ORGANIC LETTERS

2010
Vol. 12, No. 4
712−715

Selective Transformation of a Crown Ether/*sec*-Ammonium Salt-Type Rotaxane to *N*-Alkylated Rotaxanes

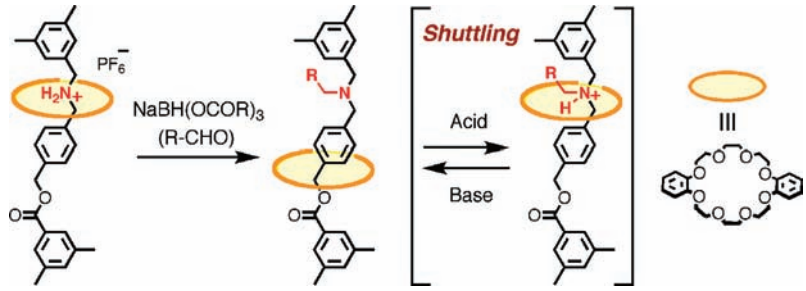
Sakiko Suzuki, Kazuko Nakazono, and Toshikazu Takata*

Department of Organic and Polymeric Materials, Tokyo Institute of Technology, Ookayama 2-12-1, Meguro-ku, Tokyo 152-8552, Japan

takata.t.ab@m.titech.ac.jp

Received November 25, 2009

ABSTRACT



Versatile functionalization of a crown ether/*sec*-ammonium salt-type rotaxane was accomplished. The rotaxane underwent reductive *N*-alkylation with sodium tri(acyloxy)borohydride or sodium tri(acyloxy)borohydride/arbitrary aldehyde in excellent yields. Structural switching based on reversible *tert*-ammonium/*tert*-amine conversion by acid and base was demonstrated as a pH-controlled molecular shuttle.

Functionalization or modification of interlocked molecules such as rotaxanes and catenanes, which have high mobility of components, is really important for the development of sophisticated supramolecular devices and materials.[1] *sec*-Ammonium/crown ether-type rotaxanes are the most suitable rotaxanes or scaffolds for functionalization because of their easy synthesis, high synthetic yield, and easy modification of their components.[2] These rotaxanes can be synthesized utilizing the strong interaction between the *sec*-ammonium salt axle and the crown ether wheel; direct functionalization using the ammonium nitrogen as the base point is considered the most convenient protocol. However, in addition to neutralizing the ammonium moiety, introducing a functional group onto the ammonium nitrogen of the rotaxanes has been a challenge, and it has caused a delay in the development of applications of rotaxanes. N-Functionalization of rotaxanes first only involved N-acylation;[3] subsequently, we successfully performed selective N-methylation of *sec*-ammonium salt/crown ether-type rotaxane.[4] We found that tertiarization of nitrogen facilitates the neutralization of ammonium rotaxane, and thus expands the possible applications of rotaxanes. This successful functionalization, however, is limited to methylation. The development of versatile functionalization methods for *sec*-ammonium salt/crown ether-

(1) For reviews, see: (a) Schalley, C. A.; Wellandt, T.; Brueggmann, J.; Vögtle, F. *Top. Curr. Chem.* **2005**, *248*, 141–200. (b) Takata, T. *Bottom-up Nanofabrication: Supramolecules, Self-Assemblies, and Organized Films*; Ariga, K., Nalwa, H. S., Eds.; American Scientific Publishers: Los Angels, CA, 2009; Chapter 12, pp 311−329. (c) Fyfe, M. C. T.; Stoddart, J. F.; Williams, D. J. *Struct. Chem.* **1999**, *10*, 243–259. (d) Glink, P. T.; Stoddart, J. F. *NATO ASI Ser. C: Math. Phys. Sci.* **1997**, *499*, 609–622. (e) Balzani, V.; Credi, A.; Stoddart, J. F. *Molecular Devices and Machines: A Journey into the Nanoworld*; Wiley-VCH Verlag GmbH Co. KGaA: Weinheim, 2003.

