CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201805246

Link to VoR: http://dx.doi.org/10.1002/chem.201805246

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A Hexavalent Basket for Bottom-Up Construction of Functional Soft Materials and Polyvalent Drugs via "Click" Reaction

Taylor Neal,[a] Weikun Wang,[a] Lei Zhiquan,[a] Ruojing Peng,[a] Priti Soni,[a] Han Xie[a] and Jovica D. Badjić*[a]

Abstract: Inspired by polyvalency and its prevalence in nature, we developed an efficient synthetic route for accessing a large variety of multivalent and dual-cavity baskets from inexpensive and abundant starting materials. First, the cycloaddition of vinyl acetate to anthracene was optimized to, upon hydrolysis, give dibenzobarrelene derivative **6**, which after five functional group transformations and then cyclotrimerization gave heptiptycene dodecaester **4** in an overall 17% yield. Following, compound **4** was converted into D_{3h} symmetric **1**, composed of two fused cavitands each holding three terminal alkynes at the rim for conjugation to functional molecules using the highly efficient CuAAC reaction. To survey the reactivity of hexavalent **1**, we "clicked" 2-acetamido-2-deoxy-*β*-D-glucopyranosyl azide 3,4,6-triacetate (carbohydrate), methoxypolyethylene glycol azide (PEG, M_n = 2000; polymer) and benzyl azide (aromatic) to obtain hexavalent conjugates **12**-**14** in 50-79% yields. In summary, dual-cavity **1** is an accessible, structurally-unique and hexavalent host that can be "clicked" to a variety of functional molecules for (a) combinatorial lead identification of drugs, (b) preparation of hierarchical soft materials and (c) design of selective chemosensors, scavengers or supramolecular catalysts.

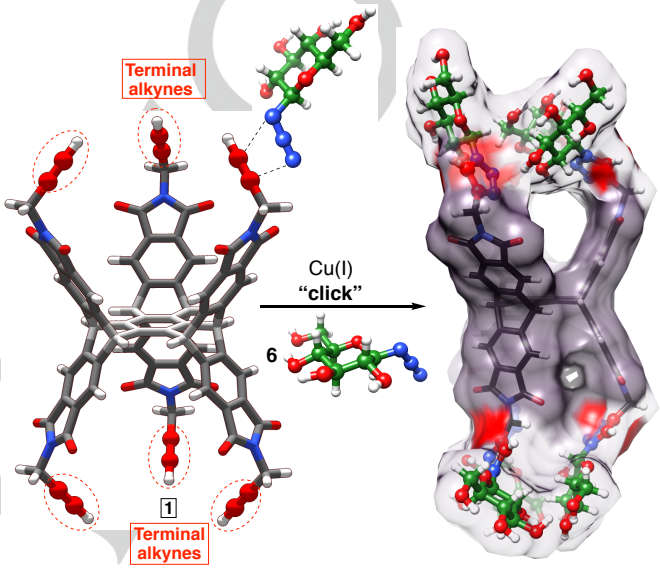

Figure 1. Energy-minimized conformer (MMFF, Spartan) of dual-cavity **1** carrying six alkynes (red) at its southern and northern ends. We hypothesized that "clicking' various substrates (*β*-D-glucopyranosyl azide is shown) to hexa-alkyne **1**, using Cu(I) catalyzed alkyne-azide cycloaddition (CuAAC), should give structurally-unique, hexavalent and allosteric hosts (see ref. 30).

