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Carborane guests for cucurbit[7]uril facilitate strong binding and on demand removal

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Abstract

High-affinity guests have been reported for the macrocyclic host cucurbit[7]uril (CB[7]), enabling widespread applications, but hindering CB[7] materials from being returned to their guest-free state for reuse. Here, we present polyhedral boron clusters (carboranes) as strongly-binding, yet easily removable, guests for CB[7]. Aided by a Pd-catalyzed coupling of an azide anion, we prepared boron-functionalized 9-amino-*ortho*-carborane that binds to CB[7] with a $K_a \approx 10^{10}$ M^{-1}. Upon basic treatment, *ortho*-carborane readily undergos deboronation to yield anionic *nido*-carborane, a poor guest for CB[7], facilitating recovery of guest-free CB[7]. We showcase the utility of the modified *ortho*-carborane guest by recycling a CB[7]-functionalized resin. With this report, we introduce stimuli-responsive decomplexation as an additional consideration in the design of high-affinity host-guest complexes.

Graphical Abstract

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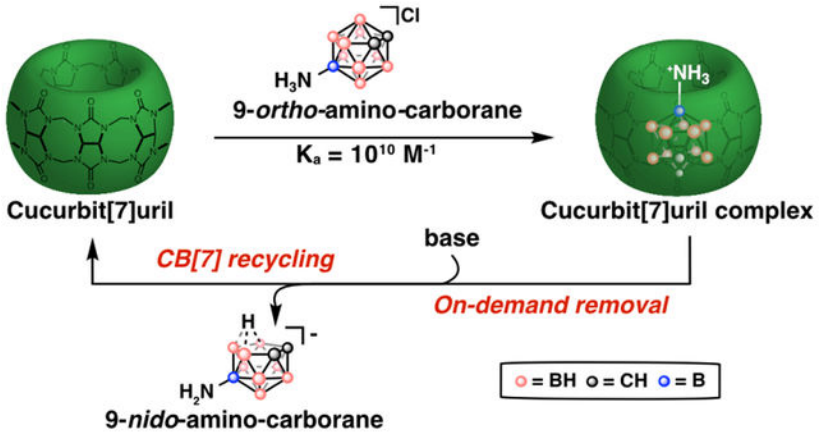
Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Figures S1–S23, Table S1 and additional experimental details including synthetic and experimental procedures, NMR and IR spectra, fluorescence spectra and X-ray crystallographic data (PDF)



Molecular recognition is ubiquitous in nature with the biological processes relying on non-covalent interactions between biomolecules.[1,2] Chemists have been inspired to develop host-guest complexes with comparable degrees of specificity for applications in functional materials,[3] sensors,[4] biological assays,[5] and therapeutics.[6–9] Early molecular recognition work involved crown ether, cyclophane, and cyclodextrin hosts that exhibit modest binding affinities ($K_a \leq 10^5$ M^{-1}).[10] Recently, focus has been on the development of high-affinity ($K_a \geq 10^9$ M^{-1}) host-guest complexes that rival the binding affinities of Nature's best molecular recognition systems: antibody-antigens and (strept)avidin-biotin.[11] High binding affinity complexes facilitate the expansion of host-guest chemistry to applications in dilute, complex settings and decrease the need to exploit multivalency.[12] However, large K_a values also lead to difficulties in readily dissociating the pair, limiting the reversibility and flexibility of the system (Figure 1A).[13] Here we present "decomplexation", the ability to remove a guest on demand, as an important feature in the design of high-affinity host-guest pairs (Figure 1B).

Cucurbiturils, cyclic oligomers of glycoluril linked by methylene units, have become the host of choice for high-affinity complexes.[14,15] The heptamer, cucurbit[7]uril (CB[7]) displays the largest binding affinities, with the highest reported K_a being 10^{17} M^{-1} for complexation with 1,6-*N*-trimethylammonium diamantane.[16] Other notable high-affinity guests for CB[7] are adamantylamine (K_a=10^{12} M^{-1}) and derivatives (K_a=$10^{4–17}$ M^{-1})[16,17] and functionalized ferrocenes (K_a=$10^{9–15}$ M^{-1}).[15] These guests all display excellent size and shape complementarity with the cavity and alignment of cationic functionality with the carbonyl rings.[18]

These high binding affinities have led to the exploration of the CB[7] scaffold as a biotin-(strept)avidin mimic.[19–23] CB[7] has also found use in small molecule separation,[24] dynamically crosslinked polymers,[3,25] surface patterning[26,27] and sensor development.[28] In most of these applications, CB[7] is immobilized on solid-supports and the high binding affinity of guests with CB[7] render these materials one-time use. If compounds captured by the immobilized CB[7] need to be released, a higher affinity guest is introduced to displace the captured material, leaving complexed CB[7]. The difficulty in returning surfaces and

devices containing CB[7] to their initial guest-free state limits the use of CB[7] to highly specialized applications where cost and scale are not significant factors.