(2) (a) Chitta, R.; D'Souza, F. *J. Mater. Chem.* **2008**, *18*, 1440–1471. (b) Takata, T. *Polym. J.* **2006**, *38*, 1–20. (c) Takata, T.; Kihara, N.; Furusho, Y. *Adv. Polym. Sci.* **2004**, *171*, 1–75. (d) El-Khouly, M. E.; Ito, O.; Smith, P. M.; D'Souza, F. *J. Photochem. Photobiol. C: Photochem. Rev.* **2004**, *5*, 79–104. (e) Gunter, M. *Eur. J. Org. Chem.* **2004**, *8*, 1655–1673.

(3) (a) Kihara, N.; Tachibana, Y.; Takata, T. *Chem. Lett.* **1999**, *28*, 506–507. (b) Tachibana, Y.; Kawasaki, H.; Kihara, N.; Takata, T. *J. Org. Chem.* **2006**, *71*, 5093–5104.

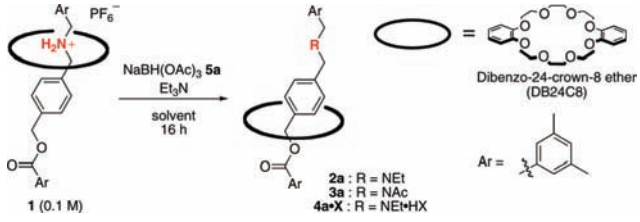
(4) Nakazono, K.; Kuwata, S.; Takata, T. *Tetrahedron Lett.* **2008**, *49*, 2397–2401.

10.1021/ol902719m
Published on Web 01/20/2010

type rotaxanes is, therefore, necessary to enhance the applicability of rotaxanes. Recently, we have efficiently introduced a variety of alkyl groups to the ammonium nitrogen of a rotaxane. In this paper, we report the synthesis of *tertiary*-amine-type rotaxanes by direct reductive N-alkylation using tri(acyloxy)borohydride or aldehyde/tri(acyloxy)borohydride. The acidification/neutralization-based shuttling behavior of the resulting *tert*-amine-type rotaxane is also described as an example of its application.

[2]Rotaxane **1** has been synthesized as a standard substrate for N-functionalization.[5] We first attempted to N-functionalize **1** through the representative reductive N-alkylation method[6] using an aliphatic aldehyde and $NaBH_3CN$ as the typical reducing agent in refluxing THF. However, no reaction took place but **1** was recovered. Gribble et al. and Liberatore et al. reported reductive N-ethylations with a mixture of $NaBH_4$ and acetic acid,[7] where $NaBH(OAc)_3$ (**5a**) generates acetaldehyde *in situ* by self-reduction with a *sec*-amine to afford N-ethlylated amine via the reduction of an iminium intermediate. Therefore, we changed the reagent to $NaBH(OAc)_3$ (**5a**), which has a reducing ability similar to $NaBH_3CN$. The results of the reductive N-ethylation of **1** to **2a** with **5a** are summarized in Table 1. A mixture of **1** and excess **5a** (15 equiv) was heated in a solvent for 16 h. The starting rotaxane **1** was completely consumed in refluxing THF, but N-acetylated rotaxane (**3a**) was quantitatively obtained without the formation of **2a** (Entry 1). Under the conditions, the N-acylation is presumed to occur with $NaB(OCOR)_4$ or $B(OCOR)_3$, as reported in the N-acylation of amines with $NaBH_4$/RCOOH.[7b−d]

Table 1. N-Ethylation of Rotaxane **1**



entry[a]	solvent	**5a** (equiv)	Et_3N (equiv)	temp (°C)	convn[b] (%)	**2a** (**3a**) (%)
1	THF	15	−	reflux	100	0 (100)
2	THF	15	20	reflux	78	78 (0)
3	THF	15[c]	−	reflux	100	100 (0)
4	dioxane	15	20	reflux	100	33 (67)
5	CPME	15	20	reflux	100	10 (90)
6	CPME	15	20	70	62	62 (0)
7	NMP	15	20	50	39	39 (0)
8	NMP	15	20	70	100	100 (0)
9	NMP	15	−	70	100	100 (0)
10	NMP	5	20	70	10	10 (0)

[a] General condition: **1**:50 μmol, solvent: 0.5 mL. [b] Calculated by ^{1}H NMR after alumina short column chromatography. [c] $Me_4NBH(OAc)_3$ was used instead of **5a**.

