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Host–Guest Systems |*Hot Paper*|

Incarceration of Higher-Order Fullerenes within Cyclotriveratrylene-Based Hemicarcerands Allows Selective Isolation of C_{76}, C_{78}, and C_{84} from a Commercial Fullerene Mixture

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Abstract: Size-complementary cyclotriveratrylene (CTV)-based hosts can incarcerate C_{76}, C_{78}, and C_{84}, thus allowing the selective isolation of these higher-order fullerenes from a commercially available mixture of fullerenes. The hemicarceplexes, formed after the encapsulation of the size-complementary fullerenes within the hosts, are isolated by column chromatography and released at elevated temperature, thereby leading to the isolation of C_{76}/C_{78} and C_{84} in good purities (up to 95 and 88%, respectively).

Introduction

Since the discovery of buckminsterfullerene (C_{60}) in 1985, various fullerenes have found applications in photovoltaics, semiconductors, and biopharmacology.[1] Although low solubility in common organic solvents makes it difficult to purify fullerenes, at present we have access to relatively large supplies of high-purity C_{60} and C_{70}, the most abundant fullerenes in extracts of carbon soot obtained from the combustion of graphite through the arc discharge method as a result of the development of several ingenious separation methods.[2] Nevertheless, the higher-order fullerenes C_{76}, C_{78}, and C_{84}, which have unique stereochemical and electrochemical properties relative to C_{60} and C_{70}, remain difficult to access, even though these species are the most abundant in commercially available mixtures of higher-order fullerenes obtained after the extraction of C_{60} and C_{70}. The purification of these higher-order fullerenes relies mainly on multiple cycles of HPLC, thus limiting their supply in high-purity ($\geq$98%) forms and significantly elevating the prices (up to ca. US$360 mg^{-1}).[3] Host–guest chemistry has become a reliable means of selectively separating C_{60} and C_{70},[2c,4] but has rarely been applied to the purification of higher-order fullerenes.[5] The pioneering host–guest systems for the separation of C_{60} and C_{70} from their mixtures have relied mainly on size differences; unfortunately, many of the higher-order fullerenes in commercial mixtures are similar in terms of abundances and sizes (compare C_{70}, C_{76}, C_{78}, C_{82}, C_{84}, and C_{86}; Figure 1a),[6] thus making their separation through host–guest approaches even more challenging and, therefore requiring subtle changes in the host structures to afford reasonable selectivities. Herein, we report kinetic and thermodynamic studies of the incarceration and release of hemicarceplexes formed from size-complementary higher-order fullerenes[7] and cyclotriveratrylene (CTV)-based hosts[8] and the application of this approach to the selective isolation of C_{76}/C_{78} and C_{84} from a commercially available mixture of higher-order fullerenes. The higher-order fullerenes C_{76}/C_{78} and C_{84} isolated by using this approach had reasonably good purities (up to 95 and 88%, respectively), which simplified their subsequent HPLC separations and improved their purities further (up to $\geq$99.5%).

Results and Discussion

Previously, we used molecular cage **1** (Figure 1d) to isolate C_{70} in high purity ($\geq$99.0%) directly from a fullerene extract,[9] thus taking advantage of room-temperature-isolable hemicarceplexes (formed from the sequestration of complementary guests within hemicarcerands) and releasing the guests at elevated temperatures. Because the higher-order fullerenes are not much bigger than C_{70}, their selective complexation of these compounds would require host molecules with only slightly larger cavities and openings. Thus, we anticipated that hosts **2** and **3**, with a greater numbers of bridging methylene units, might be applicable for the selective isolation of C_{76}, C_{78}, and C_{84} from a commercial mixture of higher-order fullerenes.

We synthesized (Scheme 1) molecular cages **2** and **3** in seven steps from 3,4-dihydroxybenzaldehyde (**4**). Selective monoalkylation of **4** at its most acidic phenolic group (i.e., the *para* position) with 1,12-dibromododecane gave aldehyde **5**, which we subjected to $NaBH_4$-mediated reduction of the formyl group to give bromide **6**. Another selective alkylation of

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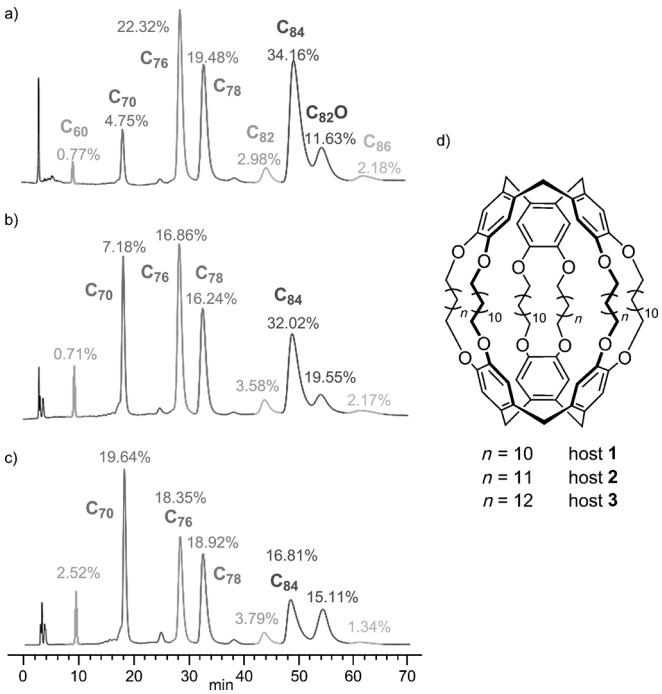
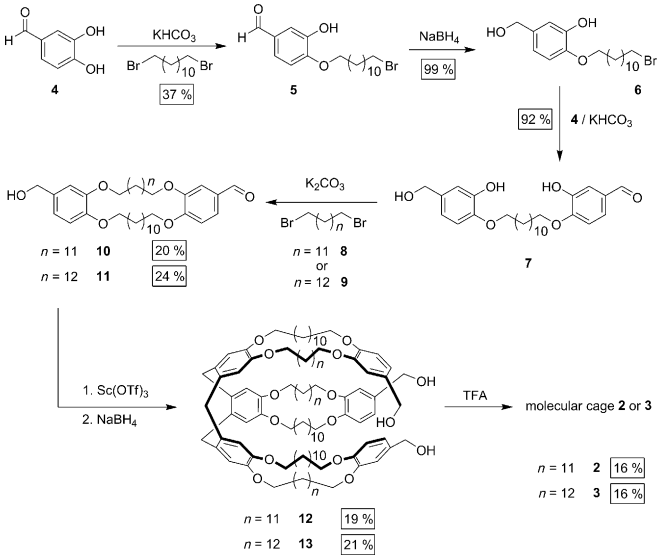


Figure 1. a–c) HPLC profiles of a) the commercially available mixture of higher-order fullerenes and b, c) the residue mixtures after the first (b) and second (c) extraction cycles of C_{76}/C_{78} and C_{84}. d) Chemical structures of molecular cages **1**–**3**.



Scheme 1. Synthesis of molecular cages **2** and **3**.