To enable recycling of CB[7]-containing materials, we designed a high-affinity guest for CB[7] that upon chemical treatment could be transformed into a weak guest for easy removal. This guest could either be employed as the primary guest in the experiment or be used to displace an application-specific guest and then undergo decomplexation to allow regeneration of the CB[7] material. Notable previous efforts to reduce binding affinity and facilitate guest removal have used electrochemical or pH-dependent switching; however, complete removal from the cavity requires salt treatment or organic solvent (see SI Note 1).[29–34] High-affinity guest removal from CB[7] has only been achieved via excessive salt treatment.[23,35]

In our search for guests to fit the criteria of both high binding affinity to CB[7] and the ability of triggered decomplexation, we looked to guests with shape complementarity to the cavity of CB[7] that could be readily transformed into a fragment that is poorly encapsulated by CB[7].[17,36–38] Icosahedral carboranes ($C_2B_{10}H_{12}$) appeared primed to meet these requirements. These 3D aromatic clusters[39–41] bear a close topological similarity to adamantane[42,43] and one of the three isomers, *ortho*-carborane, has previously been employed as a guest for CB[7], although no K_a was reported.[44] Importantly, carboranes undergo Lewis base-mediated B–H vertex removal (termed “deboronation”) to generate the *nido*-7,8-$C_2B_9H_{11}$ anion (Figure 1B).[45–47] *Ortho*- and *meta*-carboranes have significantly different rates of deboronation, and distinct dipole moments.[42,48] We set out to explore the binding affinities of derivatives of these two carborane isomers with CB[7] and their potential for removal upon deboronation to create a reliable recycling system for CB[7].

The electronic non-uniformity of carboranes is widely recognized, resulting in different electronic influences on bound substituents depending on the cage vertex.[49] Given the similar inductive electronic effects of B-bound substituents on carboranes compared to bulky alkyl groups, we targeted *N*-substitution at the B9 vertices of the carboranes to most closely mimic the electronic environment of adamantylamine. Despite a variety of methods to functionalize *ortho*- and *meta*-carborane,[50–54] the synthetic methodology developed for the amination of 9-Br-*meta*-carborane[55] is incompatible with 9-Br-*ortho*-carborane (**1**) due to basic conditions leading to deboronation. Alternative routes to nitrogen-substituted *ortho*-carboranes were similarly unsuccessful.[56]

Thus, a new synthetic route (Figure 2A) to furnish the B9 aminated *ortho*-carborane target was necessary. Treatment of **1** with NaN_3 under Pd-catalyzed cross-coupling conditions afforded the desired 9-N_3-*ortho*-carborane (**2**)[49] in 67% yield. This is a rare example of Pd-catalyzed cross-coupling of an azide anion.[57] Staudinger reduction and hydrolysis with concentrated HCl gave the desired hydrochloride salt **4**, confirmed by crystallography (Figure 2E). To probe the effect of a permanent positive charge on the guest, trimethylammonium derivatives **5** and **7** were prepared (Figure 2B,C). We synthesized the analogous hydrochloride salt 9-NH_3-*meta*-carborane (**8**) by treating the corresponding amine with gaseous HCl (Figure 2D) to aid in binding affinity investigations.

The aqueous solubility of the 9-amino- and 9-ammonium-carboranes (**4**, **5**, **7**, **8**) allowed binding affinities to be determined by ^{1}H-NMR spectroscopy in acetate buffer (Figure 3, Figures S1–S4). Competition experiments against (trimethylsilyl)methylamine were performed.[17] Notably, the binding affinities are lower than those observed with adamantylamine, despite the structural analogy between carborane and adamantane.[58] Carboranes' greater inherent net dipole could be altering the positioning in the CB[7] hydrophobic pocket. We hypothesize that in **8** the net dipole allows for better positioning in the CB[7] cavity than its isomer **4**. Similarly, trimethylation affects the K_a differently for *ortho*- and 9-*meta*-aminocarboranes. The decreased K_a for **7** compared to **5** could result from competing alignment of the trimethylammonium group with the CB[7] portals and carborane net dipole within CB[7].[16,17,59] Overall, at K_a=$10^{9–11}$ M^{-1} we have established carboranes as a new class of high-affinity guests for CB[7].

