in $CDCl_3$.

rotaxane formation mediated by hydrogen bonding between DB24C8 and a boronic acid-functionalized dialkylammonium ion and boroxine formation through cyclotrimerization of three boronic acid units. Variable-temperature NMR spectroscopy experiments provided us with the thermodynamic parameters for the boroxine formation process; it appears that the structure of the C_3-symmetric [4]rotaxane **3**·PF$_6$ stabilizes the boroxine core against hydrolysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.106.

References and notes

1. For selected reviews, see: (a) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952; (b) Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463; (c) Otto, S.; Furlan, R. L. E.; Sanders, J. K. M. *Curr. Opin. Chem. Biol.* **2002**, *6*, 321–327; (d) Karan, C.; Miller, B. L. *Drug Discovery Today* **2000**, *5*, 67–75.
2. (a) Wisner, J. A.; Beer, P. D.; Drew, M. G. B.; Sambrook, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 12469–12476; (b) Kilbinger, A. F. M.; Cantrill, S. J.; Waltman, A. W.; Day, M. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 3281–3285; (c) Iwamoto, H.; Itoh, K.; Nagamiya, H.; Fukazawa, Y. *Tetrahedron Lett.* **2003**, *44*, 5773–5776; (d) Hou, H.; Leung, K. C.-F.; Lanari, D.; Nelson, A.; Stoddart, J. F.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 15358–15359; (e) Guidry, E. N.; Li, J.; Stoddart, J. F.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 8944–8945; (f) Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599–1600; (g) Wang, L.; Vysotsky, M. O.; Bogdan, A.; Bolte, M.; Böhmer, V. *Science* **2004**, *304*, 1312–1314.
3. (a) Horn, M.; Ihringer, J.; Glink, P. T.; Stoddart, J. F. *Chem. Eur. J.* **2003**, *9*, 4046–4054; (b) Leung, K. C.-F.; Aricó, F.; Cantrill, S. J.; Stoddart, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5808–5810; (c) Cantrill, S. J.; Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1363–1366; (d) Rowan, S. J.; Stoddart, J. F. *Org. Lett.* **1999**, *1*, 1913–1916; (e) Glink, P. T.; Oliva, A. I.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1870–1875; (f) Aricó, F.; Chang, T.; Cantrill, S. J.; Khan, S. I.; Stoddart, J. F. *Chem. Eur. J.* **2005**, *11*, 4655–4666; (g) Hutin, M.; Schalley, C. A.; Bernardinelli, G.; Nitschke, J. R. *Chem. Eur. J.* **2006**, *12*, 4069–4076; (h) Kawai, H.; Umehara, T.; Fujiwara, K.; Tsuji, T.; Suzuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4281–4286.
4. Lam, R. T. S.; Belenguer, A.; Roberts, S. L.; Naumann, C.; Jarrosson, T.; Otto, S.; Sanders, J. K. M. *Science* **2005**, *308*, 667–669.
5. (a) Kolchinski, A. G.; Alcock, N. W.; Roesner, R. A.; Busch, D. H. *Chem. Commun.* **1998**, 1437–1438; (b) Furusho, Y.; Hasegawa, T.; Tsuboi, A.; Kihara, N.; Takata, T. *Chem. Lett.* **2000**, *29*, 18–19; (c) Oku, T.; Furusho, T.; Takata, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 966–969.
6. Fuchs, B.; Nelson, A.; Star, A.; Stoddart, J. F.; Vidal, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 4220–4224.
7. Furusho, Y.; Oku, T.; Rajkumar, G. A.; Takata, T. *Chem. Lett.* **2004**, *33*, 52–53.
8. For examples, see: (a) Fujita, M.; Fujita, N.; Ogura, K.; Yamaguchi, K. *Nature* **1999**, *400*, 52–55; (b) Hunter, C. A.; Low, C. M. R.; Packer, M. J.; Spey, S. E.; Vinter, J. G.; Vysotsky, M. O.; Zonta, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2678–2682; (c) Chang, S.-Y.; Choi, J. S.; Jeong, K.-S. *Chem. Eur. J.* **2001**, *7*, 2687–2697; (d) McArdle, C. P.; Van, S.; Jennings, M. C.; Puddephatt, R. J. *J. Am. Chem. Soc.* **2002**, *124*, 3959–3965; (e) Park, K.-M.; Kim, S.-Y.; Heo, J.; Whang, D.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2002**, *124*, 2140–2147; (f) Blanco, V.; Chas, M.; Abella, D.; Peinador, C.; Quintela, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 13978–13986.
9. (a) Tokunaga, Y.; Ueno, H.; Shimomura, Y.; Seo, T. *Heterocycles* **2002**, *57*, 787–790; (b) Tokunaga, Y.; Ueno, H.; Shimomura, Y. *Heterocycles* **2007**, *74*, 219–223.
10. Peaks for $[M-2PF_6^-]^{2+}$ and $[M-3PF_6^-]^{3+}$ ions of **3**·PF_6 were observed at *m*/*z* 1123 and 700, respectively. See supplementary data.
11. The equilibrium process includes many spices. We simplify the equilibrium, because these intermediates are not stable to detect, see: Kua, J.; Gyselbrecht, C. R. *J. Phys. Chem. A* **2007**, *111*, 4759–4766.
12. The entropy value is larger than those of usual boroxines. Although these results are unclear as yet, it seems that bulky functionality of **3**·PF_6 disturbs the solvation and/or hydration.
13. Molecular sieves was used to shift the equilibrium in favour of the [4]rotaxane. However, we could not isolate the [4]rotaxane until now, because molecular sieves may absorb HPF_6 from the ammonium salt.
14. Kua, J.; Iovine, P. M. *J. Phys. Chem. A* **2005**, *109*, 8938–8943.
15. We tried to compare the stability of boroxine **3**·PF_6 with that of boroxine from ammonium salts **1**·PF_6 using acetonitrile as a solvent, directly. However, any signals based on [4]rotaxane **3**·PF_6 were observed in the ^{1}H NMR spectrum of a mixture of DB24C8 and **1**·PF_6 at room temperature.