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Reversible encapsulation in a covalent capsule

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Demeter Tzeli^{a,*}, Ioannis D. Petsalakis^{a,*}, Giannoula Theodorakopoulos^a, Julius Rebek Jr.^{b,c}

^a Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, 48 Vassileos Constantinou Ave., Athens 116 35, Greece ^b Skaggs Institute for Chemical Biology & Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA ^c Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 20433, China

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ABSTRACT

A theoretical study has been carried out on the encapsulation of $n-C_{18}H_{38}$, $n-C_{20}H_{42}$, and dibutylstilbene in a covalent capsule with a long cylindrical cavity. Interaction energies of $-24.7(n-C_{18}H_{38})$, $-17.0(n-C_{20}H_{42})$, and -19.4(dibutylstilbene) kcal/mol are calculated. The larger coiling required of the longer guest is responsible for smaller interaction energy. The lowest energy path for guest-extraction involves gating at the opening next to the spacers of the cage, while extraction along the axis of the cage is unfavorable. The activation enthalpies are $15.1(n-C_{18}H_{38})$, $24.8(n-C_{20}H_{42})$, and 26.5(dibutylstilbene) kcal/mol, in very good agreement with the experimental value $\Delta G^{\#} = 16.8$ kcal/mol reported for the $n-C_{18}H_{38}$.

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1. Introduction

The first reported covalent hosts that mechanically completely contain their target guests were the cryptophanes [1] and the carcerands [2]. Cryptophanes were discovered by Collet and Gabard in 1981 [3] when these researchers synthesized the first cryptophane, now known as cryptophane-A. The carcerands constructed by Cram et al. [2] in 1985, completely entrap their guests so as they will not escape even at high temperatures [2]. Hemicarcerands allow guests to enter and exit the cavity at high temperatures, however they form stable complexes at ambient temperatures [4]. Over the last 30 years a great deal of research has been conducted aiming to create small, large, and of adjustable size covalent capsules and with a variety of solubilities [5–9]. Encapsulation enables rigorous control of environment and the encounters of molecules isolating them from solvent encounters at ambient temperatures in the liquid phase [10].

Synthesis and the binding behavior of a covalent capsule with a long cylindrical cavity were reported recently [9]. The particular capsule, characterized as robust [9], acts as a host to long chain alkanes and two or more hydrogen-bonded guests. The exchange of guests in and out of the capsules is slow in the NMR timescale as separate signals are seen for free and bound *n*-alkanes. Regarding the exchange rate of dibutylstilbene, which is more rigid than

* Corresponding authors. E-mail addresses: dtzeli@eie.gr (D. Tzeli), idpet@eie.gr (I.D. Petsalakis).

http://dx.doi.org/10.1016/j.cplett.2015.05.018 0009-2614/© 2015 Elsevier B.V. All rights reserved. *n*-alkanes, it is reported to be slower than the NMR time scale. The mechanism for the guest exchange process is suggested to involve motions of the capsule walls that create gating, i.e., openings [9]. In the present work, in order to confirm the above suggestion and indication, we study computationally the encapsulation and the exchange of three long chain guests in and out of the covalent capsule of [9]. Two alkanes, $n-C_{18}H_{38}$, $n-C_{20}H_{42}$, and the rigid dibutylstilbene are used as guests for the capsule with the long cylindrical cavity synthesized by Asadi et al. [9].

2. Computational details

Theoretical DFT calculations are employed in order to calculate binding energies of the guests in the capsules, while the ONIOM methodology is used to determine the lowest in energy path for the extraction of the guests and to calculate the activation energies for the three cases. In particular it is of interest to establish the location of the opening of the capsule (or gating) required for the guest-extraction.

The optimized structures of the covalent capsule (**A**) and the encapsulated complexes of $n-C_{18}H_{38}$, $n-C_{20}H_{42}$, and dibutylstilbene in **A** are shown in Figure 1. All calculated structures were fully optimized by DFT calculations using the B3LYP [11,12] and the M06-2X [13,14] functionals in conjunction with the 6-31G(d,p) basis set [15]. Our previous studies on encapsulation of heterodimers and homodimers of carboxylic acids, amides and boronic acids in reversible capsules with large [16,17], or very limited cavity [18,19] have shown that the use of the M06-2X/6-31G(d,p) method is a



Figure 1. Capsule **A**, the three guests, i.e., $n-C_{18}H_{38}$, $n-C_{20}H_{42}$, and dibutylstilbene free and encapsulated. The **A** dibutylstilbene is shown from two points of view for clarity. The M06-2X/6-31G(d,p) interaction energies between cage and guests and in parenthesis the difference energy between the free and encapsulated guest geomrtries are given. The (H atoms = white spheres, C = gray spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with stick bonds for clarity.