Introduction

Multivalent noncovalent interactions play a pivotal role in directing chemical processes in living systems.[1] Viral and bacterial infections, protein-carbohydrate and protein-protein interactions, as well as cell surface adhesions, present an archetype of polyvalency in which multiple noncovalent contacts mediate complex biological events.[2] In essence, a molecule with two or more identical groups (i.e. epitopes) binds to a multivalent receptor (or causes a clustering of receptors) with enhanced affinity (i.e. avidity)[3] to permit high fidelity in completing signal transduction or other chemical processes.[4] The standard free energy ($\Delta G°_{multi}$) corresponding to the binding of two multivalent entities, both having *i* recognition sites, is in this way more favourable than the sum of free energies ($\Delta G°_{mono}$) from *i* equivalent monovalent contacts ($\Delta G°_{poly} < i\Delta G°_{mono}$).[5] Perhaps, the omnipresence of polyvalency in nature is not surprising; it is easier to multiply existing interactions than evolve a single monovalent contact.[6] At present, there exists a great potential for employing multivalency in developing more effective antibiotics,[7] viral drugs,[8] drug-delivery modules,[9] tissue replacement materials[10] and imaging agents.[11] Moreover, multivalency[12] has also been utilized in the area of supramolecular chemistry,[3, 5b] playing an important role in the bottom-up construction of nanostructured materials,[13] nano-patterning of surfaces[14] and development of molecular machines.[15] For putting multivalency to work, selecting a proper natural[16] or non-natural[17] scaffold has been met with difficulties.[18] That is to say, the paucity of information about kinetics and thermodynamics of complex recognition events,[3, 19] which one is trying to mimic or develop, is often a source of ambiguity pertaining to the valency, spacing and dynamics of required multivalent structures.[20] Indeed, diversity-oriented approaches[13b, 21] or other creative solutions[13f, 22] have been explored for developing more effective binders, yet the scope of synthetically accessible, biocompatible and topologically different structures remains limited.[20, 23] In this vein, we hereby describe an effective synthetic method for obtaining structurally unique host **1** (Figure 1) containing six terminal alkynes at the