Next, we investigated the ability for carborane guests to be removed from CB[7] on demand. Initially, we employed unfunctionalized *ortho*-and *meta*-carborane, which have orthogonal decomplexation properties (Figure 4A). We characterized the CB[7]•carborane complexes in trifluoroacetic acid (TFA), due to limited water solubility of carboranes (Figure S5–S6).[72] We found that a stable complex between CB[7] and *ortho*- and *meta*-carborane (35–55 mM, 1.2 eq) readily formed upon sonication and could be purified by washing with organic solvent (Figure S7). Carborane is clearly seen in the aqueous solution of host-guest complex via ^{11}B-NMR spectroscopy when both *ortho*- (**9**) and *meta*-carborane (**10**) are introduced (Figure S8).

After screening a small family of Lewis bases known to deboronate *ortho*-carborane (**9**) (Figure 4B, Figure S9–S13, Table S1), we established 20% aqueous piperidine at 60 °C as optimal decomplexation conditions for CB[7]•**9** and CB[7]•**4**. Interestingly, when CB[7] was not present, other Lewis acids deboronated **4** at similar rates to piperidine (Figure S14), suggesting that a piperidine CB[7] interaction may enhance deboronation. We hypothesize that an electrostatic attraction of piperidine with the carbonyl portal improves the solubility of CB[7]•**9** (or CB[7]•**4**), facilitating deboronation (see SI Note 2, Figure S15).

As predicted, when subjecting the *meta*-carborane complex (CB[7]•**10**) to similar conditions, no transformation is apparent for **10** in the presence or absence of CB[7] (Figure 4B, entry 6, Figure 4C–F, Figure S16–S18). These results are consistent with the diminished electrophilicity of the boron vertices adjacent to carbon vertices in *meta*-carborane (**10**) versus *ortho*-carborane (**9**) and demonstrate the potential for orthogonal chemical behavior of sterically identical guest molecules encapsulated by CB[7].

To showcase the utility of the on demand decomplexation offered by the *ortho*-carborane guests, we used **9** to isolate CB[7]-OH (Figure 5A). CB[7]-OH is an important intermediate for the creation of CB[7] conjugates, materials, and devices. CB[7] can be readily monohydroxylated by treatment of CB[7]•**12** with persulfate salts; however, we found efficient removal of **12** from the CB[7]-OH cavity to be difficult (Scheme S1–S2).[35] Gratifyingly, **12** could be displaced with **9** in less than 30 min in a H_2O/TFA mixture (Figure 5B,C, blue). Upon TFA removal, treatment with piperidine for 1 h followed by a dichloromethane wash provided guest free CB[7]-OH (Figure 5B,C, red). In our hands, this

is the fastest and highest yielding procedure to isolate guest-free CB[7]-OH. The decomplexation method was also used to prepare guest-free CB[7]-N_3 (Figure S19).[60,61]

To demonstrate the ability to recycle CB[7]-constructs via decomplexation of *ortho*-carborane guests, we conjugated CB[7]-N_3[60,62] to bicyclononyne-functionalized Wang resin (Wang-BCN, Figure 6A, Scheme S3) using copper-free click chemistry and confirmed successful immobilization using fluorescein adamantylamine conjugate **13** (K_a=10^8 M^{-1}, Figure S20–S21). The resulting Wang-CB[7] resin was added to Jurkat lysate (2 mg/mL) containing **13** to selectively isolate the fluorescent guest from a complex mixture (Figure 6B, Step A). After washing away cell lysate, displacement with **4** rapidly releases **13** (Figure 6B, Step B). Finally, treatment with piperidine deboronates **4** to produce **14** and regenerate Wang-CB[7] (Figure 6B, Step C).[73]

The success of each step was monitored through the fluorescence of Wang-CB[7] (red) and compared to fluorescent Wang-CB[7]•**13**, where displacement by **4** was omitted (green) and non-fluorescent Wang-CB[7], where addition of **13** and **4** were omitted (gray) (Figure 6C). The cycle was repeated twice, at which point the signal became too low due to significant loss of resin in the washing steps (Figure S22–S23). We expect this limitation can be overcome by using a more water-compatible solid support. Recycling of the resin represents a novel method of reusing precious CB[7]-constructs that can be applied for payload isolation in biological and materials applications. Work toward even milder conditions for decomplexation is underway.

