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Toward a Reversible Isolation of a C_{20} Fullerene Inside a Tetraureacalix[4]arene Dimer. A Theoretical Study

Grygoriy Dolgonos,*,†,‡ Oleg Lukin,*,¶ Marcus Elstner,§ Gilles H. Peslherbe,† and Jerzy Leszczynski‖

Centre for Research in Molecular Modeling, Department of Chemistry and Biochemistry, Concordia University, Montréal, Québec, Canada, H3G 1M8, Institute of Polymers, Department of Materials, ETH Zurich, HCI G 527, 8093 Zurich, Switzerland, Theoretical Physics, Faculty of Science, University of Paderborn, 33098 Paderborn, Germany, and Computational Centre for Molecular Structure and Interactions, Department of Chemistry, Jackson State University, Jackson, Mississippi 39217

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The potential stabilization of normally unstable C_{20}, the smallest fullerene, via its encapsulation inside a tetraureacalix[4]arene dimer has been analyzed using molecular mechanics calculations with different force fields, the self-consistent-charge density-functional tight-binding with dispersion correction (SCC-DFTB-D) model, and standard density-functional-theory (DFT) calculations. The interaction energies obtained for the C_{20} complex have been compared with analogous values calculated for numerous complexes of the tetraureacalix[4]arene dimer with other guests. Results of the calculations with all force fields and SCC-DFTB-D predict that the binding of C_{20} occurs with the highest selectivity. On the other hand, standard DFT calculations fail to correctly describe the stabilization of the complexes under study as standard DFT generally does not treat dispersion interactions properly. Predicted relative stabilities of the complexes are discussed in conjunction with available experimental data. Molecular dynamics simulations reveal the instability of the guest-free capsular dimer, which decomposes on a 1-ns time scale, while dimeric complexes with guests remained intact during the 5-ns simulation time, indicating the guest-driven formation of the molecular capsule.

Introduction

Stabilization of highly reactive species by means of their compartmentalization inside covalently closed or self-assembled molecular containers offers an excellent opportunity to obtain and to store structures not available by conventional methods.[1] This provides a good alternative to low-temperature solid matrices and near-vacuum gas phases, because the stabilization in the interior of molecular hosts often takes place at ambient conditions. Some of the most impressive examples of this phenomenon include the isolation of highly unstable cyclobutadiene,[2] *o*-benzyne[3] and 1,2,4,6-cycloheptatriene[4] inside carcerands, the existence of the helium molecule[5] or a single nitrogen atom[6] inside fullerenes, and a cationic adduct of triethylphosphine and acetone captured by a self-assembled organometallic cage.[7] This is currently an area of fruitful interplay between experiment and theory, because many of the reported short-lived species were either predicted or structurally rationalized by quantum chemical calculations.[1d]

The smallest fullerene, C_{20}, composed of 12 pentagons, sets a good benchmark for both theory and experiment. The C_{20} fullerene cage is presently considered to be unstable under ambient conditions on account of its high curvature and reactivity. Initially, it was thought that during the synthesis of C_{20}, the cage would rearrange into other, more stable 20-atom carbon species, such as a bowl or ring. However, on the basis of coupled-cluster calculations, Taylor and co-workers predicted the higher stability of the C_{20} fullerene compared to other 20-atom carbon isomers.[8] The C_{20} fullerene was later successfully detected and characterized in the gas phase by means of photoelectron spectroscopy and mass spectrometry.[9] The slight ambiguity in the reported experimental work (caused by the fact that the smallest fullerene could not be isolated) finally disappeared after the reports of Grimme et al.[10] and Saito et al.[11] who analyzed with the aid of high-level quantum chemical calculations both the relative stability and the reported experimental photoelectronic spectra of the C_{20} fullerene and confirmed the formation of the spherical aromatic molecule.

