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COMMUNICATION

On the enhanced reactivity and selectivity of triazole formation in molecular flasks. A theoretical rationale†‡

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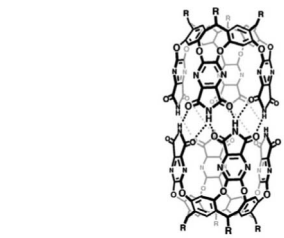
The azide–alkyne cycloaddition assisted by a self-assembled molecular flask developed by Rebek and coworkers (*Org. Lett.*, 2002, 4, 327) has been simulated by means of the ONIOM methodology, thereby evidencing the reliability of this theoretical approach to model such large encapsulated systems. Experimental evidences accounting for this transformation within the supramolecular assembly such as the significant rate enhancement, complete regioselectivity, and product inhibition as the reaction proceeds have been qualitatively disentangled through estimation of the energy barriers and the structural characteristics of the corresponding host–guest complexes.

Interest in the design and applications of nanoscale molecular flasks has increased very fast in the last years. The use of self-assembled molecular flasks as reaction vessels in enzyme-like catalyzed reactions is one of the most promising fields in contemporary organic chemistry.[1] The self-assembly of complex structures is accomplished through non-covalent, weak interactions such as hydrogen and metal–ligand bonds. By a judicious choice of diverse ligands, a wide range of self-assembled cages may be constructed,[2] many exhibiting a series of promising and fascinating molecular recognition properties.

Due to their self-assembled nature, most molecular flasks do not interact specifically with guests through covalent bonds. Instead they influence the reaction rates by means of non-covalent interactions, which lead to an increase in the molarity of the substrates.[3] The reactants tend to occupy the whole space within the capsule thus increasing their concentration with respect to the bulk solvent. Likewise, guest conformations and/or molecular pre-organizations that are especially stable may be favored by the shape and volume of both the cavity and the reaction partners and lead to an unusual reactivity.[1] On the other hand, reaction rate enhancement due to stabilization of the transition states within the cavities has also been proposed.[1]

Numerous reactions catalyzed by molecular flasks have been described, including Diels–Alder reactions,[4] photochemical [2 + 2] homodimerizations[5] and heterodimerizations,[6] oxidations,[7] and rearrangements.[8] One of the most interesting examples of reactions assisted by molecular flasks was reported by Rebek and coworkers,[9] due to the importance of the azide–alkyne cycloaddition reaction and the remarkable regioselectivity obtained. Using the capsule **1** as catalyst, they were able to prepare 1,4-diphenyl-1*H*-1,2,3-triazole (**4**) by regioselective 1,3-dipolar cycloaddition of phenylacetylene (**2**) to phenylazide (**3**) in mesitylene as solvent (Scheme 1). The reaction was not only completely regioselective in the presence of **1**, but also 30 000 fold faster when the molecular flask assisted the cycloaddition.[9] The authors could detect by means of NMR analysis the Michaelis complex prior to the cycloaddition process, which consists of the two reactants included in **1**, with an adequate orientation that gives rise to the 1,4-regioisomer.



Scheme 1

The remarkable efficiency of **1** in accelerating the transformation was ascribed to three factors.[1b,9] Firstly, an increase in the molarity of reactants, thus enhancing the reaction rate. Mesitylene is a too large a molecule to enter into the molecular flask **1**, and therefore in the absence of reactants the capsule will be empty surrounded by solvent molecules. When phenylazide and phenylacetylene are added to the mixture, they will fill the empty space within **1**, saturating the catalyst. While the concentration of the reactants used lies in the mM order, the encapsulated reactants will 'enjoy' a concentration of ~4 M.[1b,9] Secondly, the half life of the encapsulated complex is ~1 s, and accordingly the reactants would be in an appropriate orientation to afford the triazole for

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† Dedicated to the memory of Prof. Rafael Suau.