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10.1002/chem.201805246

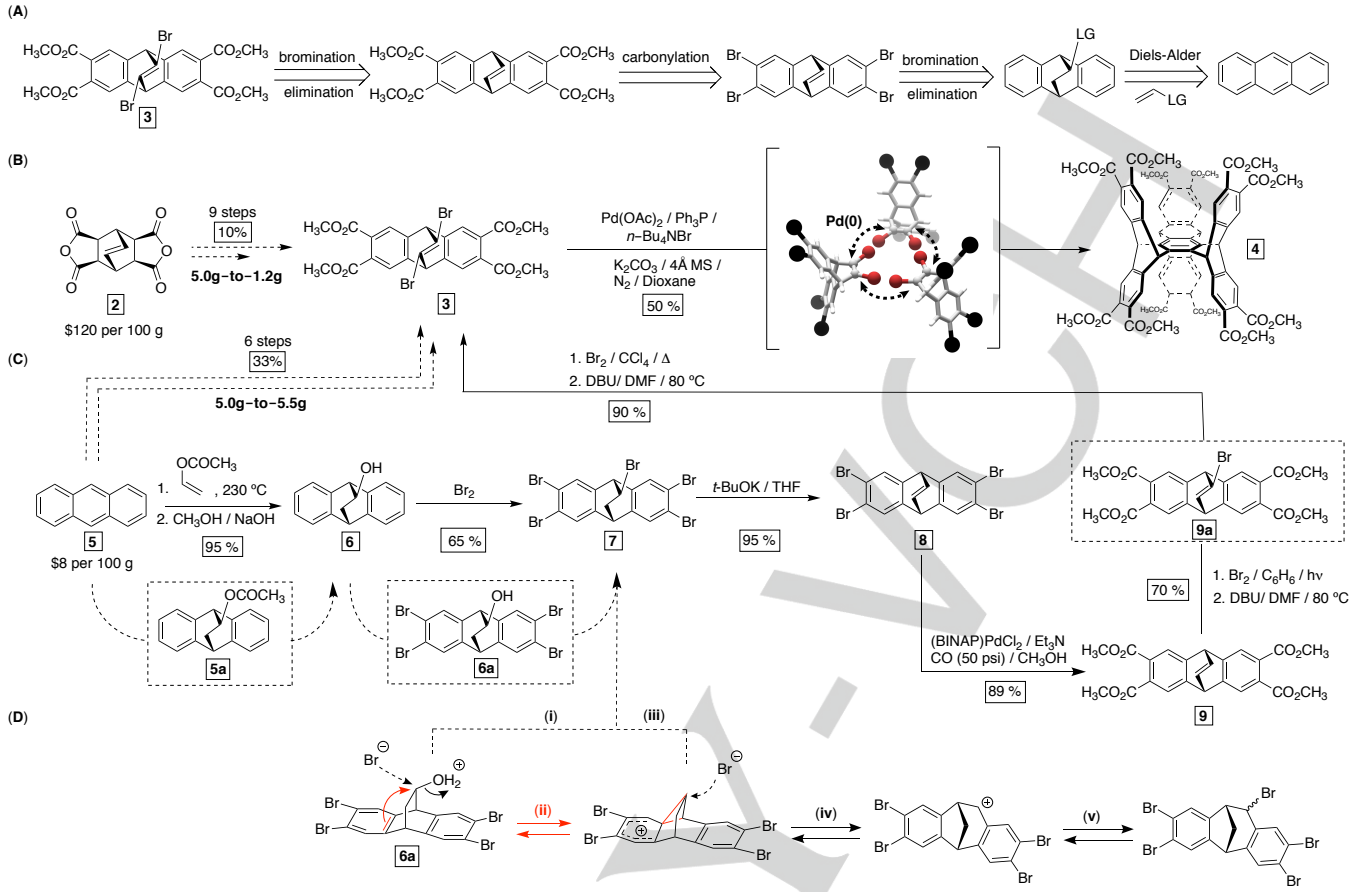

Figure 2. (A) Retrosynthetic scheme pertaining to the preparation of the key intermediate **3**. (B) Earlier reported methodology for the conversion of dianhydride **2** into dual-cavity **4**. (C) More effective and optimized synthesis of compound **3** using anthracene and vinyl acetate as inexpensive starting materials. (D) Hypothesized intermediates occurring in the conversion of **6** into **7**.

periphery of its two fused cavitands.[24] To demonstrate the utility of dual-cavity **1** as a building block in modular synthesis, we used the highly efficient CuAAC[25] "click" reaction for conjugating six carbohydrates, PEG polymers and aromatics carrying azide functional groups (Figure 1). Since such polyvalent baskets could be designed to assemble into vesicles,[26] six recognition groups[18b] could be branching from their curved surface[27] with a potential use in the preparation of functional soft materials.[13a, 18a, 28] Hexavalent **1** could also serve as a building block in combinatorial lead identification and optimization studies,[29] with the benefit of using a small molecule(s) to occupy juxtaposed cavities and act as effectors[30] for tuning the function (Figure 1).

Results and Discussion

Some time ago,[24] we developed a synthetic method for obtaining dodecaester derivative of heptiptycene **4** (Figure 2B) in <5% overall yield. In brief, commercially available dianhydride **2** was converted into dibromoalkene **3** in nine linear steps.[24] Following, palladium-catalyzed cyclotrimerization of **3** was optimized[24] to give dual-cavity **4** in circa 50% yield.[30] The procedure is labour-intensive with 5 grams of compound **2** giving 0.4 grams of dual-cavity **4** (Figure 2B). It takes about ten weeks for an experienced chemist to complete the synthesis, with the process necessitating costly reagents, copious amounts of organic solvents and tedious purification steps commonly resulting in the loss of product.

