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COMMUNICATION

Upper-Rim Functionalization and Supramolecular Polymerization of a Feet-to-Feet-Connected Biscavitand

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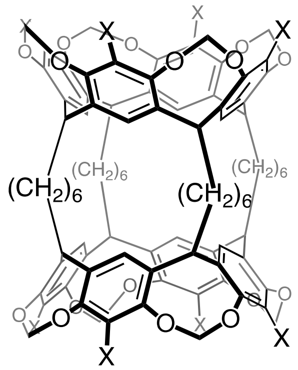
An octaiodobiscavitand was synthesized by an aromatic Finkelstein iodination reaction in good yield. Sonogashira and Suzuki coupling reactions of the octaiodobiscavitand gave rise to upper-rim-functionalized biscavitands that self-assembled to form the supramolecular polymer in the solid state.

A cavitand is readily prepared from a resorcinarene by the introduction of interatomic bridges on the upper rim. The rigid bowl-shaped structures enforce the cavities that accommodate guest molecules such as organic and cation compounds.[1, 2] Guest molecules inside the cavities are protected, resulting in their potential applications in areas such as reactive intermediate isolation,[3, 4] molecular sensors[5, 6] and molecular catalysis by encapsulation.[7-9] These fascinating functions rely on the shape, size and dimension of the cavity. Deepening the cavity expands its possible applications as a catalyst and a molecular container. Therefore, the upper-rim functionalization of a cavitand to deepen its cavity has been actively studied. Carbon-carbon bond forming reactions, such as the Suzuki–Miyaura reaction,[10-12] the Sonogashira reaction,[13-15] and other reactions,[16] have often been employed to introduce functional groups onto the upper rim of a cavitand. A tetrabromocavitand,[17] a teraiodocavitand,[18, 19] and a tetraboronic pinacolyl ester cavitand[20, 21] have already been reported as convenient scaffolds for the construction of deepened cavities by palladium-mediated carbon-carbon forming coupling reactions.

During our study on the host-guest chemistry of cavitands,[22-24] bisresorcinarenes possessing two resorcinarenes linked with four alkyl chains in a feet-to-feet fashion were introduced.[25] The interaromatic bridges yielded a biscavitand, showing allosteric guest binding.[26-28] To expand the biscavitand chemistry, upper rim functionalization is required to deepen the cavities through carbon-carbon bond forming reactions. Octaiodobiscavitand **1** can deepen its cavities through the introduction of various substituents by means of carbon-carbon bond forming reactions. Herein, we report the synthesis of octaiodide-functionalized biscavitand **1**, which is converted to a cavity-extended biscavitand through palladium-catalyzed cross-coupling reactions, and a supramolecular polymer formed by self-assembly of **4** in the solid state (Fig. 1).



1: X = I
2: X = Br
3: X = Ph
4: X = C≡C−Ph

Fig. 1 Structure of biscavitands **1**–**4**.

The synthesis of octaiodobiscavitand **1** is outlined in Scheme 1. The iodination reaction of **5** using common iodination reactants such as N-iodosuccimide,[29] N-iodosaccharin,[30] and iodine[31] was not successful. Octabromobisresorcinarene **6** was easily prepared through the reaction of **5** with N-bromosuccimide (NBS). The interaromatic bridges of **6** were constructed through the reaction with bromochloromethane in the presence of cesium carbonate. Octabromobiscavitand **2** was obtained in fairly good yield (Scheme 1).[32] The bromo groups were converted to iodo groups to improve the reactivity for the cross-coupling reactions. The iodination reaction of **2** was first examined through halogen-lithium exchange reactions.[17,33]

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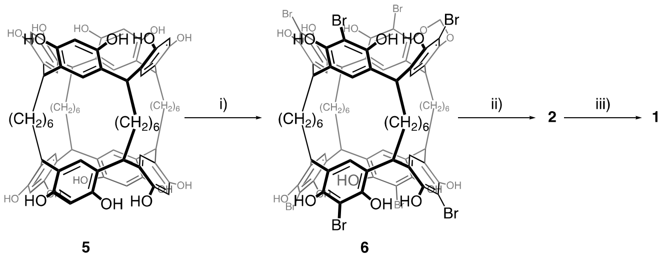
However, the poor solubility of **2** in THF hampered formation of the octalithiated biscavitand.



Scheme 1. Synthesis of an octaiodobiscavitand. Reaction conditions: i) NBS, 2-butanone, 79%; ii) bromochloromethane, Cs_2CO_3, DMSO, 70%; iii) CuI, KI, DMI.