We added triethylamine (TEA) as a base to the reaction system for activating stable rotaxane **1** and/or accelerating the reaction, since TEA is reported to be more effective than strong bases such as DBU or Hunig's base in the N-acylation reaction.[3] In fact, the addition of excess TEA (20 equiv) resulted in the selective formation of the desired products N-ethylated rotaxane **2a** (78% yield), a free *tert*-amine, which was isolated after short column chromatography on alumina (Entry 2). To clarify the effect of TEA, $Me_4NBH(OAc)_3$ (TABH) was used instead of **5a** in the *absence* of TEA. With TABH, **2a** was selectively obtained in 100% yield even without TEA (Entry 3). From the results, TEA plays a role in not only deprotonating the ammonium moiety of **1** but also activating **5a** as a ligand coordinating to it.

To understand the details of the reaction (Entry 2), we observed ^{1}H NMR spectra of the crude product, which showed the initial formation of *tert*-ammonium salt-type rotaxane **2a/HX (= 4a•X)**, but not **2a**. Strong P−F bond absorptions observed in the IR spectrum of the product clearly indicated the formation of **4a•PF$_6$** even in the presence of excess TEA. Alumina column chromatographic purification resulted in the successful isolation of neutral rotaxane **2a**. The isolation of pure **2a** without any salt structure might be attributed to the efficient removal of HPF_6 in the successive heterogeneous chromatographic system on the basic stationary phase.

The effect of polar aprotic solvents such as 1,4-dioxane and cyclopentyl methyl ether (CPME) was investigated. Whereas these solvents accelerated the N-acetylation to **3a** at high temperatures (Entries 4−5), the N-ethylation to **2a** proceeded selectively at lower temperatures (70 °C) in CPME, although the reaction was sluggish (Entry 6). The use of a more polar basic solvent *N*-methylpyrrolidone(NMP) gave excellent results (Entries 7−10): no N-acetylation took place. Furthermore, the use of NMP yielded **2a** in 100% conversion even in the absence of TEA (Entry 9). In this case, NMP most likely disturbs the strong hydrogen bonding between the *sec*-ammonium salt axle and the crown ether wheel of **1** to facilitate the neutralization of **1** and increase the ratio of "free" *sec*-amine in the equilibrium. It is concluded that the optimum condition involves excess **5a** and TEA in NMP at 70 °C, probably accelerating the reaction by the synergistic effect of TEA and **5a**.

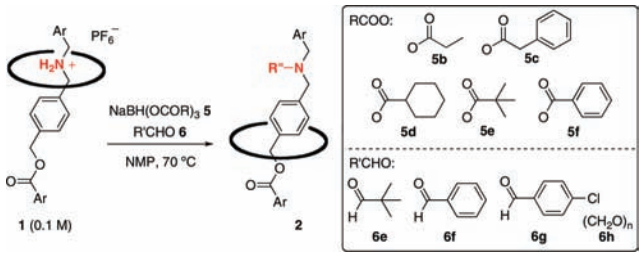
The introduction of various alkyl groups to **1** was investigated under the optimized condition, and the results are summarized in Table 2. Several $NaBH(OCOR)_3$ (**5**) used here were prepared from $NaBH_4$ and the corresponding carboxylic acids according to a reported method.[7b] Inspection of the data of Table 2 reveals that linear alkyl chains such as propyl and phenethyl groups can be introduced on the

(5) (a) Kawasaki, H.; Kihara, N.; Takata, T. *Chem. Lett.* **1999**, *28*, 105–106. (b) Makita, Y.; Kihara, N.; Takata, T. *Chem. Lett.* **2007**, *36*, 102–103.

(6) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904. (b) Hutchins, R. O.; Natale, N. R. *Org. Prep. Proc. Int.* **1979**, *11*, 201–246. (c) Lane, C. F. *Synthesis* **1975**, *3*, 135–146.

(7) (a) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proc. Int.* **1985**, *17*, 317–384. (b) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F. M. *J. Org. Chem.* **1975**, *40*, 3453–3456. (c) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812–7814. (d) Pelter, A.; Levitt, T. E. *Tetrahedron* **1970**, *26*, 1899–1908. (e) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971–1031.