In a quest for a more effective method for obtaining dibenzobarrelene **3**,[31] we came up with a retrosynthetic strategy for rapidly accessing this key intermediate (Figure 2A). First, we reasoned that a catalytic polycarbonylation of 2,3,6,7-tetrabromo dibenzobarrelene might, on the basis of a literature precedent,[32] be possible to promote with $Co_2(CO)_8$ catalyst. To obtain the tetrabromo compound, we hypothesized that regioselective brominations of a dibenzobarrelene derivative could give satisfactory results (Figure 2A).[33] Finally, [4+2] cycloaddition of an alkene carrying a proper leaving group to anthracene could, perhaps, be optimized[34] to yield the desired dibenzobarrelene. The planned synthetic protocol is inexpensive, requiring a short period of time for completion. Moreover, several principles of green chemistry[35] are also incorporated: (a) atom economy with maximization of the overall yield and minimization of waste (b) scalability with minimal loss in efficiency and (c) facile purifications using time-efficient precipitation or crystallization procedures.

In line with the strategy, we began by optimizing the cycloaddition of vinyl acetate to anthracene (Figure 2C).[36] Because all of the atoms from the diene and dienophile are

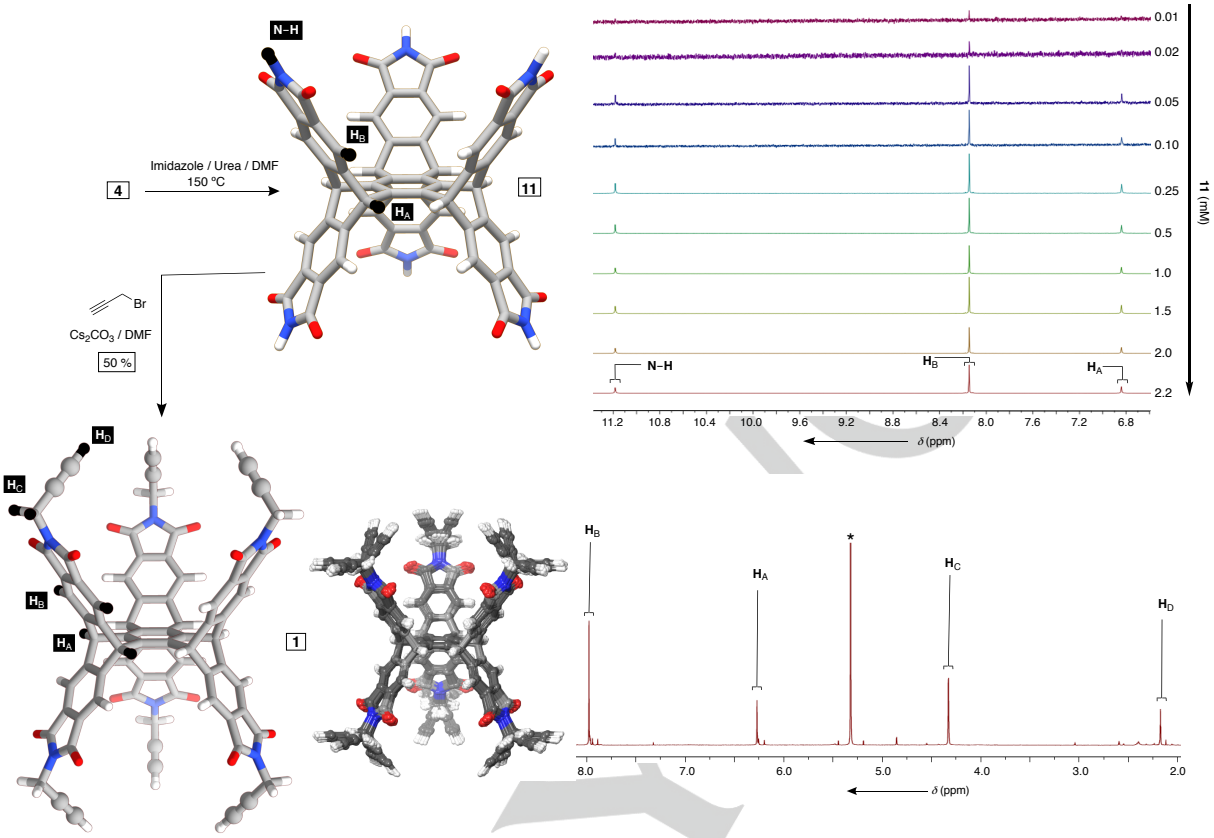

Figure 3. The preparation of hexa-imide **11** and hexa-alkyne **1** from **4**. (Top) Variable concentration ^{1}H NMR spectra (600 MHz, 298 K) of **11** in $(CD_3)_2SO$. (Bottom) ^{1}H NMR spectrum of compound **1** (700 MHz, 298 K) in CD_2Cl_2. A structural representation of 100 conformers of **1** (from 0 to 0.1 kcal/mol of relative steric energy) obtained from the Monte-Carlo conformational search (OPLS3, Schrodinger) in implicit water solvent.

being incorporated into the product, this transformation embodies the highest degree of atom economy.[37] Alder and Rickert carried out the same cycloaddition in 1939,[36] prescribing its completion in xylene at 220 ºC (autoclave) so that the yield of dibenzobicyclo[2.2.2]octadiene cycloadduct **5**a was in the range of 40 to 50%.[34, 38] Interestingly, we realized that this same transformation became practically quantitative when two molar equivalents of neat vinyl acetate were used as both reactant and solvent (Figure 2C). In fact, the reaction can be run safely on a 5g scale in a 10 mL vessel placed in a sand bath at 230 ºC. While compound **5**a could be isolated by precipitation, we decided to, without any purification, treat it with NaOH to form racemic **6** in an overall 95% yield.