4 with bromide **6** afforded triol **7**, which we treated with dibromide **8** (or **9**) to produce the macrocycle **10** (or **11**). We obtained a trialdehyde after the $Sc(OTf)_3$-catalyzed condensation of three units of macrocycle **10** (or **11**) into the first CTV unit.[10] $NaBH_4$-mediated reduction afforded triol **12** (or **13**), which condensed under acidic conditions to form the second CTV unit, thereby affording the molecular cage **2** (or **3**). The overall yields for the syntheses of hosts **2** and **3** were 0.2 and 0.3%, respectively. Because these cages present six long alkyl chains, **2** and **3** are quite soluble in less-polar organic solvents (e.g., CH_2Cl_2, $CHCl_3$, and $CHCl_2CHCl_2$), but not very soluble in more-polar organic solvents (e.g., CH_3CN and THF). Thus, we expected that the complexation of higher fullerenes within these two hosts would significantly increase the solubility of the fullerenes in less-polar solvents.

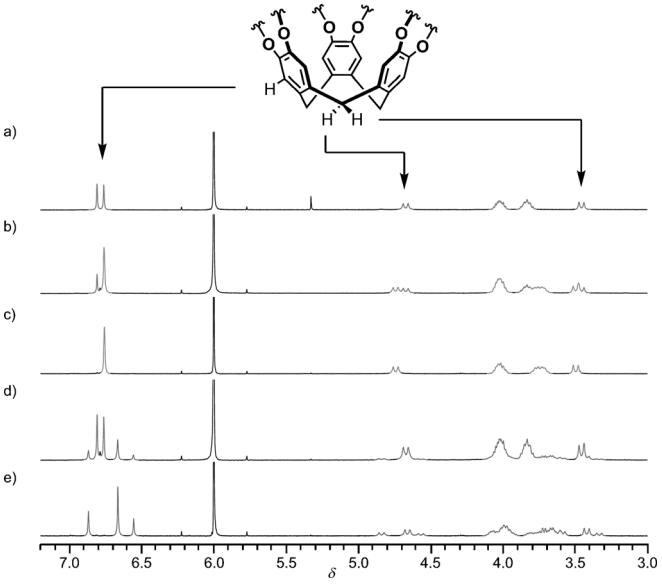


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_2CDCl_2$, 298 K) of a) the free host **2**; b, d) mixtures of host **2** (2.25 mM) and C_{76} (1.5 mM; b) and C_{78} (1.5 mM; d) after sitting at 298 K for 48 h; c, e) the purified hemicarceplexes C_{76}@**2** (c) and C_{78}@**2** (e).

The ^{1}H NMR spectrum of a solution of host **2** (2.25 mM) and C_{76} (1.5 mM) in $CDCl_2CDCl_2$ displayed a single new set of signals that correspond to the formation of the hemicarceplex C_{76}@**2** after the mixture had been left at 298 K for 48 hours (Figure 2). The stability of C_{76}@**2** was confirmed by isolation with column chromatography (SiO_2); there were no noticeable signals that correspond to the free host **2** in the ^{1}H NMR spectrum (Figure 2 c). In contrast, the ^{1}H NMR spectrum of a solution of **2** (2.25 mM) and C_{78} (1.5 mM) displayed three sets of new signals after the mixture had been left at 298 K for 48 hours (Figure 2 d). It has been demonstrated previously that a CTV-based molecular cage can distinguish between the two structural isomers of the metallofullerene $Sc_3N@C_{80}$, thus reporting the differences in their incarcerated forms by using ^{1}H NMR spectroscopic analysis.[11] Because three major structural isomers (i.e., D_3(3), C_{2v}(4), C_{2v}(5)) are generally present in samples of C_{78},[12] we suspected that the three new sets of signals arose from the incarceration of these three major structural isomers of C_{78} within **2**. The observation of an intense signal at *m/z* 2707.3 that corresponds to the $[C_{78}@\mathbf{2}]^+$ ion in the mass spectrum of the chromatographically isolated C_{78}@**2** and an isomeric distribution ratio in its ^{1}H NMR spectrum (Figure 2 e) similar to that of the original mixture (Figure 2 d) supported the notion that C_{78}@**2** was indeed a mixture of three different complexes. In contrast, a solution of **2** (2.25 mM) and C_{84}

(1.5 mM) in $CDCl_2CDCl_2$ gave no noticeable signals for the corresponding hemicarceplex C_{84}@**2** in its ^{1}H NMR spectrum after sitting at 298 K for 48 hours, thus suggesting that squeezing the relatively large C_{84} through the openings of host **2** requires more energy than the passage of the relatively small C_{76} and C_{78}. Indeed, this process did not occur at a measurable rate under these conditions.

Quan and Cram defined the activation energy required for a guest to enter the cavity of a hemicarcerand and the free energy for the formation of a hemicarceplex as the intrinsic and constrictive binding energies, respectively.[13a] The use of ^{1}H NMR spectroscopic analysis to monitor the dissociation of purified C_{76}@**2** and C_{78}@**2** in $CDCl_2CDCl_2$ at 298 K, until equilibrium had been reached, afforded association constants of K_a = 6800 and 9400 M^{-1}, respectively, for these hemicarceplexes.[14] By monitoring the changes of the integration ratios of the free host **2** and the hemicarceplexes, we determined the dissociation half-lives and rate constants of the hemicarceplexes at 298 K to be $t_{1/2}$ = 16.9 h and $k_d = 1.1\times10^{-5}$ s^{-1}, respectively, for C_{76}@**2** and $t_{1/2}$ = 33.6 h and $k_d = 5.7\times10^{-6}$ s^{-1}, respectively, for C_{78}@**2** (Figure 3). Therefore, the calculated association rate constants of host **2** to C_{76} and C_{78} were $k_a = 7.5\times10^{-2}$ and 5.4×10^{-2} $M^{-1}s^{-1}$, respectively. Based on these numbers, we estimated the intrinsic and constrictive binding energies of the hemicarceplexes at 298 K to be E = 5.2 and 19.0 kcal mol^{-1}, respectively, for C_{76}@**2** and E = 5.4 and 19.2 kcal mol^{-1}, respectively, for C_{78}@**2**. As expected, the smaller C_{76} molecule can squeeze through the openings of host **2** more readily than C_{78}, but the larger C_{78} molecule can fill the cavity of the host better, thus making C_{78}@**2** more stable than C_{76}@**2**, as revealed by the slower dissociation kinetics and larger association constant K_a of the former hemicarceplex.

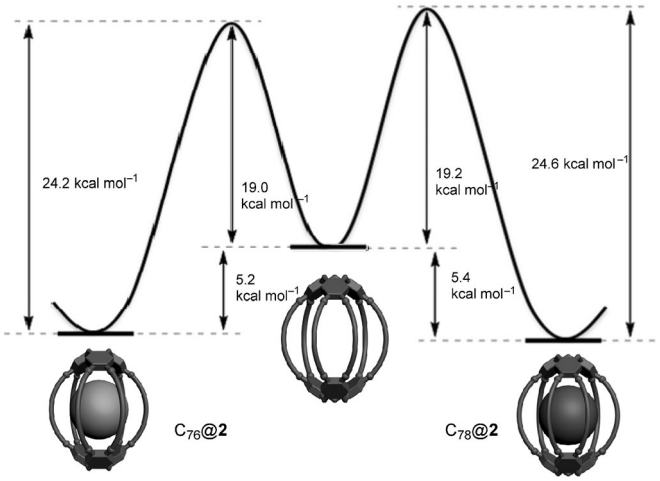


Figure 3. Constrictive and intrinsic binding energies for the complexation of C_{76} and C_{78} with host **2** in $CDCl_2CDCl_2$ at 298 K.