Table 1. Aromatic Finkelstein Iodination of biscavitand **2**.

Entry	Solv.	Temp. (°C)	Reaction time	Conversion (%) (X = Br, H, I)		
				Br	I	H
1	DMF	145 °C	3 h	88	12	0
2		145 °C	60 h	0	80	20
3	HMPA	145 °C	3 h	83	17	0
4		145 °C	60 h	0	81	19
5	DMI	200 °C	3 h	0	70	30
6		170 °C	3 h	19	65	16
7		145 °C	3 h	80	20	0
8		145 °C	12 h	47	53	0
9		145 °C	60 h	0	100 (81[a])	0
10		145 °C	120 h	0	49	51

[a] Isolation yield. All conversions were determined by the deconvolution of the ^1H NMR spectra of the reaction mixtures (Figs. S6–11, ESI†).

An aromatic Finkelstein iodination (AFI) reaction offers the facile preparation of aromatic iodides from corresponding aromatic bromides and chlorides with copper halide salts.[34-36] **2** was used to find reaction conditions suitable for iodination with a large excess of copper iodide (CuI) and potassium iodide (KI) (Scheme 1). When the reactions were carried out at 145 °C for 3 h in DMF and in HMPA (Table 1, entries 1 and 3), the aromatic protons Ha were shifted slightly downfield, which was indicative of the conversion of the bromo groups to the iodo groups (Fig. 2a,b). Given that the eight iodo groups of **2** were subjected to the reaction, the moderate yields implied that mono-, di-, triiodo derivatives, etc. were expected to be formed, which were difficult to isolate. When the reaction time was increased, more than 80% of the bromo groups were converted to iodo groups (entries 2 and 4). New signals at approximately 6.56 ppm emerged (Fig. 2c), which are assigned to the aromatic protons adjacent to the oxygens by comparison of a simple resorcinarene cavitand **7** in the ^1H NMR spectra (Fig. 2f). The partially hydrogenated derivatives were not separable at all.

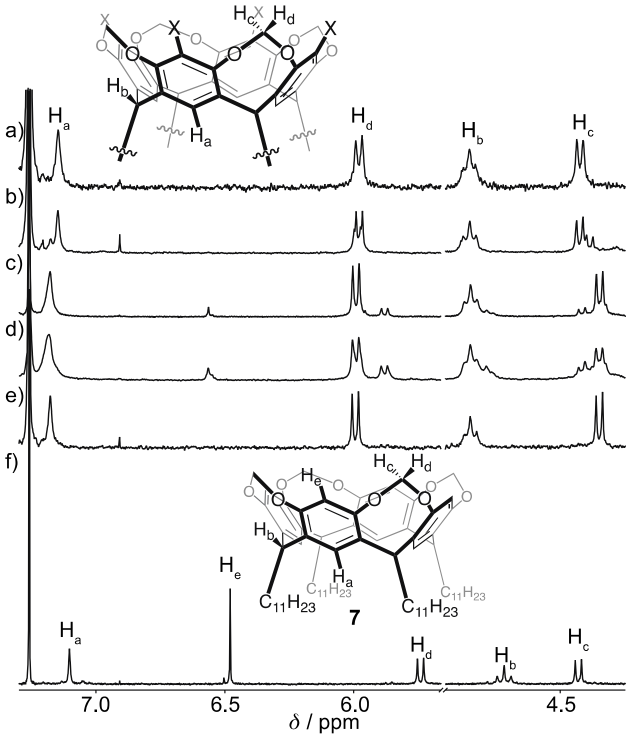
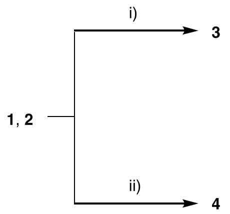


Fig. 2 ^1H NMR spectra of a) **2**, b) the crude product for entry 1 c) the crude product for entry 2, d) the crude product for entry 5, e) the crude product for entry 8, and f) a simple methylene bridged cavitand **7**.

Sugiura and coworkers reported that a facile AFI reaction for the preparation of aromatic iodides was accelerated in 1,3-dimethyl-2-imidazolidinone (DMI).[37] The reaction conditions in DMI were applied to the iodination of **2** for 3 h at three different temperatures (entries 5–7). At 200 °C, the bromides were converted cleanly for 3 h, although 30% of the iodo groups were reduced (Fig. 2d). When the temperature was reduced at 170 °C, 16% of the partially reduced derivatives were still formed. It is known that the reactions are in equilibrium conditions.[38] The reactions were carried out at 145 °C for various reaction times. The reactions were studied for 3, 12, 60 and 120 h (entries 7–10). Finally, octaiodobiscavitand **1** was obtained in 81% yield when the reaction mixture was heated for 60 h (entry 9, Fig. 2e), while the reaction carried out for 120 h yielded a certain amount of the reduced derivatives (entry 10).