These results have stimulated our theoretical studies aimed at the design of suitable molecular hosts that can stabilize C_{20} under ambient conditions. Utilizing the building principle of nested fullerenes (so-called “buckyonions”),[12] one of us has recently shown on the basis of molecular mechanics calculations that C_{20} can become stable inside a larger fullerene consisting of at least 140 carbon atoms.[13] However, further rational synthetic transformations of the stabilized particle would be hampered by the covalently locked shell of the outer fullerene. In this article, we offer an alternative solution to this dilemma. On the basis of theoretical calculations, we propose a tetraureacalix[4]arene dimer as a suitable self-assembled host for highly selective and efficient binding of C_{20}, with the option of controlled release. Numerous experimental studies have revealed that self-assembled molecular capsules of tetraureacalix[4]arene derivatives possess a nearly spherical cavity and can strongly and reversibly bind guests with complementary sizes and shapes.[14] Given the large size of the system, the selection

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* To whom correspondence should be addressed.

† Concordia University.

‡ Current address: Laboratoire de Physique des Interfaces et Couches Minces (LPICM), Ecole Polytechnique, 91128 Palaiseau Cedex, France.

¶ ETH Zurich.

§ Paderborn University.

‖ Jackson State University.

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of an appropriate theoretical model is limited. One of the most suitable methods for our purpose is molecular mechanics (MM), since it explicitly takes into account nonbonding interactions that are responsible for the stability of supramolecular associates. It is, however, important to evaluate MM results by applying additional, higher-level methods of molecular modeling. Consequently, in this work we carried out calculations of the capsular complexes involving C_{20} as well as other experimentally studied or potentially interesting guests employing four different MM force fields and the self-consistent-charge-density-functional tight-binding with dispersion correction (SCC-DFTB-D) hybrid method[15,16] as well as the standard density functional theory (DFT). The feasibility of the reversible isolation of C_{20} inside the tetraureacalix[4]arene dimer, the predicted relative stabilities of complexes with other guests, and the applicability of the computational methods are discussed in the context of interaction energies as well as molecular volumes and shapes.

Computational Methods

Molecular Mechanics Calculations and Molecular Dynamics Simulations. The geometry optimization of the complexes and their constituents was carried out using the MM+,[17] AMBER,[18] and CHARMm[19] force fields as implemented in Hyperchem 7.0[20] as well as the MMX force field[21] as implemented in PCMODEL 7.5.[22] The optimization procedure was carried out using the conjugate-gradient algorithm with a root-mean-square deviation of 0.01 kcal/(mol Å) as the criterion of convergence in all cases. Interaction energies have been calculated as the difference between the steric energy of the complex and the sum of the steric energies of its constituents. Negative values of interaction energies correspond to complex stabilization.

Molecular dynamics simulations were performed using the Insight II package[23] and the CVFF force field[24] with the Discover 98 module (both of Accelrys Inc.). Simulations for each system were run for 5 ns with a 1-fs time step at 300 K (NVT ensemble), following 100 ps of equilibration time.

Self-Consistent-Charge Density-Functional Tight-Binding (SCC-DFTB) Calculations. The SCC-DFTB method, developed by Elstner et al. and described in detail elswhere,[15,16] is a good compromise between accuracy of the calculations and computational cost. It is derived from DFT by expanding the total energy functional up to second order with respect to charge density fluctuations around the reference density. Because of some approximations, such as fitted two-center integrals and atom−atom repulsion potentials, this approach is at least 3 orders of magnitude faster than DFT with a 6-31G(d) basis set,[25] while it is known to retain a good description of the geometrical and energetic parameters as well as vibrational frequencies[26] for small organic molecules,[16] hydrogen-bonded complexes,[27] DNA bases,[28] Schiff bases,[29] and polypeptides.[30]