After confirming that molecular cage **2** can form hemicarceplexes selectively with C_{76} and C_{78}, but not C_{84}, at 298 K, we used **2** (450 mg) to directly extract C_{76} and C_{78} from a mixture of higher-order fullerenes (600 mg) in $CHCl_2CHCl_2$ (30 mL). Figure 4 presents the flow chart of the isolation process. After heating the mixture at 308 K for 40 hours to incarcerate the fullerenes, we evaporated the solvent under reduced pressure, suspended the solid residue in CH_2Cl_2, and filtered the suspension to recycle the insoluble higher-order fullerenes ("solid A"). We concentrated the filtrate and purified it chromatographically to afford the free host **2**, free higher-order fullerenes ("solid B"), and a mixture of hemicarceplexes. We dissolved the free molecular cage **2** from the chromatography step with solids A

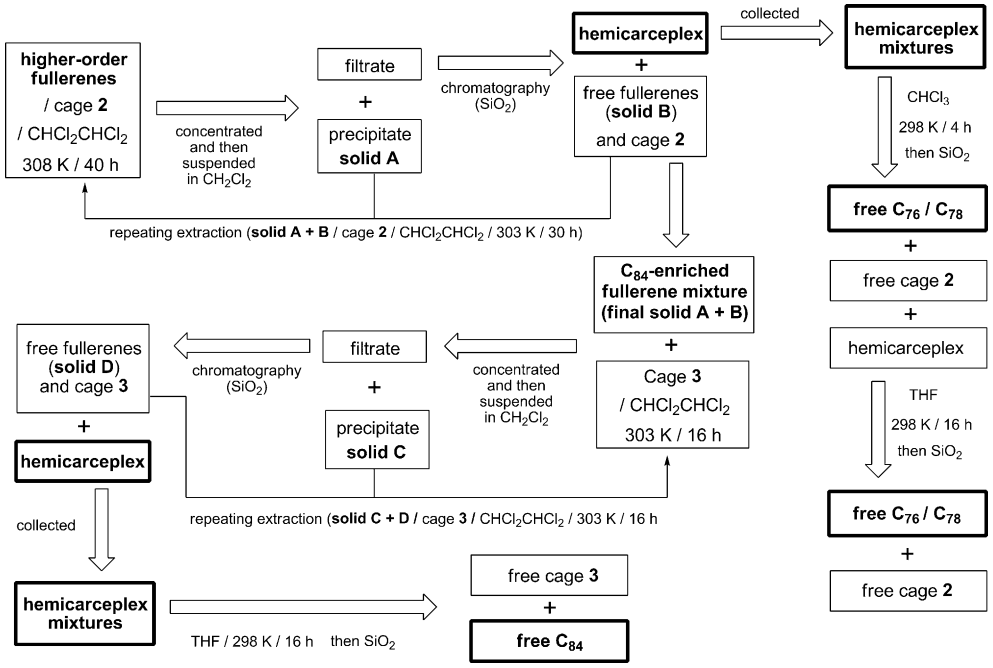


Figure 4. Flow chart for the isolation of C_{76}/C_{78} and C_{84} from a commercial mixture of higher-order fullerenes. This sequence was performed twice, with the "final solid C + D" used as the starting "higher-order fullerenes" (top left corner) the second time around.

and B in $CHCl_2CHCl_2$, and subjected this mixture to another cycle of the extraction process. After three repeated extraction cycles, we dissolved the combined hemicarceplexes (316 mg) in $CHCl_3$ and left the mixture at 298 K for 4 hours to release the incarcerated fullerenes. After flash column chromatography (SiO_2), we isolated hemicarceplexes (177 mg), higher-order fullerenes (40 mg), and **2** (65 mg). The HPLC trace of the fullerenes indicated that **2** was quite efficient at incarcerating the fullerenes C_{76} and C_{78} from the mixture because these species were predominant among all the released fullerenes, with a combined purity of approximately 94% (Figure 5a). The electrospray ionization (ESI) mass spectrum of the hemicarceplex mixture after extracting the higher-order fullerenes mixture with **2** (solid B) revealed signals for hemicarceplexes C_{82}@**2** and C_{84}@**2** in addition to signals for C_{76}@**2** and C_{78}@**2**; thus, the incarceration of C_{84} by **2** proceeded at a reasonable rate at 308 K. Thus, the isolation of C_{76}/C_{78} in high purity from the higher-order fullerene mixture was presumably the result of relatively slow association and dissociation kinetics for the incarceration and release of the relatively large C_{82} and C_{84} molecules from their corresponding hemicarceplexes.

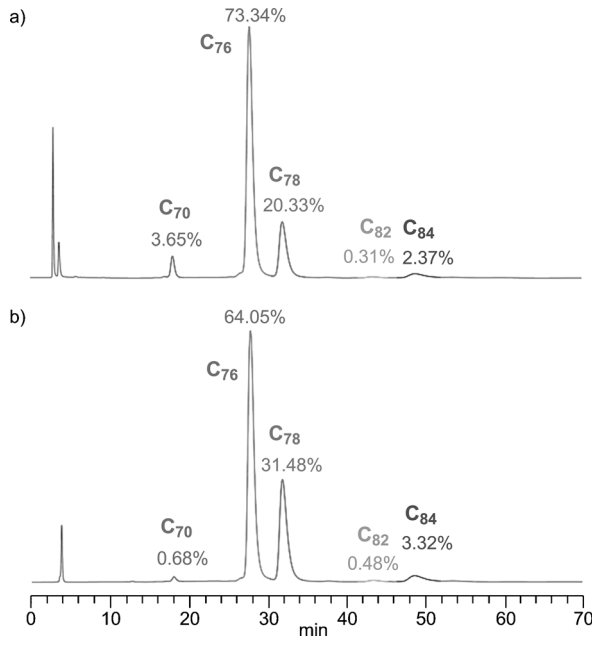


Figure 5. HPLC profiles of the solids obtained after the first (a) and second (b) guest-release processes from the hemicarceplex fullerene@**2**.

Next, we dissolved the mixture of hemicarceplexes (177 mg) in THF and left the solution at 298 K for 16 hours to release the incarcerated higher-order fullerene guests again. We then centrifuged the dark suspension to precipitate both the free fullerenes and the molecular cage **2**. After dissolving the black residue in CS_2, we subjected the solution to flash chromatography through a short column to separate the free fullerenes (55 mg) from the free host **2** (83 mg).[15] A significant amount (ca. 20%) of the larger C_{78} molecule was present in the fullerene mixture released in the first run, yet the smaller C_{76} molecule remained as the predominant species (ca. 64%) in the second (Figure 5b). The difference in the dissociation kinetics of the two hemicarceplexes appears to be too small for separation of these two fullerenes through selective release of the less-sizable C_{76} from **2**. The combined purity of C_{76} and C_{78} did not, however, vary much between the first and second rounds of the guest being released (ca. 94 and 95%, respectively), thus suggesting reasonably good selectivity for host **2** toward C_{76} and C_{78} during guest incarceration and release among all of the higher-order fullerenes in the extract. The presence of significant amounts of C_{76} and C_{78} in the released higher-order fullerenes mixture suggests that these two fullerenes are so similar in size that any differences in their complexation kinetics to **2** are too insignificant to allow selective encapsulation or release of one of them from the higher-order fullerene or hemicarceplex mixture, respectively.