Scheme 2. Suzuki-Miyaura cross-coupling and Sonogashira coupling of the octahalobiscavitand. Reaction conditions: i) $PdCl_2(PPh_3)_2$, Ph_3As, Cs_2CO_3, phenyl

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boron acid ester, dioxane/water, 75%; ii) $PdCl_2(PPh_3)_2$, PPh_3, CuI, phenylacetylene, *i*-Pr_2NH, THF, 80%.

To confirm the reactivity of halogenated compounds **1** and **2** in the cross-coupling reactions, the Suzuki-Miyaura and Sonogashira cross-coupling reactions were studied with phenylboronic acid ester and phenylacetylene, respectively (Scheme 2). The reactions of iodide **1** gave octafunctionalized biscavitands **3** and **4** in good yields, whereas that of **2** did not. Therefore, octaiodobiscavitand **1** was found to have potential for cross-coupling reactions.

The functionalized biscavitands **3** and **4** were characterized using ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. The D_{4h} symmetry of **3** and **4** was evidenced by the ^1H and ^{13}C NMR spectra (Figs. S4 and S5, ESI†). **4** crystallized with a triclinic unit cell in the space group P–1 (#2) from a chloroform solution by the slow diffusion of hexane at room temperature over two days (Fig. 3). One molecule of **4** was located in the unit cell. Two chloroform molecules were disordered over the two sites and entrapped within both cavities. The packing of **4** shows that the terminal phenyl acetylene groups are embedded into the expanded cavity of the neighboring biscavitand. Two of the four benzene rings at the upper rim form an attractive π-π stacking interaction with a stacking distance of 3.46(1) Å (Fig. S18, ESI†). The repeating head-to-head association of **4** results in a supramolecular polymer.[39-41]

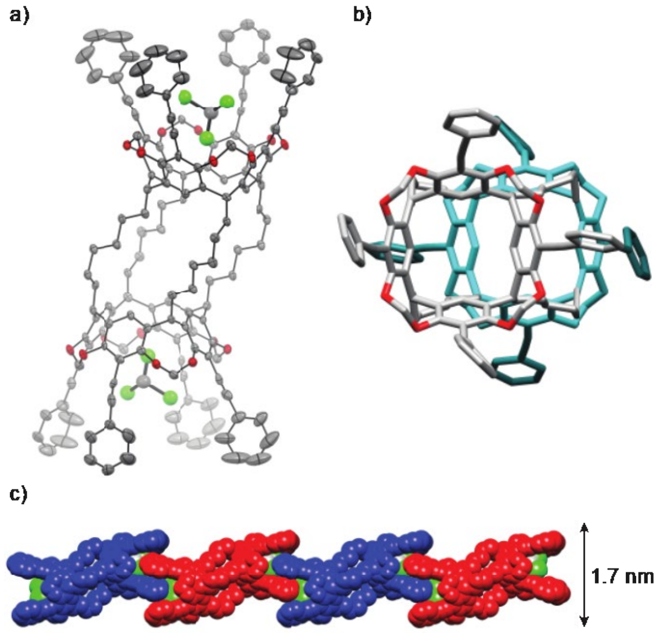

Fig. 3 Crystal structure of **4**. (a) Side views and (b) top views. (Color scheme: gray: carbon, red: oxygen, green: chloride). (c) Partially packed slice from the crystal cell of **4**. Alternating host **4** molecules are shown in blue and red. The hydrogen atoms are omitted for clarity except on entrapped solvents.

The fine morphologies of the assemblies were observed using an atomic force microscope (AFM).[42, 43] The cast films were prepared by spin-coating a chloroform solution of **1**, **3** and **4** ([**1**] = [**3**] = [**4**] = 1.0 × 10^{-5} mol L^{-1}) onto a mica surface to obtain morphological information. The fibrous morphologies prepared from **4** are shown in Fig. 4, which clearly indicates the anisotropic growth of the self-assembly of **4**.[44] A uniform height of approximately 2.0(1) nm was observed in the topographical image, which is fairly consistent with the diameter of 1.7 nm observed in the supramolecular polymer chain in the solid state (Figs. 3c, 4b). By contrast, **1** and **3** gave rise to particle-like aggregates, suggesting that a chloroform molecule filled the volume of the internal cavities of **1** and **3** and most likely interrupted the dimeric structures, which led to random aggregation of **1** and **3** (Fig. S19 and Fig. S20, ESI†).