In summary, we present carboranes as high-affinity (K_a≈10^{10} M^{-1}) binders for CB[7], which may be removed on demand through deboronation chemistry. We designed 9-aminocarborane guests to mimic the size and charge of adamantylamine and took advantage of the differential reactivity of carborane isomers to prepare guests that were (*ortho*) and were not (*meta*) readily deboronated. We utilized this scaffold to efficiently prepare guest-free CB[7]-OH and showcase the opportunity to “recycle” CB[7]-constructs that can be employed in biological assays and materials applications. We envision this work will overcome limitations of traditional biotin-(strept)avidin systems and enable CB[7] sensors and technologies. Finally, this work highlights how unique stimuli-responsive features of boron clusters can aid in the development of new hybrid chemical systems.[63–71]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(73). The experiment was performed in 50% DMF/H_2O to keep the Wang resin swollen and conjugated CB[7] accessible for binding and decomplexation.$_2$

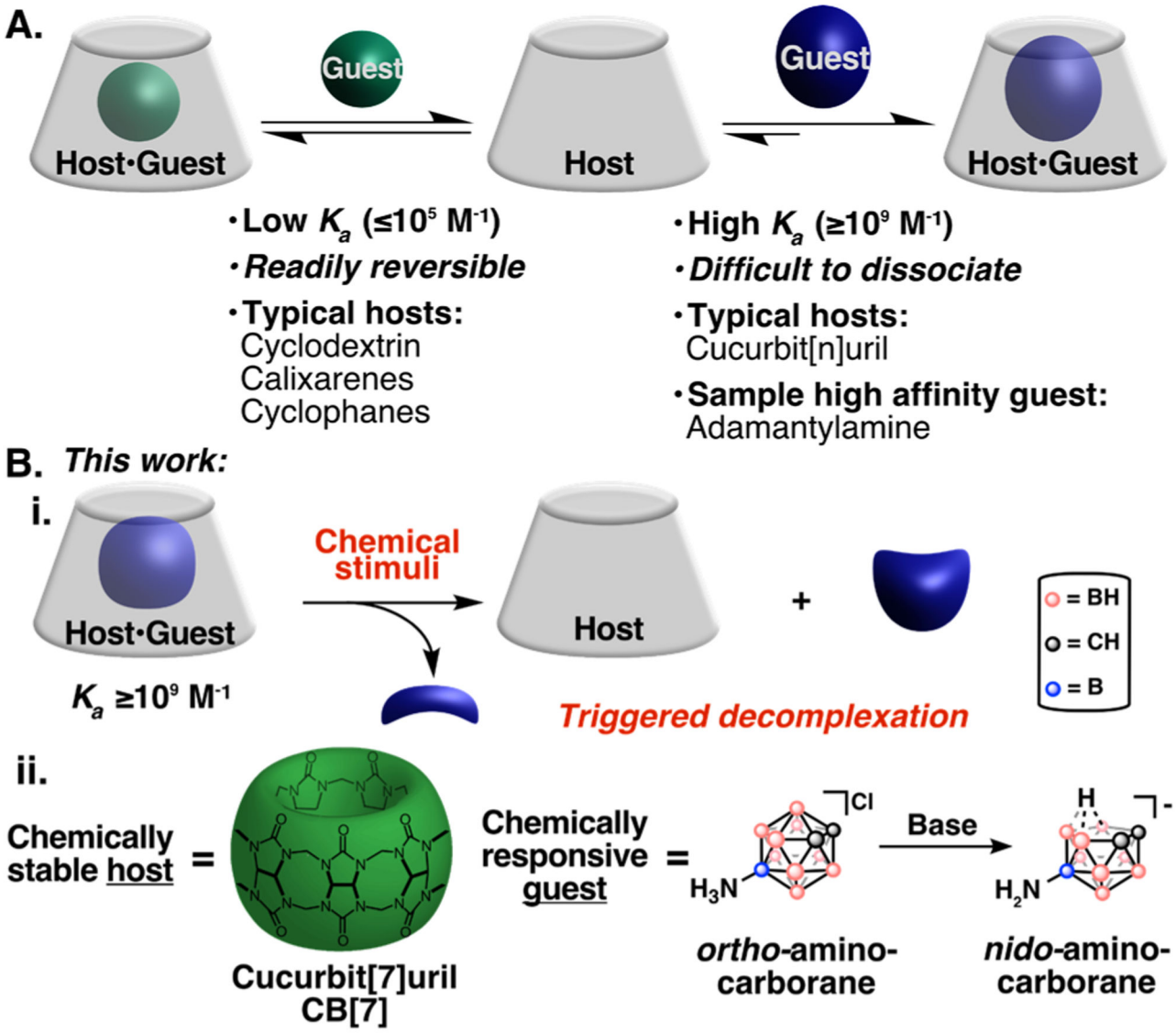


Figure 1.