Since long-range dispersion is not correctly described using exchange-correlation functionals within the DFT framework, SCC-DFTB suffers from the same deficiency, which can be overcome by including an empirical London-type dispersion term (C_6R^{-6}) in the total energy (SCC-DFTB-D method).[31] The C_6 coefficients are calculated by the Slater−Kirkwood approximation,[32] and the whole R^{-6} function is damped for small interatomic distances. Since not all C_6 coefficients were available for our purpose, we have calculated some of them on the basis of atomic polarizabilities reported by Miller,[33] in a manner similar to that described in ref 31. All atomic polarizabilities and C_6 coefficients used in this work can be found in the Supporting Information. All SCC-DFTB and SCC-DFTB-D calculations have been performed using the FORTRAN-based code of Elstner. The preliminary MM+ minimized structures of the capsule, guest molecules, and their complexes have been further optimized without any constraints with SCC-DFTB and SCC-DFTB-D. Vibrational frequencies of all optimized structures were calculated numerically, and they were all found to be real, confirming that all structures are minima. The interaction energies, ΔE, of the complexes were calculated as $\Delta E = E_{HG} - (E_H + E_G)$, where E_{HG}, E_H, and E_G are the total energies of the complex, capsule host, and guest, respectively.

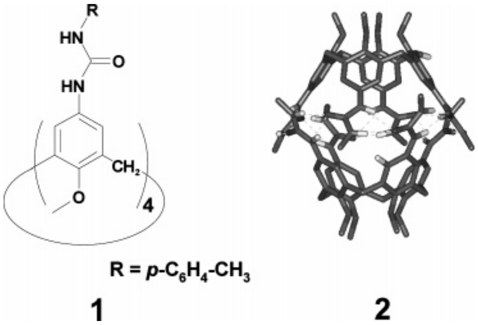

Figure 1. Schematic views of the tetraureacalix[4]arene molecule **1** and its dimer **2**.

Density-Functional-Theory (DFT) Calculations. We have performed DFT single-point calculations using the hybrid B3LYP[34] functional with a standard, double-ζ, 6-31G(d) basis set[35] for SCC-DFTB-D optimized geometries. These calculations were carried out using the Gaussian 03 program package[36] and tight self-consistent field convergence criteria.

Calculation of the van der Waals (vdW) Guest Volumes. A standard grid method[37] was applied for the calculation of the vdW guest volumes on the basis of the atomic radii of Gavezzotti (1.75, 1.17, 1.55, and 1.40 Å for C, H, N, and O atoms, respectively)[38] as implemented in the QSAR module of Hyperchem 7.[20]

Results and Discussion

The structures of the tetraureacalix[4]arene **1** and its dimer **2**, representing a molecular capsule, are shown in Figure 1, whereas the structures of all guest molecules under investigation are depicted in Figure 2. Because of the presence of 16 hydrogen bonds, the dimeric capsule **2** can strongly but reversibly encapsulate small guests on a time scale of several hours.[39] Available experimental data suggests that the encapsulation efficiency is mainly determined by the vdW volume of the available inner phase of capsule **2**, the vdW volumes of the guest, and the guest symmetry on account of a nearly spherical shape of the capsule interior.[14,39] The calculated vdW volumes along with the experimentally determined values of the complex half-life times are listed in Table 1. The interaction energies for the complexes, optimized with different computational methods, are collected in Table 2.

The calculated interaction energies are, in principle, related only to the thermodynamic stability of a given complex while available experimental data reflect the kinetic stability of the complex. Although a direct comparison between these stabilities is not possible, one may attempt to qualitatively relate calculated complex interaction energies to experimental kinetic stabilities under some assumptions. The encapsulation rate constant k_1 is much larger than the complex decomposition rate constant k_2 on account of the almost instant host−guest complex formation, which makes k_1 very difficult to measure directly.[40] Therefore, hypothesizing very close values of the encapsulation rate