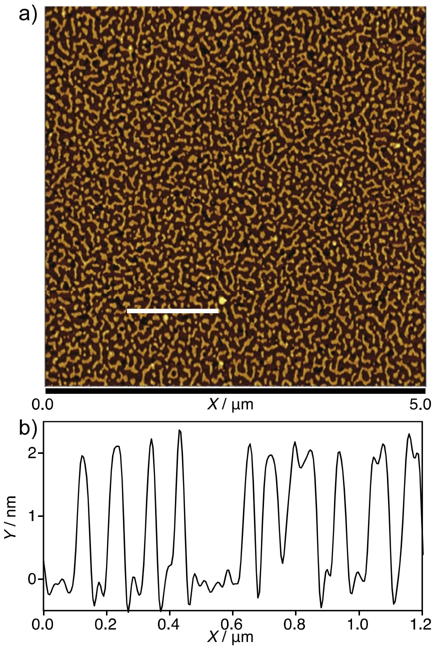

Fig. 4 (a) AFM images of cast films prepared from chloroform solutions of **4**. (b) The height profile of the white line in Fig. 4a.

In summary, we synthesized feet-to-feet-connected octaiodobiscavitand **1** in good yields. High-yielding Suzuki-Miyaura and Sonogashira coupling reactions of **1** with phenyl boron acid ester and phenylacetylene compared with bromide **2** provided octafunctional biscavitands **3** and **4**. X-ray diffraction analysis of **4** confirmed that the upper rim of biscavitand **1** was successfully functionalized with aromatic substituents. We believe that the versatility of octaiodobiscavitand **1** can allow this material to serve as a platform for the synthesis of many novel homoditopic host molecules in a facile manner.

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Conflicts of interest

There are no conflicts to declare.

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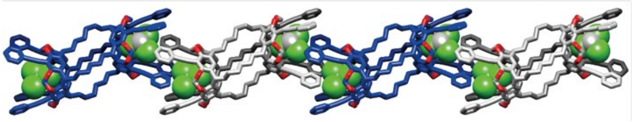
Notes and references