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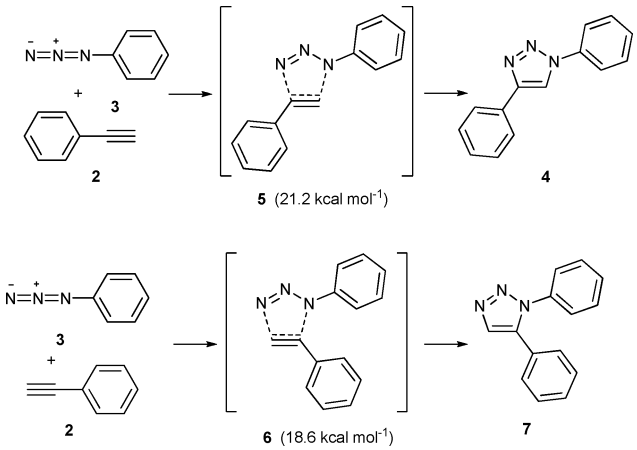
a relatively long period. In stark contrast, in the bulk solvent the pre-reaction complex would survive for a few nanoseconds only. Probably, the most intriguing feature to be assessed from a computational viewpoint is the special stabilization or structural changes, if any, of the transition states inside the capsule with respect to those occurring in the bulk solvent. The regioselectivity could be explained by means of a pre-organization of the reactants, since the accommodation of the substrates within **1** would be more suitable for the 1,4-approach.

The modeling of reactions such as the azide–alkyne cycloaddition within a molecular flask like **1** through theoretical calculations is highly desirable. The origin of both the rate enhancement and selectivity achieved in such capsules could thus be unveiled, particularly whether structural and/or energy changes associated with the formation of transition structures, rather than a concentration effect, would be primarily involved in the catalysis. However, organic reactions assisted by molecular flasks have not yet been simulated. The high computational cost derived from the large number of atoms involved makes these computations a daunting task. Gratifyingly, the development of ONIOM methods[10,11] allows calculation of large systems with a moderate time cost. The principle of an ONIOM strategy is that different parts in large molecular systems play different roles in the chemistry involved, and thus they can be modeled at different levels of theory.

Herein we describe a computational investigation on the reactivity and regioselectivity of the 1,3-dipolar cycloaddition of phenylacetylene (**2**) and phenylazide (**3**) assisted by a molecular flask (**1**) using an ONIOM method. The reaction rate enhancement along with the complete selectivity for the 1,4-regioisomer have been evaluated by means of the structural and energetic changes in the pre-reaction complex and transition states taking place in the presence of **1**.

The calculations have been performed using the ONIOM method incorporated in the Gaussian09 package.[12] The reactive species (**2** + **3**) were modeled using the B3LYP[13] and the M06-2X[14] DFT functionals, employing the 6-311G(d,p) basis set, while the semiempirical method PM6[15] was employed for the atoms corresponding to the molecular flask **1**. Frequency calculations at 298.15 K on all the stationary points were carried out at the same level of theory as the geometry optimizations to ascertain the nature of the stationary points. Ground and transition states were characterized by none and one imaginary frequency, respectively. All the relative energies presented in the manuscript are referred to enthalpies calculated at the ONIOM[M06-2X/6-311G(d,p):PM6] level. The results at B3LYP level are included in the Electronic Supporting Information‡.

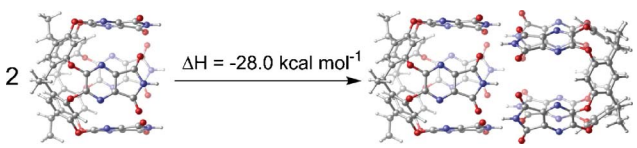
We first calculated the energetics for the 1,3-dipolar cycloadditions of phenylacetylene (**2**) with phenylazide (**3**) without the assistance of any catalyst, at the standard M06-2X/6-311G(d,p) level, to compare the energy barriers for the catalyzed and uncatalyzed processes. Scheme 2 shows the relative energies for the stationary points involved in the 1,4- and 1,5-approaches. As expected, the formation of triazoles **4** and **7** takes place through transition structures (**5** and **6**) with similar energies, thus explaining the lack of regioselectivity for the uncatalyzed reaction.[9] These energy barriers will be compared with those of the molecular flask-catalyzed reaction as we shall see later. The formation of **4** and **7** are highly exothermic processes, with ΔH = –67.2 kcal mol^{-1} and –65.4 kcal mol^{-1}, respectively. This high