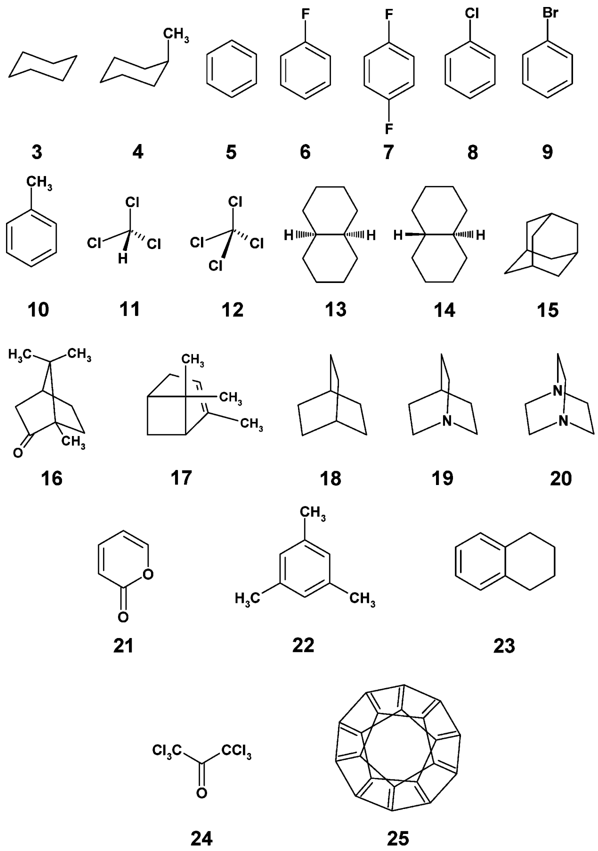

Figure 2. Structures of the guest molecules investigated in this work.

TABLE 1: Experimental Guest-Tetraureacalix[4]arene Dimer Complex Half-Life Times and Calculated van der Waals Volumes (Å^3) of the Free Guests

guest	$\tau_{1/2}$, h[a]	vdW volume, Å^3
3	1880	102.6
4	1780	119.5
5	20	86.7
6	74	89.0
7	1470	91.3
8	40	101.2
9	23	108.5
10	4.2	103.7
11	2.9	73.6
12	1120	88.4
13		158.9
14		158.7
15		147.5
16		160.8
17		156.0
18		125.5
19		120.6
20		115.8
21		82.3
22		137.5
23		142.9
24		153.9
25		180.0

[a] From ref 39.

constants, k_1, for different guests, the thermodynamic stability expressed through the equilibrium constant, $K = k_1/k_2$, mainly depends on the complex decomposition rate constant k_2. This assumption allows us to roughly compare the experimental and calculated stabilities of the tetraureacalix[4]arene dimer complexes. (Although the equilibrium constants, and thus the thermodynamic stability of the complexes, depend on the complex stabilization free energies, one may assume very similar entropic contribution to the stabilization free energies of the various host−guest complexes, and we will attempt to relate thermodynamic stabilities to the complex stabilization energies.)

Force field calculations result in negative interaction energies for all complexes under investigation (Table 2). In a few cases, the calculated data do not exactly follow the experimental trends in the kinetic stability of the capsular complexes, for example, calculations predict stabilities ∼20% higher for the toluene **10** complex than for the benzene **5** one; similarly, fluorobenzene **6** and 1,4-difluorobenzene **7** have similar stabilization energies while they have very different half-life times. As mentioned earlier, a direct comparison between experimental half-life times and calculated interaction energies is not possible, but trends can be observed if one groups the guests according to similar experimental or calculated values. From the available experimental decomposition rates of the dimeric complexes, one can expect that the complexes with cyclohexane **3** and methylcyclohexane **4** have larger interaction energies than those with monosubstituted benzene derivatives **6**, **8**, **9**, and chloroform **11**. At the same time, similar interaction energies can be expected for the monosubstituted benzenes **6**, **8**, and **9**, since their measured half-life times are close. Indeed, the calculated interaction energies of complexes with the **6**, **8**, and **9** guests do not differ significantly (i.e., by no more than 5 kcal/mol for all force fields). Interestingly, vdW volumes of tetrachloromethane **12**, benzene **5**, and fluorobenzene **6** are similar but **12** forms a more stable complex with **2**, according to the MMX and MM+ interaction energies, which are consistent with the experimental kinetic stabilities. Likewise, the **4** and **18**−**20** guest molecules, with vdW volumes of 115 ± 5 Å^3, form more stable complexes, compared to those for bromobenzene **9** (108.5 Å^3) and mesitylene **22** (137.5 Å^3), according to all force fields. A similar trend is also observed in the case of adamantane **15**, which is more stabilized by complexation than tetraline **23** and hexachloroacetone **24** according to MM+, MMX, and AMBER force fields, despite their very close vdW volumes. These results are indicative of the importance of the shape selectivity in molecular recognition within the molecular capsule, as the near-spherical shape of the capsule cavity exhibits a preference for binding spherical guests.