[39] Next, we examined regioselective bromination of **5**a and **6**.[33] The electrophilic aromatic substitution (EAS) of **5**a, using bromine with catalytic quantities of iron,[40] led to the formation of **7** in rather disappointing <10% yield. On the contrary, a slow addition of neat bromine[41] [42] to **6** gave pentabromo-bicyclic **7** in 65% yield with purification requiring a quick filtration of the reaction's product. Allegedly, the substitution of hydroxyl group in **5** with nucleophilic bromide anion was initiated with HBr, generated in the EAS reaction as the side product. In this regard, dibenzobicyclo[2.2.2]octadienes of type **5**a/**6**/**6**a are, in aliphatic substitutions, prone to Wagner-Meerwein rearrangements[38] as mediated by phenylium and secondary carbocationic intermediates (Figure 2D).[43] In light of such reports,[38, 42, 44] we hypothesize that the principal formation of **7** could be resulting from the electron withdrawing bromides within **6**a (or other polybrominated intermediates, Figure 2D) reducing the extent of π-to-σ* homohyperconjugation[38] to retard the departure rate of the leaving group and concurrently lower the stability of carbocationic intermediates. In this way, the reaction pathway (i) in Figure 2D dominates over (ii-v) to give **7** as the kinetic product. In another scenario, a greater thermodynamic stability of [2.2.2] over [3.2.1] bicyclic frameworks[42, 44] could lead to the formation of **7** as the thermodynamic product if all of the reactions are reversible on the time scale of the experiment. A facile and effective elimination of HBr from **7** was promoted with *t*-BuOK, with the work-up necessitating a few extractions to give sufficiently pure **8** in 95% yield. To complete the carbonylation[45] of 2,3,6,7-tetrabromo dibenzobarrelene **8**, we considered two procedures: (a) palladium-catalyzed carbonylations optimized for heterocyclic and electron-rich aromatics[46] and (b) photo-catalytic and cobalt-based methodology for polycarbonylations.[32] Both methods gave satisfactory results, albeit relatively inexpensive (BINAP)$PdCl_2$ was found to, under mild reaction conditions,[46] facilitate the conversion of **8** into **9** in excellent 89% yield (Figure 2C). As in this transformation the reactant must undergo four consecutive reactions, the yield of each step is 97% on average! The conversion is scalable,