Table 2. N-Alkylation of Rotaxane **1**



entry	conditions [a]			product		NMR
	5 (equiv)	6 (equiv)	time (h)	R"	2	yield (%)
1	**5b** (15)	None	16	C_3H_7	**2b**	100
2	**5c** (15)	None	16	C_2H_5Ph	**2c**	38
3	**5d** (15)	None	40	CH_2cHx	**2d**	100
4	**5e** (15)	None	72	CH_2t-Bu	**2e**	26
5	**5e** (5.0)	**6e** (10)	48		**2e**	25
6	**5f** (15)	None	16	Bn	**2f**	0
7	**5f** (15)	**6f** (5.0)	16		**2f**	67
8[b]	**5f** (15)	**6f** (5.0)	16		**2f**	8
9	**5f** (5.0)	**6f** (10)	16		**2f**	100
10	**5a** (5.0)	**6f** (10)	16		**2f**	100
11	**5a** (15)	**6f** (5.0)	16		**2f** **2a**	17 83
12	**5f** (5.0)	**6g** (20)	16	*p*-ClBn	**2g**	79
13	**5a** (5.0)	**6h** (10)	16	Me	**2h**	100

[a] General condition: **1**: 50 μmol, TEA: 1.0 mmol, NMP: 0.5 mL. [b] Reaction in the absence of TEA.

nitrogen atom of **1** simply by reactions with **5b** and **5c**, respectively, although N-phenethylation to **2c** was slow (Entries 1−2). Cyclohexyl and neopentyl groups as branched alkyl ones were also introduced in prolonged reaction times, although the introduction of the neopentyl group was insufficient within 72 h, probably because of the steric hindrance (Entries 3−4). The addition of pivalaldehyde had little effect even with further prolongation of time (Entry 5).

The introduction of aromatic groups was examined. The reaction of **1** with $NaBH(OCOPh)_3$ (**5f**) in NMP at 70 °C afforded no *N*-benzylated product **2f** (Entry 6). Since the reducing agent **5f** did not seem active enough to produce "benzaldehyde" *in situ* by self-reduction, benzaldehyde (**6f**) was independently added to the system involving **5f**. The addition of **6f** (5 equiv) was very effective in yielding **2f** (67%) (Entry 7). Since the reaction without TEA significantly decreased the yield of **2f** (Entry 8), we concluded that TEA activates the reducing agent **5f**. An excess benzaldehyde effectively increased the yield of **2f** even with less **5f** (Entry 9). Meanwhile, the combination of **5a**, instead of **5f**, and benzaldehyde also resulted in 100% yield of **2f**; however, a large excess **5a** compared to aldehyde gave a mixture of **2a** and **2f** (Entries 10−11). From these results, aromatic carboxylic acid-based reducing agents $NaBH(OCOAr)_3$, like **5f**, cannot undergo self-reduction to yield ArCHO, but can selectively reduce the iminium intermediate generated from the added ArCHO and *sec*-ammonium roaxane **1**. In fact, the *p*-chlorobenzyl group could be introduced to **1** to afford **2g** in 79% yield by treating **1** with **5f** and *p*-chlorobenzaldehyde (Entry 12). Furthermore, when paraformaldehyde (**6h**) was used along with **5a**, *N*-methylated rotaxane **2h** was selectively obtained in 100% yield (Entry 13). These results reveal that the self-reduction of $NaBH(OCOR)_3$ **5** yielding aldehyde (R-CHO) is much slower than the formation of the iminium intermediate. Thus, we conclude that a variety of N-alkylations of unusually stabilized *sec*-ammonium salt/crown ether-type rotaxanes like **1** can be achieved with **5** (and **6**) under appropriate conditions.