The most interesting result of the molecular mechanics calculations is that the highest interaction energy is obtained for the C_{20} complex with all four force fields. The smallest fullerene **25** has an optimum volume and a highly symmetrical spherical shape that matches the capsule interior extremely well, leading to the strongest vdW host−guest interactions. The vdW volume of C_{20} is close to that of the cavity of **2**, 180 Å^3 versus 190−200 Å,[3,41] respectively. This volume ratio is similar to those of other stable host−guest molecular systems, such as nested fullerenes.[12] At the same time, our results cast some doubt on the optimal 55% volume filling, claimed recently as a general requirement for the guest size in complexes of self-organizing molecular capsules.[41]

Important insight into the stabilities of the capsular complexes of tetraureacalix[4]arenes can be gained from molecular dynamics (MD) simulations. Analysis of the 5-ns MD trajectories of the capsular complexes with C_{20} and adamantine, as well as the empty capsule, reveals that the empty dimer decomposes on a 1-ns time scale while the dimeric complexes containing guests remain stable during the whole simulation time. This finding about the empty dimer cannot really be inferred experimentally, because tetraureacalix[4]arenes always encapsulate some guest molecules (e.g., solvent) upon dimerization and no such guest-free dimers have been characterized so far.

TABLE 2: Interaction Energies (kcal/mol) of the Guest-Tetraureacalix[4]arene Dimer Complexes Calculated with Various Force Fields, Semiempirical and Hybrid DFT

guest	MMX	MM+	AMBER	CHARMm	SCC-DFTB[a]	SCC-DFTB-D[a]	DFT[b]
3	−25.7	−25.4	−26.7	−25.4	−0.9	−28.3	10.0
4	−25.2	−26.3	−32.1	−27.8	−0.1	−32.3	21.3
5	−12.6	−19.0	−20.2	−21.9	−1.5	−25.9	4.8
6	−14.9	−18.7	−21.0	−21.9			
7	−13.4	−18.0	−20.5	−23.6			
8	−15.0	−17.7	−25.2	−22.8			
9	−14.6	−16.4	−22.1	−26.8			
10	−14.8	−21.6	−25.7	−25.7	−1.7	−31.2	15.2
11	−20.2	−18.0	−16.1	−17.3			
12	−22.7	−22.5	−19.7	−20.5			
13	−27.6	−22.1	−35.0	−15.0	7.2	−35.0	28.5
14	−21.1	−19.3	−36.1	−24.7	7.9	−32.7	26.1
15	−34.1	−31.4	−38.2	−24.1	0.7	−41.2	28.0
16	−32.8	−32.0	−37.0	−26.6	0.1	−43.0	27.4
17	−25.3	−24.8	−28.9	−28.1	4.7	−36.4	32.0
18	−32.3	−30.4	−32.5	−26.6	−1.1	−35.2	17.6
19	−32.6	−30.5	−32.4	−27.4	−0.8	−34.3	15.7
20	−31.7	−29.5	−32.5	−26.4	−1.6	−33.1	13.3
21	−13.5	−19.9	−21.0	−23.9	−5.0	−27.0	−0.1
22	−11.6	−10.8	−20.1	−27.0	9.0	−29.9	32.0
23	−12.3	−17.5	−32.7	−29.2	6.2	−32.9	21.7
24	−30.0	−25.7	−35.8	−32.7			
25		−32.8	−51.2	−36.8	−5.2	−84.9	48.2