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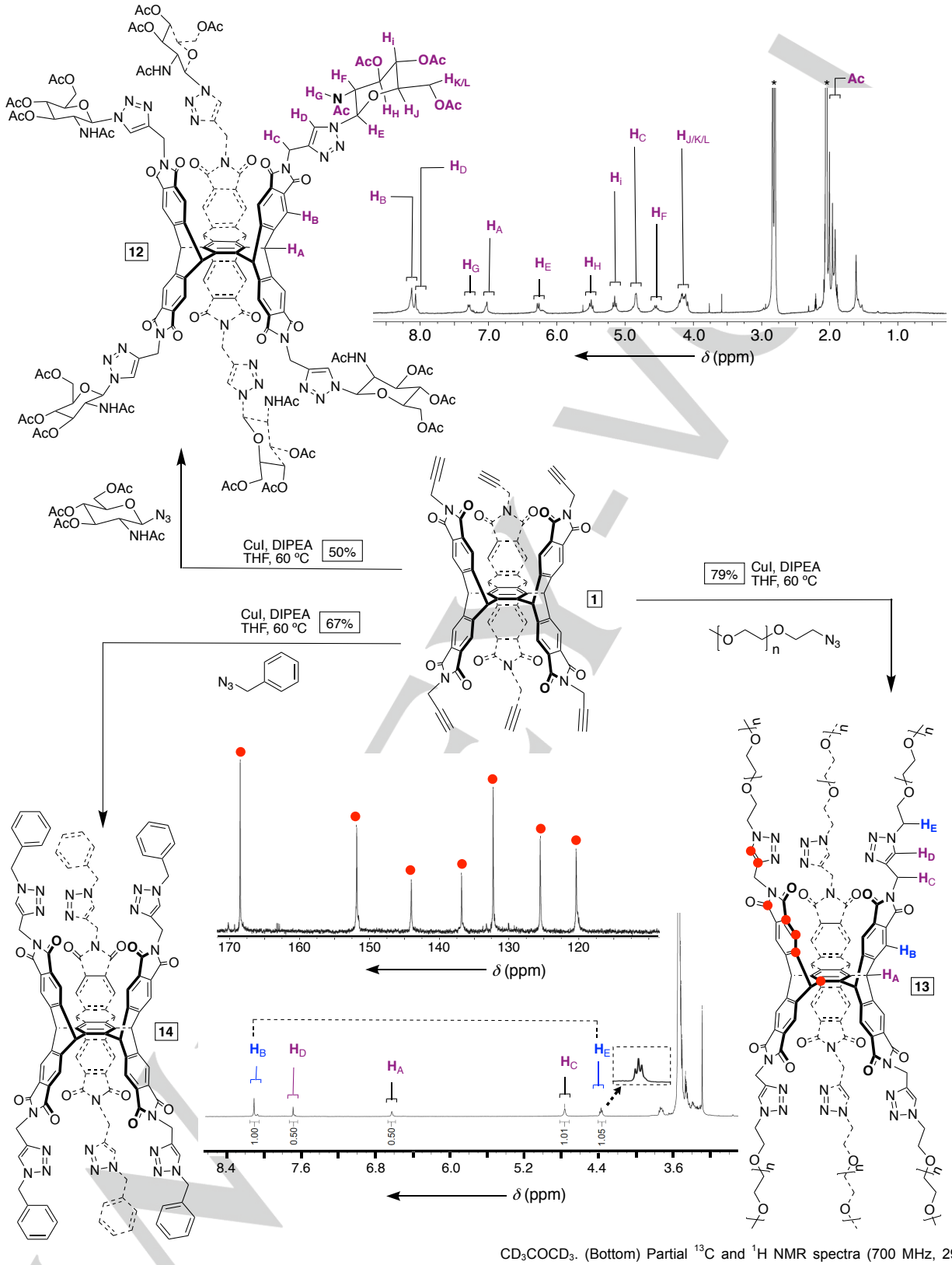