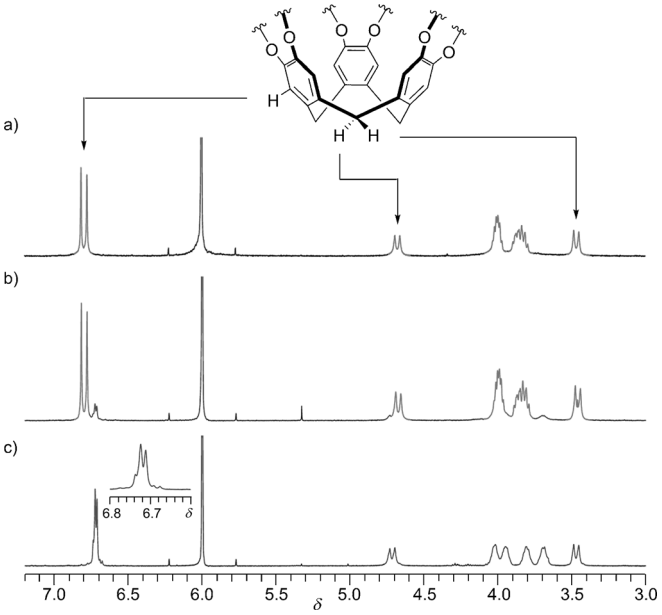


Figure 6. ^{1}H NMR spectra (400 MHz, $CDCl_2CDCl_2$, 298 K) of a) the free host **3**; b) a mixture of **3** (2.25 mM) and C_{84} (1.5 mM) after sitting at 298 K for 48 h; c) purified C_{84}@**3**.

In contrast to host **2**, the ^{1}H NMR spectrum of a solution of host **3** (2.25 mM) and C_{84} (1.5 mM) in $CDCl_2CDCl_2$ displayed new sets of signals for hemicarceplex C_{84}@**3** after sitting at 298 K for 48 hour (Figure 6). Similar to hemicarceplex C_{78}@**2**, the encapsulation of many structural isomers of C_{84} by **3** was reflected in the presence of several overlapping aromatic signals from the host. The appearance of two major, yet unequal, signals at $\delta = 6.71$ and 6.72 ppm and several minor signals for the aromatic protons of the CTV units is consistent with C_{84} containing two major isomers (i.e., D_2(IV) and D_{2d}(II)) and several minor ones.[16] By using ^{1}H NMR spectroscopic analysis to monitor the dissociation kinetics of the chromatographically purified hemicarceplex C_{84}@**3** in $CDCl_2CDCl_2$ at 298 K, until equilibrium had been reached, we determined the association constant and dissociation rate constant of the hemicarceplex

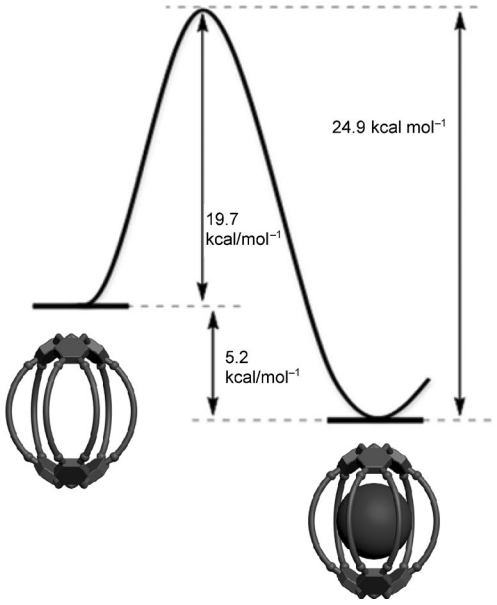


Figure 7. Constrictive and intrinsic binding energies for the complexation of C_{84} with host **3** in $CDCl_2CDCl_2$ at 298 K.

C_{84}@**3** to be $K_a = 6500\ M^{-1}$[14] and $k_d = 3.5 \times 10^{-6}\ s^{-1}$, respectively. These values correspond to a dissociation half-life and free energy of $t_{1/2} = 55.5$ h and $E = 24.9$ kcal mol^{-1}, respectively (Figure 7). Accordingly, the association rate constant and free energy for the host **3** incarcerating C_{84} were $k = 2.3 \times 10^{-2}\ M^{-1}\ s^{-1}$ and $E = 19.7$ kcal mol^{-1}, respectively. Because the complexes formed from relatively small C_{76} and C_{78} molecules with host **3** in $CDCl_2CDCl_2$ were insufficiently stable to allow isolation of their hemicarceplexes at room temperature, we expected significant dissociation of these complexes to occur during chromatography when isolating hemicarceplex C_{84}@**3**. If so, we could use **3** to selectively isolate C_{84} from the higher-order fullerene mixture.

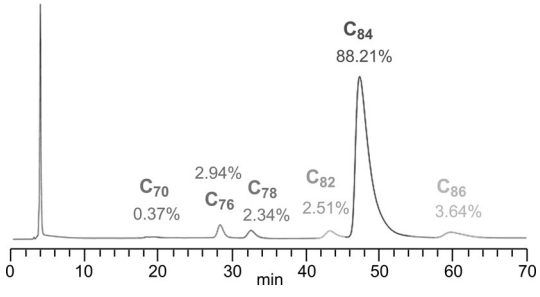


Figure 8. HPLC profile of the solid obtained after applying the guest-release process to the fullerene@**3** hemicarceplexes.

Because the selective extraction of C_{76} and C_{78} increased the molar fraction of C_{84} in the recycled mixture of higher-order fullerenes ("final solid A + B"; 494 mg), we attempted to extract C_{84} from this mixture by treatment with the relatively large molecular cage **3** (494 mg) in $CHCl_2CHCl_2$ at 303 K for 16 hours. The processes for isolating hemicarceplex C_{84}@**3** and dissociating its components were similar to those procedures described above for the extraction of C_{76}/C_{78}. The higher-order fullerene C_{84} (80 mg) obtained from dissociation of hemicarceplex C_{84}@**3** (282 mg), collected from two repeated extraction cycles (via "solid C" and "solid D") and precipitation from THF, had a purity of 88%, based on HPLC analysis (Figure 8).[17] The presence of considerable amounts of C_{82} and C_{86} in this isolated sample of C_{84} suggests that host **3** could not differentiate these three fullerenes efficiently.