[a] Slater-Koster integrals are not available for some elements. On account of the limitations of the current version of the SCC-DFTB code, calculations have been performed only for complexes containing C, H, N, and O atoms. [b] B3LYP/6-31G*//SCC-DFTB-D.

The MD results are certainly consistent with the lack of experimental observation of guest-free dimers and are indicative of the guest-promoted dimerization of the tetraureacalix[4]arenes.

To substantiate the molecular mechanics results concerning the higher stability of the C_{20} complex, we also performed calculations using SCC-DFTB, a semiempirical DFT method, as explained in the Computational Methods section. Although the C_{20} complex remains the most stable, the calculated SCC-DFTB interaction energies for the majority of guests (Table 2) are very small, reflecting slight or no interaction between the host and guests. This obviously contradicts the high stabilities of the capsular complexes found in numerous experiments. The SCC-DFTB results are revealing of the forces that contribute to the complex stabilities. The dispersion forces that often operate in noncovalent complexes are poorly described by semiempirical and hybrid DFT methods. Therefore, only after augmentation of SCC-DFTB with the London-type dispersion term (D) do calculations result in significant complex stabilization energies and suggest the C_{20}@**2** complex to be the most stable (cf. Table 2). The SCC-DFTB-D interaction energies for complexes with all guests are in fairly good qualitative agreement with those obtained from the force field calculations (cf. Table 2).

The importance of properly considering dispersive forces for supramolecular systems stabilized mainly by nonbonded interactions can further be inferred from the values of complex interaction energies obtained with standard, hybrid DFT. With the exception of only the complex with one of the smallest guests, α-pyrone **21**, no stabilization was found for these systems and destabilization was found to increase rapidly upon increase of the vdW guest volume, in stark contrast to not only our MM and SCC-DFTB-D results but also to strong experimental evidence for the exceptional stability of such complexes. This finding is in line with the general conclusion that hybrid DFT methods perform poorly for dispersion interactions,[42] and in principle, only wave-function-based correlated methods can describe these subtle interactions properly. Such computationally intensive calculations are, however, not currently feasible for these systems.

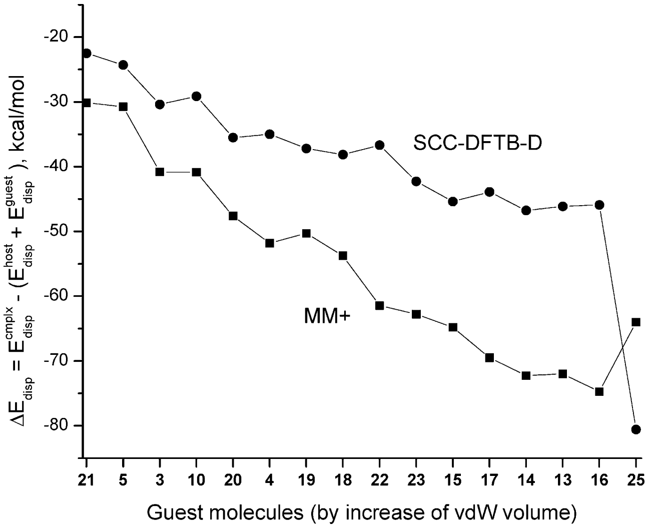

Figure 3. Stabilization energies due to dispersion predicted by MM+ and SCC-DFTB-D versus van der Waals volumes of the guest molecules.