Figure 4. Conjugation of 2-acetamido-2-deoxy-*β*-*D*-glucopyranosyl azide 3,4,6-triacetate, methoxypolyethylene glycol azide (PEG, M_n = 2000) and benzyl azide to **1** was catalyzed with Cu(I) to give **12**, **13** and **14**. (Top) ^{1}H NMR spectrum (600 MHz, 298 K) of *β*-*D*-glucopyranosyl conjugate **12** in CD_3COCD_3. (Bottom) Partial ^{13}C and ^{1}H NMR spectra (700 MHz, 298 K) of PEG conjugate **13** in CD_3OD and CD_3CN, respectively.

can be run safely on a multi-gram scale (50 psi pressure of CO) with facile and quick purification of crude **9**. To transform **9** into **3** (Figure 2C), we used published[24] yet somewhat modified bromination/dehydrobromination procedures. Finally, the homocoupling of **3** was catalyzed with $Pd(OAc)_2$ to give dual-cavity **4** in 50% yield. To sum up, using the newly optimized procedure, one should be able to convert 5 grams of anthracene into 2.0 grams of multivalent **4** in circa ten days (Figure 2C). This is in a stark contrast with the original protocol,[24] which on this scale (a) provides 440 milligrams of the multivalent host, (b) is more costly and (c) requires a considerably longer time for completion.

With a quicker access to larger quantities of **4**, we began examining the incorporation of six terminal alkynes into this molecule (Figure 3). Notably, D_{3h} symmetric **4** possesses twelve esters to require a series of highly efficient reactions for its functionalization. Inspired by our earlier work with phthalimides[47] and their biocompatibility,[48] we decided to probe the preparation of hexa-imide **11** from **4** (Figure 3). Thermally unstable urea is known to, in the presence of imidazole, serve as a source of ammonia for the effective conversion of phthalic acids into phthalimides.[49] Accordingly, we reacted imidazole and urea with **4** in DMF and obtained **11**.[50] Hexa-imide **11** is soluble in $(CD_3)_2SO$ and its ^{1}H NMR spectrum (Figure 3) showed three sharp singlets corresponding to a D_{3h} symmetric molecule. Interestingly, a two hundred-fold dilution of **11** had no effect on its ^{1}H NMR spectrum (Figure 3), which indicates an absence of hydrogen-bonded aggregates.[51] The alkylation of six phthalimides with propargyl bromide (i.e. the Gabriel synthesis) gave desired **1** in 50% yield (Figure 3), with the product showing four distinct ^{1}H NMR resonances. The IR spectrum of **1** (Figure S30) revealed a broadened stretch at about 3278 cm^{-1}, corresponding to alkyne C^{sp}-H vibrations. The broadening could result from different conformers of **1** in which terminal alkynes are pointing to or away from the cavity. Indeed, the results of a molecular mechanics calculation (Monte-Carlo conformational search with OPLS-3 field; Figure 3) suggested a negligible energy difference for terminal alkynes assuming in/out orientations about the rim of **1**.