good choice and in agreement with other ab initio methods, i.e., MP2 and CCSD(T) [20]. In addition, the M06-2X/6-31G(d,p) method was found that it is a good choice for the calculation of dispersion forces on benzene dimer, which is a prototype for dispersion forces

between nonpolar molecules, and benzene–fullerene [21]. Furthermore, the effect of inclusion of diffuse functions was examined previously and it was found to be not significant for the encapsulated dimers [18]. The interactions energies of the guest with the cage were calculated and the values were corrected with respect to the basis set superposition error (BSSE) via the counterpoise procedure [22,23].

For the calculation of the lowest in energy path for the extraction of the guests from the cage, the ONIOM methodology [24,25], where the systems were defined as two regions (layers), was used. The high layer consists of the guests calculated at the M06-2X/6-31G(d,p) level of theory and the low layer is the capsule calculated at the PM6 level of theory. The applicability of the ONIOM for encapsulated systems was examined before and even in cages where the guests are significantly compressed and the results were in good agreement with the full DFT calculations [14,17]. Additionally, the ONIOM method has been employed in calculations of reactions in capsules for which experimental data existed and it was found reliable and adequate for such large encapsulated system [26]. Details of the calculations of the paths determined in the present work are provided along with the results in the following section.

All calculations were carried out using the GAUSSIAN 09 program [27].

3. Results and discussion

All three methods, i.e., B3LYP/6-31G(d,p), M06-2X/6-31G(d,p), and the fast ONIOM(M06-2X/6-31G(d,p):PM6) give similar geometries for the encapsulated molecules $n-C_{18}H_{38}$, $n-C_{20}H_{42}$, and dibutylstilbene, shown in Figure 1 and Supplementary Information.

Their M06-2X/6-31G(d,p) corrected for BSSE interaction energies between cage and guest (or binding energy) are also given in Figure 1. The largest interaction energy is observed for the encapsulated *n*-C₁₈H₃₈, i.e., -24.7 kcal/mol. The encapsulated *n*-C₁₈H₃₈ is twisted by 72° along its axis and the energy of free alkane at its encapsulated geometry lies energetically at 4.5 kcal/mol above the global minimum of the free $n-C_{18}H_{38}$ (also given in Figure 1). The larger $n-C_{20}H_{42}$ in the capsule is more disturbed than the $n-C_{18}H_{38}$ alkane, with its carbon chain up to the 11th C atom twisted by 41° along its axis and then bent, so as to fit inside A, see Figure 1. Accordingly, the interaction energy is -17.0 kcal/mol, smaller than that of the C₁₈ encapsulated system. The energy of free $n-C_{20}H_{42}$ at its encapsulated geometry lies energetically at 11.7 kcal/mol above its global free minimum (cf. Figure 1). For the encapsulated dibutylstilbene the calculated interaction energy is -19.4 kcal/mol and the encapsulated structure lies energetically 4.0 kcal/mol above its global free minimum. Finally, we should note that B3LYP/6-31G(d,p) does not yield binding of the encapsulated complexes even though optimization converges to minimum energy geometries, showing that hydrogenbonding interactions are very important for these systems. On the contrary, the ONIOM(M06-2X/6-31G(d,p);PM6) method gives similar results to M06-2X/6-31G(d,p) for the energetics, with ONIOM(M06-2X/6-31G(d,p);PM6) interaction energies at -26.0 $(n-C_{18}H_{38})$, $-19.0(n-C_{20}H_{42})$, and -21.3(dibutylstilbene) kcal/mol. This fact is an additional evidence to the reliability of the ONIOM method for the systems of interest in the present work.

It should be noted that at the lowest minimum energy structure of the capsule the four diamine spacers that connect the two cavitands [9] are not symmetrically located. They are twisted so as to maximize the hydrogen interactions. However, when the guests are encapsulated, the spacers are more symmetrically located and they are positioned farther than their position of the empty cage with respect to the center of the cage.



Figure 2. Reaction enthalpy vs. reaction coordinate is given for the lowest in energy path for the extraction of the *n*-C₁₈H₃₈ from the capsule **A**. The intermediate structures are shown. (H atoms = white spheres, C = gray spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with wireframe bonds for clarity.