(**A**) Schematized synthetic host-guest pairs with low (green) and high (blue) binding affinities. (**B**) (i) This work presents triggered decomplexation as an advantageous property for high-affinity host-guest complexes, (ii) which we demonstrate with a cucurbit[7]uril (CB[7]) and *9*-amino-*ortho*-carborane host-guest pair that undergoes decomplexation with base.

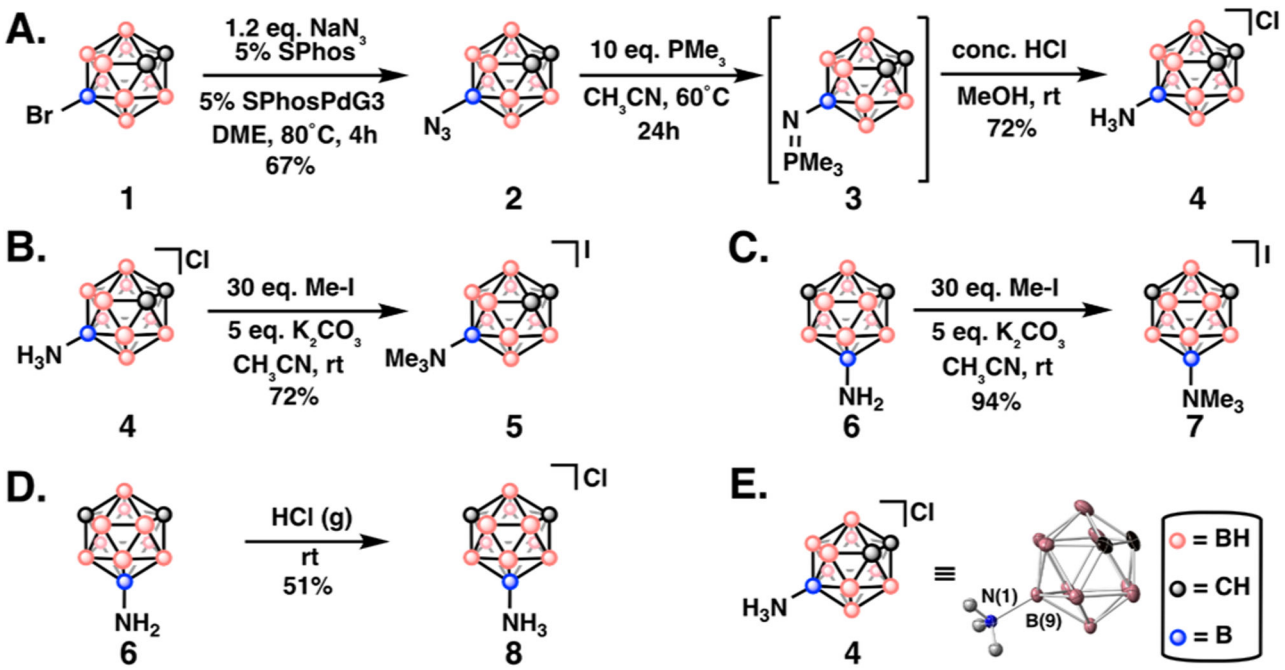
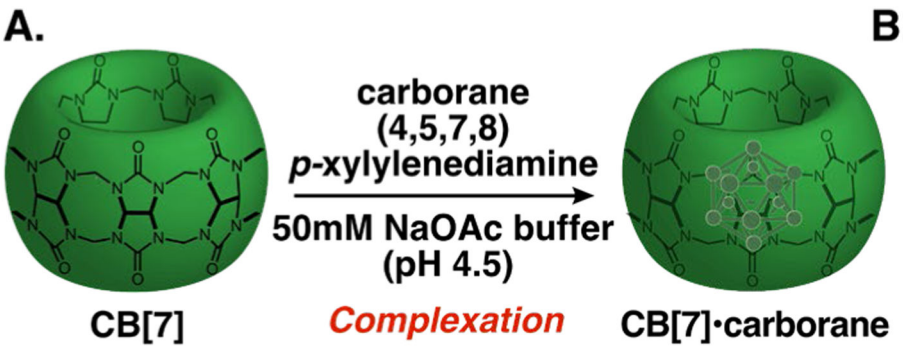


Figure 2.

(**A**) Synthetic route to 9-amino-*ortho*-carborane (**4**) through 9-azido-*ortho*-carborane (**2**). (**B, C**) Treatment of **4** and **6** with Me-I affords trimethylated derivatives **5,7**. (**D**) Formation of salt **8**. (**E**) Single crystal X-ray diffraction of **4** (chloride counterion and cage-based hydrogens removed for clarity).