The Huisgen 1,3-dipolar cycloaddition of terminal alkynes to azides, catalyzed with Cu(I),[25a] is quintessential click chemistry[52] that has been of great service to bioconjugation and supramolecular chemistry, materials science and drug discovery.[25b, 29, 53] In the case of hexa-alkyne **1**, we probed the "clicking" of three different classes of molecules (Figure 4): *β*-D-glucopyranosyl azide, PEG-azide polymer (M_n = 2000) and benzyl azide. In each instance, CuI promoted the consecutive formation of six 1,4-disubstituted triazoles in tetrahydrofuran solvent to give **12**-**14** in 50-79% yield. In particular, the ^{1}H NMR spectrum of the carbohydrate conjugate **12** showed a set of signals corresponding to, on average, a D_{3h} symmetric compound (Figure 4, top). For assigning the resonances, we used ^{1}H-^{1}H COSY (Figure S32) and ^{1}H-^{13}C HSQC (Figure S33) correlations. We posit that the ^{1}H NMR signals are broadened due to a reduced rate of the rotation of proximal carbohydrate moieties about the central concave scaffold. In addition, singlets from acyl groups possess similar chemical shifts (c.a. 2.0 ppm, Figure 4) and are not magnetically shielded to indicate that carbohydrates reside outside the host's cavities; note that glucopyranosyl units akin to those in **12** are often conjugated to active components of drug molecules, but not necessarily act as drugs themselves. In case of dendritic polymer **13** (Mw = 13248, Figure S36), however, we noted a single set of ^{1}H and ^{13}C NMR signals (Figure 4, bottom). The result is in line with the heptiptycene cage being fully functionalized with six PEG chains (Mn = 2000): (1) ^{1}H NMR integration ratio of $\mathbf{H}_B$ (from the host):$\mathbf{H}_E$ (from polymeric residues) = 1.00:1.05, (2) seven ^{13}C NMR singlets from the aromatic part of the molecule and (3) no ^{1}H signals at 2.1 ppm from terminal alkynes (Figure S34); note that a significant population of partly functionalized molecules would make ^{13}NMR spectrum more complex and, presumably, reveal the presence of terminal alkynes. The bolaamphiphilic and dendritic polymers of type **13** are expected to, in water, assemble into unique polymersomes[28] with stimuli-responsive characteristics. At last, the conjugation of benzyl azide to **1** gave product **14** in 67% yield (Figure 4) with ^{1}H/^{13}C NMR spectra corresponding to, on average, a D_{3h} symmetric molecule (Figure S37-39). The effective formation of these types of molecules opens a way for rapidly accessing a variety of hosts capable of assembling into nanostructured soft materials.[26]

Conclusion

In conclusion, we have developed and optimized a streamlined synthetic methodology for obtaining gram quantities of multivalent and dual-cavity basket **1**. In nine synthetic steps, requiring circa two weeks for completion, one can convert inexpensive and abundant anthracene and vinyl acetate reactants into a functional and allosteric **1** holding six terminal alkynes at the periphery of its two fused cavitands. Importantly, **1** could be "clicked" to a variety of functional molecules (i.e. carbohydrates, polymers or aromatics) for creating dendritic and polymeric hosts. These structurally unique products could be easily diversified and screened for biological activity[54] or probed for assembling into soft materials.[26] At present, we are examining the assembly, biological activity and recognition characteristics of these intriguing compounds and will report on results in future.

Acknowledgements

This work was financially supported with funds obtained from Army Research Office (W911NF-17-1-0140). We thank graduate student Vageesha L. G. Gunawardana (OSU) for helping with the synthesis of dual-cavity **1**.

Keywords: Click Reaction • Multivalency • Supramolecular Chemistry • Molecular Recognition • Drug Design

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10.1002/chem.201805246

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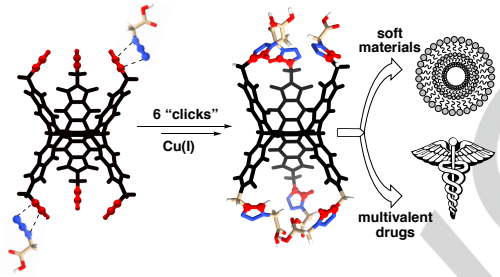
A structurally unique host with six terminal alkynes, at the periphery of its fused cavitands, can be clicked to carbohydrates, polymers and aromatics for obtaining a variety of multivalent drugs and nanostructured soft materials.



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A Hexavalent Basket for Bottom-Up Construction of Functional Soft Materials and Polyvalent Drugs via "Click" Reaction