The ^{1}H NMR spectra of *N*-propylated *tert*-amine-type rotaxane **2b** is shown in Figure 1b, which well supports the proposed structure. Signal assignment was easily carried out, as indicated in the spectra of both **2b** and **1**. In addition to the three singals of the propyl group, two sets of aminobenzylic proton signals ($H_{d,e}$) were upfield-shifted by approximately 1 ppm as a couple of singlets by the conversion of **1** to **2b**. Furthermore, the oxybenzylic proton signal (H_h) of **2b** shifted downfield by 0.7 ppm compared to **1**; this shift was in agreement with the previous observation that the signal is downfield-shifted due to the deshielding effect of the benzo moiety of DB24C8 in concert with the movement of DB24C8 to the ester moiety.[3,4] This result is also consistent with that of X-ray crystal structure analysis of *N*-methylated *tert*-amine-type rotaxane **2h** in which DB24C8 is located at the oxybenzyl moiety of the axle.[4] Both the downfield shift of the aromatic protons and the upfield shift of the methyl group of the end-cap groups can be explained by the effect of the movement of DB24C8. Other rotaxanes **2** showed similar spectral characteristics assignable to their structures.

Since we had access to "free" amine-type rotaxanes **2**, we examined their most important dynamic behavior, that is, the acid/base-dependent movement of the components using **2b** as an example (Figure 1). First, **2b** was treated with a strong acid HPF_6 (65 wt% aq.) The structural change caused by the formation of *tert*-ammonium moiety was confirmed by the ^{1}H NMR spectral change from **2b** to **4b•PF$_6$**, as shown in Figure 1b and c. The oxybenzylic proton signal (H_h) is the most sensitive index to estimate the position of the DB24C8 moiety, as mentioned above. In fact, the signal was upfield-shifted to 5.3 ppm, just correspondeding to that of *sec*-ammonium salt-type rotaxane **1** (Figure 1a). Two benzylic proton signals around the ammonium moiety ($H_{d,e}$) were downfield-shifted due to the emergence of the cationic character of the nitrogen atom and the deshielding effect of DB24C8. Other proton signals were well assignable to **4b•PF$_6$**, although most signals were split by the generation of the chiral center at the nitrogen atom.

Meanwhile, **4b•PF$_6$** was treated with Na_2CO_3 (5% aq.). The spectrum of the isolated product showed the quantitative

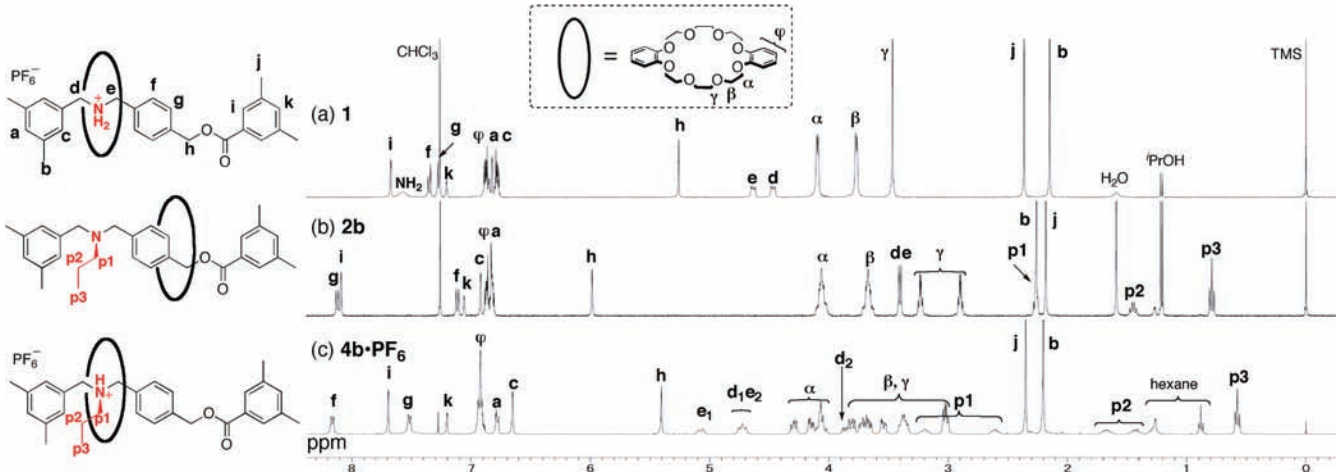
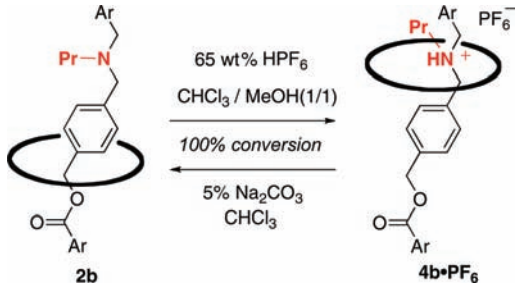