HPLC analysis (Figure 1b) of the solid mixture of higher-order fullerenes ("final solid C + D") obtained after the sequential extractions of C_{76}/C_{78} (with **2**) and C_{84} (with **3**) revealed significant decreases in the contents of these three fullerenes by using the signal of C_{70} as a reference. Nevertheless, these three fullerenes remained the predominant species in the recycled fullerene mixture; accordingly, we applied recycled hosts **2** and **3** to a second extraction cycle of this fullerene mixture. As expected, the purities of the C_{76}/C_{78} and C_{84} precipitates obtained from this second extraction cycle decreased (to 80 and 81%, respectively) due to the lower molar fractions of these fullerenes in the mixture. HPLC analysis (Figure 1c) of the solid ("final solid C + D") obtained in the second extraction cycle indicated that C_{70} was the predominant species in the mixture after the two extraction cycles. The presence of large signals for C_{70} and $C_{82}O$ in this HPLC trace confirmed that large amounts of C_{76}, C_{78}, and C_{84} had been removed from the commercial mixture of higher-order fullerenes.

The use of the CTV-based hosts **2** (450 mg) and **3** (494 mg) to form hemicarceplexes with suitably sized higher-order fullerenes allowed us to isolate C_{76}/C_{78} (total = 126 mg) and C_{84} (total = 112 mg) directly in purities of 80–95 and 81–88%, respectively, from a commercially available mixture of higher-order fullerenes (600 mg). Based on the HPLC profile of the commercial mixture of higher-order fullerenes, the total contents of C_{76}/C_{78} and C_{84} were approximately 251 and 205 mg, respectively. Therefore, the two extraction cycles allowed us to isolate approximately 46 and 47% of the C_{76}/C_{78} and C_{84}, respectively, from the commercial mixture of higher-order fullerenes.

Because the higher-order fullerenes obtained from our simple extraction processes and column chromatography were in good purities, there is no need to perform recycling HPLC for further purification. Thus, by performing a single standard HPLC separation (Cosmosil 5 m PBB, semipreparative, 10.0 × 250 mm; sample injection volume = 2.5 mL) using toluene (a relatively poor solvent for higher-order fullerenes) as the eluent, we obtained 16 and 8 mg of C_{76} and C_{78} (84 and 89% separation yields), respectively, in high purity ($\geq$99.5%; Figure 9a,b) from 30 mg of the fullerene solid obtained from the second guest-release process of hemicarceplex fullerene@**2** (C_{76}: 64.1, C_{78}: 31.5%; Figure 5b). Similarly, 7 mg (78% separation yield) of high-purity C_{84} $\geq$99.5%; Figure 9c) was obtained from the same HPLC separation from 10 mg of the fullerene solid collected from the guest-release process of the hemicarceplex fullerenes@**3** (C_{84}: 88%; Figure 8). The use of a preparative-scale HPLC column, a larger injection loop, and/or an eluent more suitable for fullerenes would presumably increase

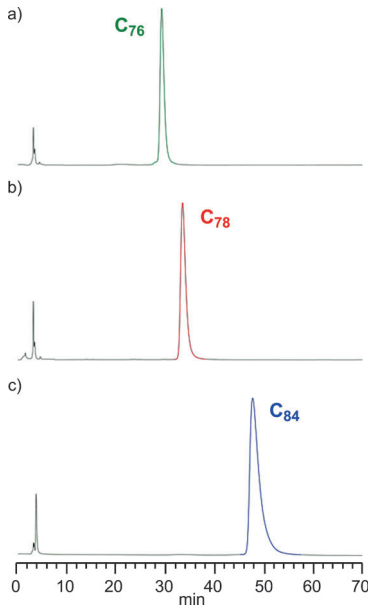


Figure 9. HPLC profiles of high-purity samples of a) C_{76}, b) C_{78}, and c) C_{84}, obtained after subjecting the samples collected from the guest-release processes of the hemicarceplex fullerene@**2** (a, b) and fullerenes@**3** (c) to a standard semipreparatory HPLC process.

the scale of this separation process; therefore, we believe that our extraction method might have potential applicability in the large-scale production of higher-order fullerenes.

Conclusion

The CTV-based host molecules **2** and **3** can form hemicarceplexes with higher-order fullerenes and, thus, can be used to selectively isolate C_{76}/C_{78} and C_{80}, respectively, in high purities (80–95 and 81–88%, respectively) from a commercially available mixture of higher-order fullerenes. By following simple extraction/column chromatography processes, subsequent straightforward HPLC separations could improve the purities to $\geq$99.5%. Thus, host–guest chemistry remains a powerful strategy for solving tough separation problems, as long as the hosts are designed to suitably balance the complexation kinetics and thermodynamics. The use of this approach should increase the supplies of high-purity C_{76}, C_{78}, and C_{84}, thus potentially allowing the discovery of further interesting applications for these higher-order fullerenes.

Experimental Section

General: All glassware, syringes, needles, and stirring bars were either oven- or flame-dried prior to use. All reagents, unless otherwise indicated, were obtained from commercial sources. Reactions were conducted under N_2 or Ar. Thin layer chromatography (TLC) was performed on Merck 0.25 mm silica gel plates (Merck Art. 5715). Column chromatography was performed on Kieselgel 60 (Merck; 70–230 mesh). Melting points were determined by using a Fargo MP-2D melting-point apparatus.

Bromide 5: A mixture of 3,4-dihydroxybenzaldehyde (16.6 g, 120 mmol), $KHCO_3$ (13.4 g, 134 mmol), and 1,12-dibromododecane (39.4 g, 120 mmol) in acetone (1200 mL) was heated under reflux for 40 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (3×200 mL) and H_2O (600 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified chromatographically on SiO_2 (EtOAc/hexanes (1:10)) to afford bromide **5** as a white solid (16.9 g, 37%). M.p. 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 1.19–1.46 (m, 16H), 1.74–1.84 (m, 4H), 3.35 (t, J = 6.8 Hz, 2H), 4.07 (t, J = 6.8 Hz, 2H), 6.04 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 9.77 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 25.8, 28.0, 28.6, 28.8, 29.2, 29.2, 29.3, 32.7, 33.9, 69.2, 110.8, 113.9, 124.5, 130.2, 146.1, 151.3, 190.9 ppm (two signals were missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{19}H_{30}BrO_3^+$: m/z 385.1378; found: 385.1380 $[M+H]^+$.

Bromide 6: $NaBH_4$ (827 mg, 21.9 mmol) was added to a solution of bromide **5** (16.9 g, 43.9 mmol) in MeOH (220 mL) and CH_2Cl_2 (220 mL) at 0 °C and then the mixture was stirred at room temperature for 2 h. The organic solvents were evaporated under reduced pressure and the residue partitioned between CH_2Cl_2 (3×200 mL) and H_2O (600 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), and concentrated to give bromide **6** as a white solid (16.9 g, 99%), which was used directly in the next step without further purification. M.p. 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 1.23–1.47 (m, 16H), 1.74–1.88 (m, 4H), 3.38 (t, J = 6.8 Hz, 2H), 4.01 (t, J = 6.8 Hz, 2H), 4.55 (d, J = 5.2 Hz, 2H), 5.67 (s, 1H), 6.77–6.83 (m, 2H), 6.92 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 26.0, 28.1, 28.7, 29.2, 29.3, 29.4, 29.5, 29.5, 32.8, 34.0, 65.1, 69.1, 111.6, 113.5, 118.8, 134.2, 145.5, 145.9 ppm (one signal was missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{19}H_{30}BrO_2^+$: m/z 369.1429; found: 369.1436 $[M-OH]^+$.