To identify the origin of the very high stability of the C_{20} fullerene complex, we inspected the contribution to the stabilization energies because of dispersion predicted by the MM+ force field and SCC-DFTB-D for some complexes. Figure 3 shows the complex stabilization energy dispersion contribution (i.e., the difference between the dispersion energy of the complex and that of its constituents) for the complexes with the **3**−**5**, **10**, **13**−**23**, and **25** guests. Both MM+ and SCC-DFTB-D stabilization energy dispersion contributions were found to decrease upon increase of the vdW volume of the guests under investigation with the exception of C_{20}, for which MM+ predicts a value that does not follow the trend with respect to the vdW volume and SCC-DFTB-D predicts a very large stabilization energy dispersion contribution. The origin of this discrepancy lies in the actual values of the C_6 coefficients employed in both methods. In fact, the parameters for fullerene carbon atoms used in the MM+ force field are the same as those for the benzene aromatic carbon. This leads to a relatively small dispersion contribution to the MM+ stabilization energy for the complex with C_{20}, comparable to that for the complexes with the **22** and **23** guest molecules. However, since the C_6 coefficients of carbon atoms in condensed polycyclic aromatic compounds should be larger than those for benzene on account of a higher polarizability of the former compounds, MM+ clearly underestimated the dispersion contribution to the stabilization energy for the C_{20}@**2** complex. On the other hand, the SCC-DFTB-D stabilization energy dispersion contribution for the C_{20}@**2** complex is much larger in magnitude than that for other complexes under investigation by 40−45 kcal/mol (and typically twice as much than that of other complexes). This can be explained by the fact that the C_6 coefficients of the C_{20} carbon atoms calculated from atomic polarizabilities are 1.66 and 2.39 times larger than those for carbon atoms in usual aromatic and aliphatic organic compounds, respectively (see Supporting Information Table S2). Hence, the exceptionally high stability of the C_{20}@**2** complex predicted by SCC-DFTB-D is directly related to the high polarizability of the C_{20} fullerene and is the result of the interplay between relatively weak vdW repulsion and strong dispersion interactions.

Because of the remarkable predicted stability of the capsular complex with C_{20}, one may envision an experiment to isolate C_{20} for the first time under ambient conditions in a capsular environment. A promising approach, in our opinion, lies in the irradiation-promoted decomposition of perbrominated dodecahedrane into C_{20}, as successfully accomplished by Prinzbach et al.,[9] which could be carried out in a tetraureacalix[4]arene solution. The perbrominated dodecahedrane is too large to be complexed with the tetraureacalix[4]arene dimer, while the in-situ-generated C_{20} could be successfully stabilized inside the host.

Conclusions

Molecular mechanics, molecular dynamics, semiempirical and standard density-functional-theory investigations of guest encapsulation inside the tetraureacalix[4]arene dimer capsule strongly suggest that C_{20}, the smallest fullerene, would form the most stable complex of all guests investigated. The formation of the dimeric complex should prevent C_{20} from decomposing in solution and facilitate its isolation and chemical transformation. Complexes with numerous other guest molecules were also found to be stable, although no absolute quantitative agreement between calculated values of the interaction energies and available experimental data reflecting kinetic stabilities could be found. In most cases, however, complexes with high experimental kinetic stabilities were found to have larger stabilization energies. Our calculations also show that besides the unstable C_{20}, adamantane and bicyclo[2.2.2]octane and its aza- and diaza-derivatives are expected to form highly stable complexes with the tetraureacalix[4]arene dimer. With the exception of the original SCC-DFTB and standard hybrid DFT techniques, the theoretical methods employed in this work showed marked qualitative agreement and revealed the importance of dispersion forces that frequently operate in supramolecuar assemblies.

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Supporting Information Available: The atomic coordinates of all SCC-DFTB-D optimized structures, values of atomic polarizabilities, and C_6 coefficients for the SCC-DFTB-D calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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