Figure 1. ^{1}H NMR spectra of (a) *sec*-ammonium salt-type rotaxane **1**, (b) *tert*-amine-type rotaxane **2b**, and (c) *tert*-ammonium salt-type rotaxane **4b•PF$_6$** (400 MHz, $CDCl_3$, 298 K).

formation of the original *tert*-amine-type rotaxane **2b**. These transformations by the alternating addition of acid and base occurred repeatedly. Thus, we could confirm the so-called "switching" behavior of rotaxane triggered by acidification/neutralization using a "free" amine-type simple rotaxane capable of being acidified (Scheme 1). Stoddart et al. reported

Scheme 1. Shuttling Behavior of [2]Rotaxane **2b**/**4b-PF$_6$** based on the Treatment with Acid/Base



a pH controling system of rotaxane of which axle component involved two cationic sites such as *sec*-ammonium salt and paraquat groups toward DB24C8.[8] In this system, the *sec*-ammonium salt can be neutralized with diisopropylethylamine, because the paraquat group acts as a metastable cationic station to release DB24C8 from the *sec*-ammonium salt moiety. Namely, the switching in crown ether-based rotaxanes generally needs the ionic character on the axle component. The present system that involves no ionic station can threfore be regarded as a novel ionic/nonionic switching system functioning by easy treatment with simple bases and acids. Thus, the development of this switching system enhances the potential applicability of rotaxanes. Stoddart et al. have recently reported a single station [2]catenane called a push-button molecular switch.[9] Accordingly, the present *tert*-amine/ammonium conversion system may be regarded as a new molecular switch similar to that.

In conclusion, here we report a general protocol for the direct synthesis of N-functionalized "free" *tert*-amine-type rotaxanes by N-alkylation of *sec*-ammonium salt-type rotaxanes through modified reductive N-alkylation using $NaBH(OCOR)_3$, TEA, and/or the corresponding aldehyde. Even the bulky neopentyl group could be introduced at the nitrogen atom. The present N-alkylation method is superior to other modification methods of rotaxanes such as N-acylation because further N-modification is possible. A novel pH controllable molecular shuttle system was conveniently constructed using the nonionic *tert*-amine-type rotaxane thus obtained. This work is expected to promote the construction of sophisticated supramolecular systems, devices, polymeric materials, and so on.

Acknowledgment. We thank Professor Michinori Suginome of Kyoto University for helpful discussions and comments. This work was financially supported by a Grant-in-Aid for Scientific Research from MEXT, Japan (Nos. 18064008 and 19655013), and K.N. thanks the Global COE Program (Education and Research Program for Material Innovation), MEXT, Japan for financial support.

Supporting Information Available: Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902719M

(8) (a) Ashton, P. R.; Ballardini, R.; Balzani, V.; Baxter, I.; Credi, A.; Fyfe, M. C. T.; Gandolfi, M. T.; Gómez-López, M.; Martínez-Díaz, M.-V.; Piersanti, A.; Spencer, N.; Stoddart, J. F.; Venturi, M.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 11932–11942. (b) Cao, J.; Fyfe, M. C. T.; Stoddart, J. F.; Cousins, G. R. L.; Glink, P. T. *J. Org. Chem.* **2000**, *65*, 1937–1946. (c) Badjić, J. D.; Balzani, V.; Credi, A.; Silvi, S.; Stoddart, J. F. *Science* **2004**, *303*, 1845–1849. (d) Garaudée, S.; Silvi, S.; Venturi, M.; Credi, A.; Flood, A. H.; Stoddart, J. F. *ChemPhysChem* **2005**, *6*, 2145–2152.

(9) Spruell, J. M.; Paxton, W. F.; Olsen, J.-C.; Benítez, D.; Tkatchouk, E.; Stern, C. L.; Trabolsi, A.; Friedman, D. C.; Goddard, W. A., III; Stoddart, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11571–11580.