The rearrangement path for the extraction of $n-C_{18}H_{38}$ from the capsule **A** is depicted in Figure 2 and Figure 1S of the SI. At each step, one C atom is extracted from the cage, followed by a full geometry optimization of the resulting structure. The first structure, point **0**, corresponds to the most stable encapsulated structure. At the second structure, cf. point 1, one carbon atom has been extracted, at point 2 two carbon atoms have been extracted and so on and finally at point **18** all carbon atoms are extracted. As the carbon chain is being extracted from the capsule, the capsule walls move and a gate is created, also noted in other covalent cages [28,29], see Scheme 1, where two views of the point **15** structure are shown. In Ib the distances $H \cdots N$ (in Å) between two chains of the cage, at the gate and under the gate are indicated, showing a difference of 3.8 Å. Thus, the openings of the capsule at the gate are increased, the distances between N atoms or N atoms and H atoms or C atoms of different chains of the cage increase so as to allow the extraction of the molecule, while the opposite openings to the gate decrease.

All intermediate structures with the exception of the structure at point **1** of Figure 2 are minima, while structure **1** is a transition state, as the calculated frequencies indicate. The activation enthalpy for the extraction of the $n-C_{18}H_{38}$ from the cage **A** is 15.1 kcal/mol, at 298.15 K and 1 Atm. This is in very good agreement with the reported experimental value for this system of $\Delta G^{\#} = 16.8$ kcal/mol [9]. It should be noted that as the guest is coming out of the capsule, its H atoms interact with the outer walls of the capsule, see Figure 2, and this interaction is retained even at the last minimum structure, **18**, when the guest is completely out of the cage. The minimum at point **18** lies at only 5.1 kcal/mol above the lowest minimum encapsulated structure, and its binding is calculated at 20.9 kcal/mol, for the isolated system.

The minimum enthalpy and energy paths for extraction of the $n-C_{20}H_{42}$ from the capsule **A** are depicted in Figure 3 and Figure 2S of the SI. As described above for the normal decaoctane in each step one C atom is extracted from the cage. The structure at point **1** is a transition state, while the other structures of Figure 3 are



Scheme 1.



Figure 3. Reaction enthalpy vs. reaction coordinate is given for the lowest in energy path for the extraction of the n- $C_{20}H_{42}$ from the capsule **A**. The intermediate structures are shown. (H atoms = white spheres, C = gray spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with wireframe bonds for clarity.

minima including the structure that corresponds to the intermediate step 0.5, where the alkane starts to be extracted from the cage. Structure 1 determines the activation enthalpy for the extraction of the $n-C_{20}H_{42}$ from the cage **A** at 24.8 kcal/mol. The enthalpy and energy paths for extraction of the $n-C_{20}H_{42}$ from the capsule A including the calculated transition states between the minima 2-20 are shown in Figure 2S of the SI and all are energetically lower than the structure at point 1. The openings of the capsule are increased up to 2.2 Å in some structures, so as to allow extraction of the alkane, while the remaining openings are reduced and the corresponding distances are decreased up to 1.9 Å. As in the case of the shorter alkane, when the *n*-C₂₀H₄₂ guest is coming out of the cage, it forms H-bonds with the external walls of the cage. The energy that is needed for the bending of the alkane is compensated by the hydrogen interactions with the cage and in some structures the interaction energy is increased up to 6 kcal/mol, due to H-interactions, as a result, structures involving bending of the alkane, e.g., 18a in Figure 3 and structures without significant bending, cf 18b in Figure 3, are calculated to have nearly the same energy.

Both *n*-C₁₈H₃₈ and *n*-C₂₀H₄₂ alkanes can be also extracted via the axis of the cage, see Figure 4. The corresponding opening of the capsule is increased up to 0.8 Å, so as to allow the two alkanes to come out of the cage. However this extraction is energetically unfavorable. The calculated minimum structures of Figure 4 lie at about 50 kcal/mol above the encapsulated structures of Figure 1. Thus, while the activation enthalpy is 15.1 and 24.5 kcal/mol for the extractions of the $n-C_{18}H_{38}$ and $n-C_{20}H_{42}$ via the opening between the spacers of the cage (see above), the activation enthalpy is more than 50 kcal/mol via the z axis. In Figure 3S of SI are depicted some calculated structures for the extraction of the *n*-C₂₀H₄₂ via the cage's axis and their enthalpy difference from the corresponding encapsulated alkane. We should note that a barrier of about 46 kcal/mol were calculated via molecular dynamics simulations for a methyl group (actually MeCN) passing through the end of the resorcinarene [28] in a very good agreement with our calculations.