1 D. J. Cram, *Science*, 1983, **219**, 1177-1183.
2 D. M. Rudkevich and J. Rebek Jr., *Eur. J. Org. Chem.*, 1999, **1999**, 1991-2005.
3 D. J. Cram, M. E. Tanner and R. Thomas, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 1024-1027.
4 A. Galan and P. Ballester, *Chem. Soc. Rev.*, 2016, **45**, 1720-1737.
5 R. Pinalli and E. Dalcanale, *Acc. Chem. Res.*, 2013, **46**, 399-411.
6 R. Pinalli, A. Pedrini and E. Dalcanale, *Chem. Soc. Rev.*, 2018, **47**, 7006-7026.
7 J. Chen and J. Rebek Jr., *Org. Lett.*, 2002, **4**, 327-329.
8 T. Iwasawa, *Tetrahedron Lett.*, 2017, **58**, 4217-4226.
9 Y. Yu and J. Rebek Jr., *Acc. Chem. Res.*, 2018, **51**, 3031-3040.
10 S. Ma, D. M. Rudkevich and J. Rebek, *J. Am. Chem. Soc.*, 1998, **120**, 4977-4981.
11 L. Sebo, F. Diederich and V. Gramlich, *Helv. Chim. Acta*, 2000, **83**, 93-113.
12 T. Haino, M. Kobayashi, M. Chikaraishi and Y. Fukazawa, *Chem. Commun.*, 2005, 2321-2323.
13 K. Kobayashi, Y. Yamada, M. Yamanaka, Y. Sei and K. Yamaguchi, *J. Am. Chem. Soc.*, 2004, **126**, 13896-13897.
14 C. Aakeröy, N. Schultheiss and J. Desper, *CrystEngComm*, 2007, **9**, 211-214.
15 C. Gropp, N. Trapp and F. Diederich, *Angew. Chem. Int. Ed.*, 2016, **55**, 14444-14449.
16 Z. Csók, A. Takátsy and L. Kollár, *Tetrahedron*, 2012, **68**, 2657-2661.
17 D. J. Cram, S. Karbach, H. E. Kim, C. B. Knobler, E. F. Maverick, J. L. Ericson and R. C. Helgeson, *J. Am. Chem. Soc.*, 1988, **110**, 2229-2237.
18 Z. Csók, T. Kégl, L. Párkányi, Á. Varga, S. Kunsági-Máté and L. Kollár, *Supramol. Chem.*, 2011, **23**, 710-719.
19 L. Turunen, N. K. Beyeh, F. Pan, A. Valkonen and K. Rissanen, *Chem. Commun.*, 2014, **50**, 15920-15923.
20 T. M. Altamore, E. S. Barrett, P. J. Duggan, M. S. Sherburn and M. L. Szydzik, *Org. Lett.*, 2002, **4**, 3489-3491.
21 C. B. Aakeröy, P. D. Chopade, N. Schultheiss and J. Desper, *Eur. J. Org. Chem.*, 2011, **2011**, 6789-6793.
22 Y. Tsunoda, K. Fukuta, T. Imamura, R. Sekiya, T. Furuyama, N. Kobayashi and T. Haino, *Angew. Chem. Int. Ed.*, 2014, **53**, 7243-7247.
23 T. Imamura, T. Maehara, R. Sekiya and T. Haino, *Chem. Eur. J.*, 2016, **22**, 3250-3254.
24 D. Shimoyama, R. Sekiya, H. Kudo and T. Haino, *Org. Lett.*, 2020, **22**, 352-356.
25 D. Shimoyama, T. Ikeda, R. Sekiya and T. Haino, *J. Org. Chem.*, 2017, **82**, 13220-13230.
26 D. Shimoyama, H. Yamada, T. Ikeda, R. Sekiya and T. Haino, *Eur. J. Org. Chem.*, 2016, **2016**, 3300-3303.
27 D. Shimoyama and T. Haino, *J. Org. Chem.*, 2019, **84**, 13483-13489.
28 D. Shimoyama and T. Haino, *Chem. Eur. J.*, 2020, DOI: 10.1002/chem.201905036.
29 N. K. Beyeh, D. P. Weimann, L. Kaufmann, C. A. Schalley and K. Rissanen, *Chem. Eur. J.*, 2012, **18**, 5552-5557.
30 D. Dolenc, *Synlett*, 2000, **2000**, 544-546.
31 F. Gruppi, F. Boccini, L. Elviri and E. Dalcanale, *Tetrahedron*, 2009, **65**, 7289-7295.
32 P. Timmerman, H. Boerrigter, W. Verboom, G. J. Van Hummel, S. Harkema and D. N. Reinhoudt, *J. Inclusion Phenom. Mol. Recognit. Chem.*, 1994, **19**, 167-191.
33 T. Haino, M. Kobayashi and Y. Fukazawa, *Chem. Eur. J.*, 2006, **12**, 3310-3319.
34 A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 14844-14845.
35 M. Chen, S. Ichikawa and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2015, **54**, 263-266.
36 L. Li, W. Liu, H. Zeng, X. Mu, G. Cosa, Z. Mi and C.-J. Li, *J. Am. Chem. Soc.*, 2015, **137**, 8328-8331.
37 K.-I. Yamashita, M. Tsuboi, M. S. Asano and K.-I. Sugiura, *Synth. Commun.*, 2012, **42**, 170-175.
38 R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1097-1107.
39 R. M. Yebeutchou, F. Tancini, N. Demitri, S. Geremia, R. Mendichi and E. Dalcanale, *Angew. Chem. Int. Ed.*, 2008, **120**, 4580-4584.
40 F. Tancini, R. M. Yebeutchou, L. Pirondini, R. De Zorzi, S. Geremia, O. A. Scherman and E. Dalcanale, *Chem. Eur. J.*, 2010, **16**, 14313-14321.
41 J. H. Jordan, A. Wishard, J. T. Mague and B. C. Gibb, *Org. Chem. Front.*, 2019, **6**, 1236-1243.
42 L. Pirondini, A. G. Stendardo, S. Geremia, M. Campagnolo, P. Samorì, J. P. Rabe, R. Fokkens and E. Dalcanale, *Angew. Chem. Int. Ed.*, 2003, **42**, 1384-1387.
43 H. Ihm, J.-S. Ahn, M. S. Lah, Y. H. Ko and K. Paek, *Org. Lett.*, 2004, **6**, 3893-3896.
44 The ^{1}H NMR spectra of **4** were consistent in the concentrations ranging from 0.5 to 10.0 mmol L^{-1}, which indicates that **4** exists as a monomeric form in solution (Fig. S21).



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