Triol 7: A mixture of bromide **6** (16.9 g, 43.6 mmol), 3,4-dihydroxybenzaldehyde (6.64 g, 48.1 mmol), and $KHCO_3$ (4.82 g, 48.1 mmol) in DMF (440 mL) was stirred at 50 °C for 40 h and then the solvent was evaporated under reduced pressure. The residue was washed with H_2O (400 mL) and Et_2O (150 mL) to afford triol **7** as a pale-brown solid (17.8 g, 92%). M.p. 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 1.23–1.37 (m, 12H), 1.38–1.52 (m, 4H), 1.74–1.88 (m, 4H), 4.01 (t, J = 6.4 Hz, 2H), 4.11 (t, J = 6.4 Hz, 2H), 4.56 (s, 2H), 5.67 (br, 2H), 6.77–6.83 (m, 2H), 6.90–6.94 (m, 2H), 7.36–7.43 (m, 2H), 9.81 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 25.9, 26.0, 29.0, 29.2, 29.3, 29.3, 29.5, 29.5, 65.2, 69.1, 69.3, 110.9, 111.6, 113.5, 114.1, 118.8, 124.4, 130.5, 134.2, 145.5, 145.9, 146.2, 151.3, 191.0 ppm (two signals were missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{26}H_{35}O_6^-$: m/z 443.2434; found: 443.2445 $[M-H]^-$.

Macrocycle 10: A mixture of triol **7** (6.67 g, 15.0 mmol), 1,13-dibromotridecane (5.13 g, 15.0 mmol), and K_2CO_3 (16.6 g, 120 mmol) in DMF (1500 mL) was stirred at 50 °C for 5 days, and then the solvent was evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (4×250 mL) and H_2O (400 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified chromatographically on SiO_2 ($CHCl_3$) to afford macrocycle **10** as a white solid (1.86 g, 20%). M.p. 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 323 K): δ = 1.24–1.41 (m, 26H), 1.42–1.56 (m, 8H), 1.73–1.86 (m, 8H), 3.94–4.09 (m, 8H), 4.58 (d, J = 5.6 Hz, 2H), 6.82–6.85 (m, 2H), 6.90–6.95 (m, 2H), 7.37–7.41 (m, 2H), 9.81 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 323 K): δ = 26.3, 26.3, 26.4, 26.4, 29.4, 29.4, 29.6, 29.6, 29.6, 29.7, 29.8, 29.8, 29.8, 29.9, 65.4, 69.3, 69.3, 69.5, 69.8, 111.7, 112.3, 113.5, 114.6, 119.7, 126.4,

130.2, 134.1, 149.2, 149.9, 155.1, 190.8 ppm (eight signals were missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{39}H_{60}O_6^+$: *m/z* 624.4390; found: 624.4425 $[M]^+$.

Triol 12: A solution of macrocycle **10** (1.86 g, 2.98 mmol) and $Sc(OTf)_3$ (146 mg, 297 mmol) in $CHCl_3$ (54 mL) and CH_3NO_2 (6 mL) was heated under reflux for 16 h. After cooling to room temperature, water (30 mL) was added to the mixture. The organic phase was washed with brine (30 mL) and concentrated. The residue was dissolved in isopropyl alcohol (8 mL) and CH_2Cl_2 (24 mL) and then $NaBH_4$ (42 mg, 1.11 mmol) was added to the reaction mixture, which was stirred at room temperature for 2 h. The organic solvents were then evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (3×50 mL) and H_2O (50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified chromatographically on SiO_2 (CH_2Cl_2/MeOH (99:1)) to afford triol **12** as a white solid (350 mg, 19%). M.p. 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 1.22–1.35 (m, 78H), 1.37–1.51 (m, 24H), 1.68–1.80 (m, 24H), 3.46 (d, J = 13.6 Hz, 3H), 3.82–4.00 (m, 24H), 4.56 (s, 6H), 4.68 (d, J = 13.6 Hz, 3H), 6.78–6.85 (m, 12H), 6.89 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 26.3, 26.4, 26.4, 29.6, 29.7, 29.8, 29.9, 30.0, 36.5, 65.4, 69.2, 69.6, 69.8, 113.0, 114.2, 115.9, 116.3, 119.6, 132.2, 132.3, 133.9, 147.9, 148.0, 148.9, 149.6 ppm (14 signals were missing, possibly because of signal overlap) HRMS (ESI): calcd for $C_{117}H_{180}O_{15}^+$: *m/z* 1825.3322; found: 1825.3373 $[M]^+$.

Molecular cage 2: A solution of triol **12** (296 mg, 162 mmol) in $CHCl_3$ (45 mL) was added to a solution of trifluoroacetic acid (TFA; 8.1 mL) in $CHCl_3$ (85 mL) and CH_3NO_2 (32 mL) over a period of 12 h and then the mixture was stirred at room temperature for 60 h. After the addition of saturated $Na_2CO_{3(aq)}$ (100 mL), the organic phase was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified chromatographically on SiO_2 (from CH_2Cl_2 to CH_2Cl_2/MeOH (200:1)) to afford a white solid, which was recrystallized (CH_2Cl_2/hexanes) to give **2** (29.5 mg, 16%). M.p. 267–268 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 1.14–1.45 (m, 102H), 1.60–1.84 (m, 24H), 3.45 (d, J = 13.6 Hz, 6H), 3.76–3.90 (m, 12H), 3.98–4.10 (m, 12H), 4.68 (d, J = 13.6 Hz, 6H), 6.76 (s, 6H), 6.82 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 26.4, 26.5, 29.1, 29.2, 29.5, 29.7, 29.9, 30.1, 30.5, 30.5, 36.4, 68.2, 70.0, 113.8, 116.5, 131.4, 132.5, 147.1, 148.1 ppm (one signals was missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{117}H_{174}O_{12}^+$: *m/z* 1771.3005; found: 1771.3946 $[M]^+$.

Macrocycle 11: A mixture of triol **7** (6.67 g, 15.0 mmol), 1,14-dibromotetradecane (5.34 g, 15.0 mmol), and K_2CO_3 (16.6 g, 120 mmol) in DMF (1500 mL) was stirred at 50 °C for 5 days and then the solvent was evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (4×250 mL) and H_2O (400 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was purified chromatographically on SiO_2 (CH_2Cl_2/MeOH (100:0.5)) to afford a white solid (2.27 g, 24%). M.p. 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 323 K): δ = 1.21–1.39 (m, 28H), 1.45–1.54 (m, 8H), 1.73–1.87 (m, 8H), 3.94–4.09 (m, 8H), 4.58 (d, J = 6.0 Hz, 2H), 6.81–6.87 (m, 2H), 6.89–6.95 (m, 2H), 7.35–7.43 (m, 2H), 9.80 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 323 K): δ = 26.2, 26.3, 26.4, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 29.7, 29.8, 29.8, 29.8, 29.9, 65.4, 69.0, 69.2, 69.3, 69.4, 111.2, 111.8, 113.1, 114.0, 119.6, 126.6, 129.9, 133.8, 149.5, 149.6, 154.9, 191.0 ppm (eight signals were missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{40}H_{62}O_6Na$: *m/z* 661.4444; found: 661.4420 $[M+Na]^+$.