Comparing the encapsulation of the two normal alkanes, we observe larger coiling for the larger one than the smaller one, see Figure 1. This is in agreement with the experimental NMR spectra

of the two alkanes, where upfield shifts of the signal of the longer guest is observed. The coiling is responsible for the smaller interaction energy of the longer guest (-24.7 vs. -17.0 kcal/mol) due to the fact that the C₂₀H₄₂ needs to be more coiled than the C₁₈H₃₈ alkane, so as to fit in the cage. Another consequence of the coiling is that larger activation energy, by $\sim 10 \text{ kcal/mol}$, is needed for the extraction of the *n*-C₂₀H₄₂ than for the *n*-C₁₈H₃₈ alkane, since the



Figure 4. Calculated minima structures for the extraction of the $n-C_{18}H_{38}$ and $n-C_{20}H_{42}$ from the capsule **A** via its axis. T_E and T_H are the energy difference and enthalpy difference from the corresponding encapsulated minima structures. (H atoms = white spheres, C = gray spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with wireframe bonds for clarity.



Figure 5. Reaction enthalpy vs. reaction coordinate is given for the lowest in energy path for the extraction of the dibutylstilbene from the capsule A. The intermediate structures are shown. (H atoms = white spheres, C = gray spheres, O = red spheres and N = blue spheres). The atoms of the capsule are designated with wireframe bonds for clarity.

first one needs to be rotated and twisted to a larger degree so as to be extracted from the gate.

The minimum in energy path for the extraction of the dibutylstilbene from the capsule **A** is depicted in Figure 5. The openings of the cage are significantly increased compared to the openings of the cage in the cases of the alkanes, and in some structures they reach up to 3 Å. As the guest is extracted, the spacers change their orientation and as the phenylene groups of the dibutylstilbene are extracted the phenylene groups of the spacers are directed so as to be parallel to phenylene groups of the dibutylstilbene due to dispersion forces, see Scheme 2. Where two views of the structure at point **9** are given. Again, all structures in Figure 5 are minima except for the structure at 1, which is a transition state. The activation enthalpy for the extraction of the dibutylstilbene from the cage A is 26.5 kcal/mol, at 298.15 K and 1 Atm, see Figure 5, the largest value of the three guests studied here. That explains the experimental findings that the dibutylstilbene has the slowest extraction from the three guests [9].

In all above cases when the guests are extracted, the relative positions of the spacers change. However, at the final point, the cages nearly recover their initial structures with respect to the relative position of the spacers.

Finally, we should note that the hydrogen-bonding interactions are very important for these systems. The encapsulated systems are stabilized via many weak H…N interactions between the H atoms of guests and some of the thirty-two N atoms of the capsule. The H…N bond distances are about 2.6–3.0 Å, see Scheme 3a and b, where for the encapsulated n-C₁₈H₃₈ and dibutylstilbene the H…N interactions (green lines) are shown. Additional dispersion forces between phenylene groups of stilbene or alkanes and phenylene and imidazole groups of capsule contribute to the stabilization of the encapsulated systems, see pink lines of Scheme 3b. Similarly, in the course of the extraction of the guest from the cage, the intermediate minima are stabilized by the hydrogen interactions (with bond distances from 2.3 Å and longer) and the dispersion forces, see Scheme 3c and IIId.



Scheme 2.



Scheme 3.

4. Conclusions

The encapsulation of two alkanes, $n-C_{18}H_{38}$ and $n-C_{20}H_{42}$, and of the rigid dibutylstilbene in a capsule with a long cylindrical cavity was studied via DFT calculations and via the ONIOM(DFT:PM6) method. Interaction energies, as well as the lowest in energy path for the extraction of the guests and the activation enthalpies were determined.

The interactions energies of the three guests are -24.7 (n- $C_{18}H_{38}$), -17.0 (n- $C_{20}H_{42}$), and -19.4 (dibutylstilbene) kcal/mol at the M06-2X/6-31G(d,p) level of theory. The coiling is responsible for the smaller interaction energy of the longer alkane guest.

As the carbon chain is being extracted from the capsule, the capsule walls move and gating is created next to the spacers of the cage, the corresponding openings are increased, while the opposite ones are decreased. The largest gating for the extraction of the guests from the cage is observed for the case of the dibutylstilbene, where the openings are increased up to 3 Å. The extraction of the alkanes via the opening along the axis of the cage is unfavorable, more than 50 kcal/mol activation enthalpy are needed, in contrast to the extraction via the opening next to the spaces of the cage, where the activation enthalpy is 15.1, 24.8, and 26.5 kcal/mol for the *n*-C₁₈H₃₈, *n*-C₂₀H₄₂, and dibutylstilbene guests at the ONIOM(M06-2X/6-31G(d,p)):PM6) level of theory. A very good agreement with the experimental value found for the first guest, at $\Delta G^{\#} = 16.8$ kcal/mol is observed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cplett.2015.05.018

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