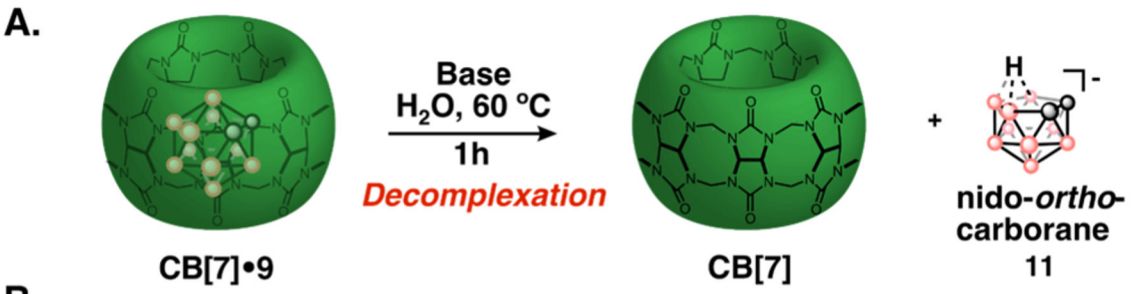


B.

#	K_a (M^{-1})
4	$(7.9\pm0.8) \times 10^9$
5	$(9.9\pm0.1) \times 10^{11}$
8	$(1.1\pm0.5) \times 10^{11}$
7	$(3.5\pm0.7) \times 10^9$

Figure 3.

(**A**) Association of carborane with CB[7]. (**B**) Binding affinities of water-soluble carborane derivatives (**4**,**5**,**7**,**8**) (1 eq.) determined by ^{1}H NMR spectroscopy competition experiments with (trimethylsilyl)methylamine (1.5 eq.) in 50mM NaOAc buffer.[17]



B.

Entry	Carborane	Base	1h	2h	8h	24h
1	**9**	$HNMe_2$ (1M THF)	9%	17%	45%	86%
2	**9**	$HNMe_2$ (40% in H_2O)	<5%	<5%	<5%	<5%
3	**9**	Pyridine	<5%	<5%	<5%	<5%
4	**9**	**Piperidine**	**>95%**	**>95%**	**>95%**	**>95%**
5	**4**	Piperidine	8%	19%	>95%	>95%
6	**10**	Piperidine	<5%	<5%	<5%	<5%
7	**8**	Piperidine	<5%	<5%	<5%	<5%

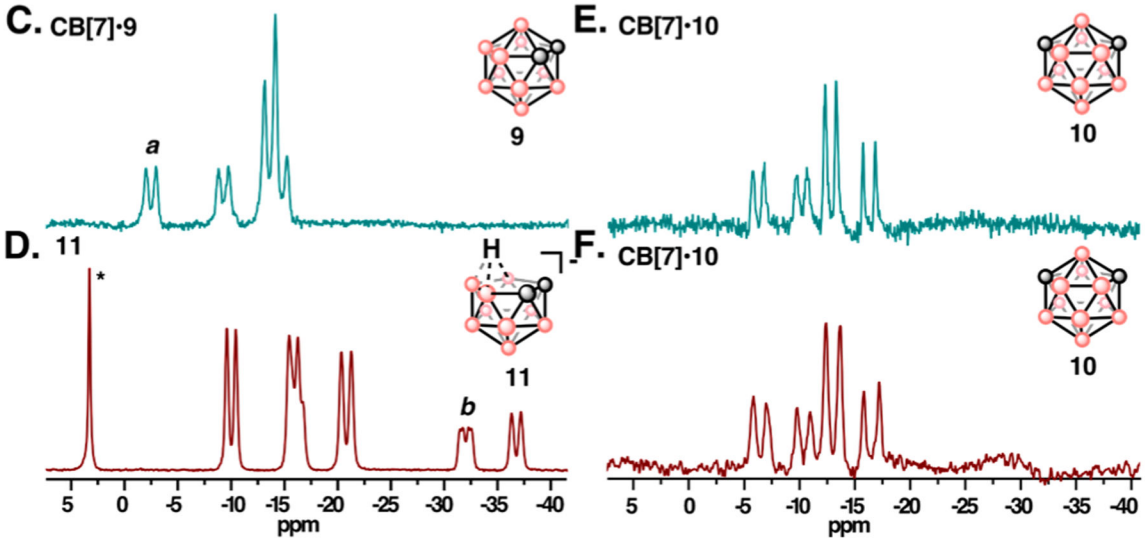


Figure 4:

(**A**) Decomplexation of the CB[7]•**9** complex through deboronation of *ortho*-carborane (**9**) with base to yield nido-*ortho*-carborane (**11**) and free CB[7]. (**B**) Conditions screened to evaluate the decomplexation of CB[7]•carborane complexes. CB[7]•carborane and base (5 equiv.) were combined in H_2O, stirred at 60 °C, and monitored by ^{11}B-NMR spectroscopy. Generation of **11** was calculated by relative integration of baseline corrected ^{11}B-NMR spectra (Figure S9–S13, Table S1) (**C-F**) ^{11}B-NMR spectra taken before (**C**) and after (**D**) 1h of subjecting CB[7]•**9** complex (**C,D**) or CB[7]•**10** complex (**E,F**) to 20% piperidine/H_2O ($^{v}/_{v}$) at 60 °C. *a, b* denote the peaks used for relative integration measurements. *denotes borate side-product known to form during deboronation of **9**.

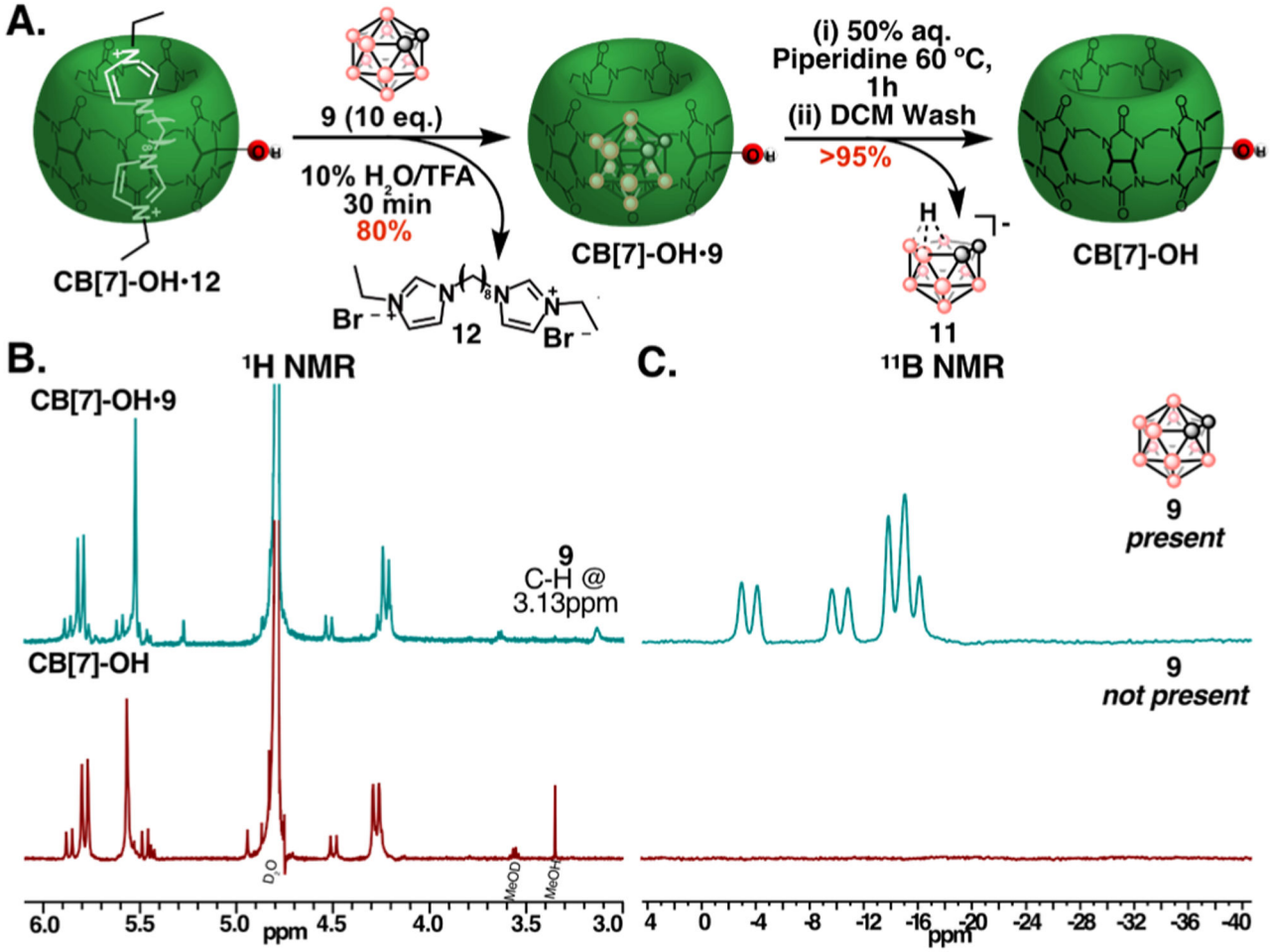


Figure 5:

(A) Isolation of guest-free CB[7]-OH by guest exchange with **9** and subsequent decomplexation with piperidine. (**B,C**) Displacement of **12** by *ortho*-carborane (**9**) and formation of CB[7]-OH•**9** (top, blue) and decomplexation and removal of (**11**) to form a guest-free CB[7]-OH cavity (bottom, red) observed by ^{1}H-NMR (B) and ^{11}B-NMR spectroscopy (C).

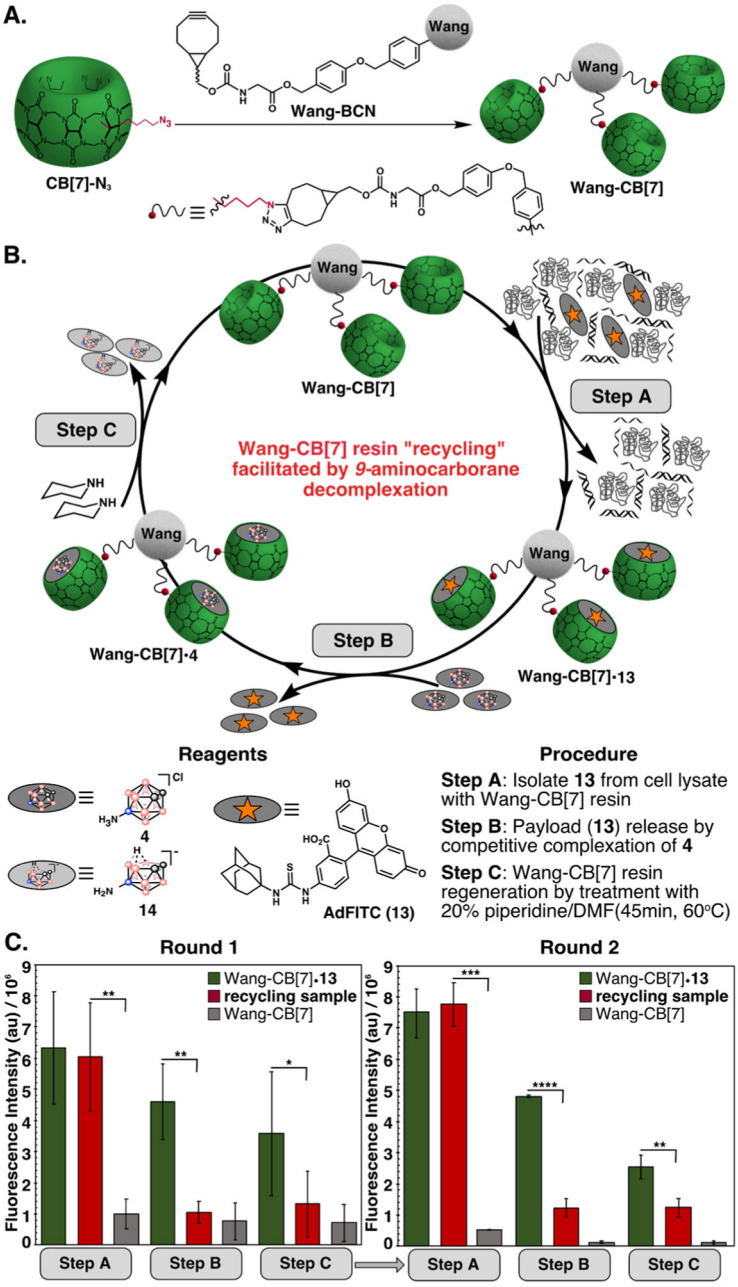


Figure 6:

(**A**) Attachment of CB[7]-N_3 to bicyclononyne (BCN)-functionalized Wang resin to produce Wang-CB[7]. (**B**) Wang-CB[7] was used to isolate payload, **13**, from Jurkat lysate in 50% DMF/H_2O (Step A), and was regenerated by complexation of **4** (Step B) followed by decomplexation (Step C). (**C**) Fluorescence of Wang-CB[7] throughout the recycling sequence (red) compared to fluorescent Wang-CB[7]•**13** (green, samples not incubated with **4** in Step B) and non-fluorescent Wang-CB[7] (gray, samples not incubated with **13** or **4** in Steps A and B). Error bars represent standard deviation of three replicate samples. *P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001.