Triol 13: A solution of macrocycle **11** (2.27 g, 3.55 mmol) and $Sc(OTf)_3$ (87 mg, 0.177 mmol) in $CHCl_3$ (35 mL) and CH_3NO_2 (3.5 mL) was heated under reflux for 16 h. After cooling to room temperature, water (20 mL) was added to the mixture. The organic phase was washed with brine (20 mL) and concentrated. The residue was dissolved in isopropyl alcohol (14 mL) and CH_2Cl_2 (42 mL) and then $NaBH_4$ (62 mg, 1.64 mmol) was added to the reaction mixture, which was stirred at room temperature for 2 h. The organic solvents were then evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (3×50 mL) and H_2O (50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified chromatographically on SiO_2 (CH_2Cl_2/MeOH (99:1)) to afford a white solid (475 mg, 21%). M.p. 133–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 1.20–1.36 (m, 84H), 1.38–1.51 (m, 24H), 1.59 (t, J = 5.6 Hz, 3H), 1.68–1.81 (m, 24H), 3.46 (d, J = 13.6 Hz, 3H), 3.82–4.03 (m, 24H), 4.57 (d, J = 5.6 Hz, 6H), 4.68 (d, J = 13.6 Hz, 3H), 6.76–6.87 (m, 12H), 6.89 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 26.3, 26.4, 26.4, 29.6, 29.6, 29.6, 29.8, 29.8, 29.9, 36.4, 65.3, 69.2, 69.4, 69.6, 113.1, 114.0, 116.1, 116.1, 119.6, 132.3, 133.8, 147.9, 148.0, 148.9, 149.5 ppm (15 signals were missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{120}H_{186}O_{15}Na$: *m/z* 1890.3689; found: 1890.3622 $[M+Na]^+$.

Molecular cage 3: A solution of the triol **13** (475 mg, 254 mmol) in $CHCl_3$ (20 mL) was added to a solution of TFA (12.7 mL) in $CHCl_3$ (200 mL) and CH_3NO_2 (50 mL) over a period of 12 h and then the mixture was stirred at room temperature for 60 h. After the addition of saturated $Na_2CO_{3(aq)}$ (100 mL), the organic phase was washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified chromatographically on SiO_2 (from CH_2Cl_2 to CH_2Cl_2/MeOH (200:1)) to afford a white solid, which was recrystallized (CH_2Cl_2/hexanes) to give **3** (73.7 mg, 16%). M.p. 248–249 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 1.14–1.47 (m, 108H), 1.60–1.93 (m, 24H), 3.46 (d, J = 13.6 Hz, 6H), 3.76–3.90 (m, 12H), 3.96–4.08 (m, 12H), 4.68 (d, J = 13.6 Hz, 6H), 6.77 (s, 6H), 6.82 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 25.9, 26.4, 29.0, 29.4, 29.8, 30.2, 30.5, 36.4, 68.2, 70.3, 114.4, 117.1, 131.7, 132.7, 147.3, 148.1 ppm (four signals were missing, possibly because of signal overlap); HRMS (ESI): calcd for $C_{120}H_{180}O_{12}$: *m/z* 1813.3475; found: 1813.3495 $[M]^+$.

Hemicarceplex C_{76}@2: A solution of the molecular cage **2** (21 mg, 18 μmol) and C_{76} (11 mg, 12 μmol) in $CHCl_2CHCl_2$ (6 mL) was stirred at 35 °C for 30 h and then the solvent was evaporated under reduced pressure. The solid residue was purified chromatographically on SiO_2 (CS_2 then CH_2Cl_2/hexanes (4:1)) to afford hemicarceplex C_{76}@**2** as a black solid (15 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_2CDCl_2$, 298 K): δ = 1.17–1.55 (m, 102H), 1.68–1.94 (m, 24H), 3.50 (d, J = 13.6 Hz, 6H), 3.66–3.82 (m, 12H), 3.95–4.10 (m, 12H), 4.74 (d, J = 13.6 Hz, 6H), 6.76 ppm (s, 12H); HRMS (ESI): calcd for $C_{193}H_{174}O_{12}^+$: *m/z* 2683.3000; found: 2683.2757 $[M]^+$.

Hemicarceplex C_{78}@2: A solution of the molecular cage **2** (15 mg, 13 μmol) and C_{78} (8 mg, 9 μmol) in $CHCl_2CHCl_2$ (4 mL) was stirred at 35 °C for 30 h and then the solvent was evaporated under reduced pressure. The solid residue was purified chromatographically on SiO_2 (CS_2 then CH_2Cl_2/hexanes (4:1)) to afford hemicarceplex C_{78}@**2** as a black solid (16 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_2CDCl_2$, 298 K): δ = 1.14–1.57 (m, 102H), 1.69–1.93 (m, 24H), 3.33 (d, J = 14.0 Hz, 1.3H), 3.42 (d, J = 13.6 Hz, 3.1H), 3.56–3.84 (m, 13.6H), 3.91–4.10 (m, 12H), 4.57 (d, J = 14.0 Hz, 1.3H), 4.66 (d, J = 13.6 Hz, 3.1H), 4.84 (d, J = 13.6 Hz, 1.6H), 6.56 (s, 2.6H), 6.66 (s, 6.2H), 6.87 ppm (s, 3.2H); HRMS (ESI): calcd for $C_{195}H_{174}O_{12}^+$: *m/z* 2707.3000; found: 2707.3005 $[M]^+$.

Hemicarceplex C_{84}@3: A solution of the molecular cage **3** (16 mg, 9 μmol) and C_{84} (6 mg, 6 μmol) in $CHCl_2CHCl_2$ (3 mL) was stirred at 35 °C for 30 h and then the solvent was evaporated under reduced pressure. The solid residue was purified chromatographically on SiO_2 (CS_2 then CH_2Cl_2/hexanes (4:1)) to afford hemicarceplex C_{84}@**3**

as a black solid (4.0 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_2CDCl_2$, 298 K): $\delta = 1.21$–1.61 (m, 108H), 1.68–1.92 (m, 24H), 3.47 (d, $J =$ 13.6 Hz, 6H), 3.63–3.75 (m, 6H), 3.76–3.88 (m, 6H), 3.90–4.10 (m, 12H), 4.71 (d, $J = 13.6$ Hz, 6H), 6.65–6.77 ppm (m, 12H); HRMS (ESI): calcd for $C_{204}H_{180}O_{12}^+$: m/z 2821.3475; found: 2821.3499 $[M]^+$.

Typical extraction procedure

First extraction cycle: A black suspension of the molecular cage **2** (450 mg) and the higher-order fullerene mixture (600 mg) in $CHCl_2CHCl_2$ (30 mL) was heated at 308 K for 40 h and then the solvent was evaporated under reduced pressure. CH_2Cl_2 (40 mL) was added to the residue and then the suspension was filtered. The filtrate was concentrated and the residue purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)). The recovered higher-order fullerene mixture and the molecular cage **2** were mixed in $CHCl_2CHCl_2$ (10 mL); the extraction process was repeated two more times. Combined, these three repeated extractions provided a hemicarceplex mixture (316 mg), free higher-order fullerenes (494 mg), and the free molecular cage **2** (198 mg).

The hemicarceplex mixture (316 mg) was dissolved in $CHCl_3$ (32 mL) and left at room temperature for 4 h to release the incarcerated higher-order fullerenes. The mixture was concentrated and the residue purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)) to afford a hemicarceplex mixture (177 mg), free higher-order fullerenes (40 mg), and the free molecular cage **2** (65 mg).

The recycled hemicarceplex mixture (177 mg) was dissolved in THF (16 mL) and left at room temperature for 16 h to release the incarcerated higher-order fullerenes. The black solid obtained after centrifugation of the suspension was purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)) to afford free higher-order fullerenes (55 mg) and the free molecular cage **2** (83 mg).

The higher-order fullerene mixture recovered from the first three extractions (494 mg) was mixed with the molecular cage **3** (494 mg) in $CHCl_2CHCl_2$ (91 mL) and then the black suspension was heated at 303 K for 16 h. The solvent was evaporated under reduced pressure and the residue suspended in CH_2Cl_2 (40 mL). After filtration, the filtrate was concentrated and the residue purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)). The recovered higher-order fullerene mixture and molecular cage **3** were mixed in $CHCl_2CHCl_2$ (78 mL) and then the extraction process was repeated. Combined, these two repeated extractions provided a hemicarceplex mixture (282 mg), free higher-order fullerenes (275 mg), and the free molecular cage **3** (268 mg).

The hemicarceplex mixture (282 mg) was dissolved in THF (34 mL) and then the solution was left at room temperature for 16 h. The black suspension was centrifuged and the collected solid was purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)) to afford free higher-order fullerenes (80 mg) and the free molecular cage **3** (121 mg). The recycling recoveries of the free hosts **2** and **3** in this extraction cycle were 77 and 79%, respectively.

Second extraction cycle: The recycled molecular cage **2** (183 mg) and higher-order fullerene mixture (275 mg) were mixed in $CHCl_2CHCl_2$ (12 mL) and then the black suspension was heated at 308 K for 40 h. After evaporating the solvent under reduced pressure, the residue was suspended in CH_2Cl_2 (20 mL) and filtered. The filtrate was concentrated and the residue purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)). The recovered higher-order fullerene mixture and molecular cage **2** were mixed in $CHCl_2CHCl_2$ (10 mL) and then the extraction process was repeated two more times. Combined, these three repeated extractions provided a hemicarceplex mixture (116 mg), free higher-order fullerenes (227 mg), and the free molecular cage **2** (90 mg).

The hemicarceplex mixture (116 mg) was dissolved in $CHCl_3$ (12 mL) and left at room temperature for 4 h to release the incarcerated higher-order fullerenes. The mixture was concentrated and purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)) to afford a hemicarceplex mixture (64 mg), free higher-order fullerenes (15 mg), and the free molecular cage **2** (20 mg).

The recovered hemicarceplex mixture (64 mg) was dissolved in THF (6 mL) and then the solution was left at room temperature for 16 h to release the incarcerated higher-order fullerenes. The black solid obtained after centrifugation of the suspension was purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)) to afford free higher-order fullerenes (16 mg) and the free molecular cage **2** (27 mg).

The higher-order fullerene mixture recovered from the first three extractions (227 mg) was mixed with molecular cage **3** (151 mg) in $CHCl_2CHCl_2$ (28 mL) and then the black suspension was heated at 303 K for 16 h. The organic solvent was evaporated under reduced pressure and the residue suspended in CH_2Cl_2 (20 mL). After filtration, the filtrate was concentrated and the residue purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexane (4:1), followed by CH_2Cl_2/MeOH (98:2)). The recovered higher-order fullerene mixture and molecular cage **3** were mixed in $CHCl_2CHCl_2$ (23 mL) and the extraction process was repeated. Combined, these two repeated extractions provided a hemicarceplex mixture (103 mg), free higher-order fullerenes (167 mg), and the free molecular cage **3** (101 mg).

The hemicarceplex mixture (103 mg) was dissolved in THF (12 mL) and then the solution was left at room temperature for 16 h. The black suspension was centrifuged and the collected solid purified chromatographically on SiO_2 (CS_2, then CH_2Cl_2/hexanes (4:1), followed by CH_2Cl_2/MeOH (98:2)) to afford free higher-order fullerenes (32 mg) and the free molecular cage **3** (40 mg). The recycling recoveries of the free hosts **2** and **3** in this extraction cycle were 75 and 94%, respectively.

HPLC analysis: Cosmosil-packed 5PBB analytical column, 4.6 × 250 mm; mobile phase = toluene; UV detection = 285 nm; elution rate = 1 mL min^{-1}. Separation: Cosmosil-packed 5PBB semipreparative column, 10 × 250 mm; mobile phase = toluene; UV detection = 285 nm; elution rate = 5 mL min^{-1}.

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Keywords: cyclotriveratrylenes · cage compounds · fullerenes · hemicarceplexes · host–guest systems

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[14] Because of the low solubility and possible slow decomposition of the higher fullerenes in organic solvents, we determined the equilibrium constants from the dissociation pathways; nevertheless, slow decomposition of the higher-order fullerenes released in solution remained possible and, therefore, the equilibrium constants and their derived kinetic and thermodynamic parameters should be considered only as rough estimates.

[15] The total amount of free host **2** recycled from the full isolation cycle was 346 mg, thus giving a recycling recovery of 77%.

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[17] The total amount of free host **3** recycled from the full isolation cycle was 389 mg, thus giving a recycling recovery of 79%.

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FULL PAPER

Host–Guest Systems

*K.-S. Liu, M.-J. Li, C.-C. Lai, S.-H. Chiu**

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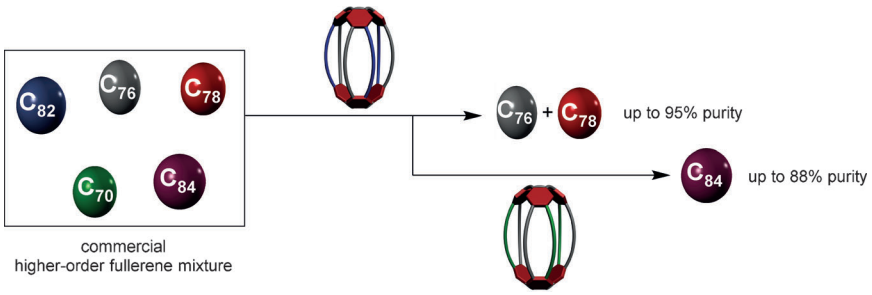
Incarceration of Higher-Order Fullerenes within Cyclotriveratrylene-Based Hemicarcerands Allows Selective Isolation of C_{76}, C_{78}, and C_{84} from a Commercial Fullerene Mixture



A successful release: Two cyclotriveratrylene (CTV)-based hosts can form hemicarceplexes with higher-order fullerenes, which allows the selective isolation of C_{76}/C_{78} and C_{80} in high purities (80–95 and 81–88%, respectively) from a commercially available mixture of higher-order fullerenes (see picture).