Scheme 2 Energy barriers for the uncatalyzed 1,3-dipolar cycloaddition of phenylacetylene (**2**) and phenylazide (**3**).

stability of the triazole moiety makes the 1,3-dipolar cycloaddition of azides and alkynes an irreversible process.

The self-assembly of the molecular flask **1** is based on hydrogen bonds. The imide groups present in the starting monomer can afford up to 8 three-centered intermolecular hydrogen bonds to form the dimer. We calculated the assembly of **1** from two separated monomers at the PM6 level of theory (Scheme 3). The resulting structure exhibits the expected 8 hydrogen bonds, which gives rise to a stabilization of 28.0 kcal mol^{-1} (*i.e.* 3.5 kcal mol^{-1} from each imide group). The relatively weak interactions between imide groups allow the dynamic opening and closing of the capsule, so the species inside and outside of the cavitand are in equilibrium.



Scheme 3 Self-assembly of the molecular flask **1**.[16]

The inner volume of **1** determines the number of molecules that can be accommodated inside this structure. With 452.6 Å^3 and in agreement with experimental data,[9] **1** only can hold two molecules of the reactants as the calculated volumes of **2** and **3** are 144.2 Å^3 and 154.5 Å^3, respectively (Fig. 1).

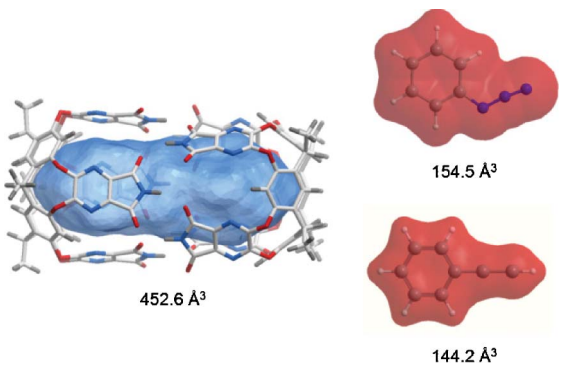


Fig. 1 Inner volume of **1** as well as molecular volumes of phenylazide and phenylacetylene.

Compounds **2** and **3** can be hosted in the molecular flask **1** with two different orientations, which can lead either to the 1,4- or 1,5-regioisomers (Fig. 2). Inside the capsule the reactants are oriented in a proper manner to accomplish the cycloaddition.

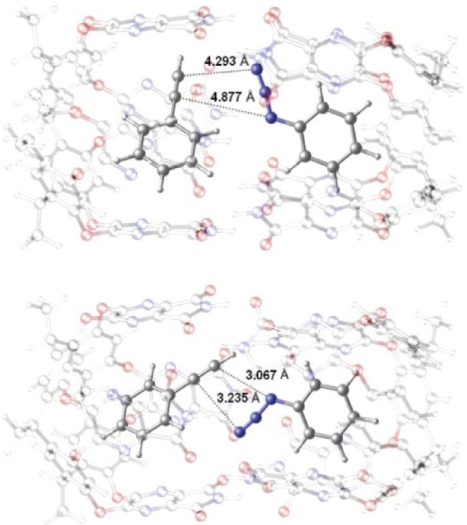


Fig. 2 Optimized structures of the pre-reaction complexes **8** (top) and **9** (bottom). The atoms corresponding to the capsule **1**, calculated at the PM6 level, are depicted semitransparent for the sake of clarity.

The C–N distances in the complex **9**, 3.07 and 3.24 Å (Fig. 2), are lower than those of the corresponding van der Waals complex calculated in the absence of **1**. This adequate orientation of the alkyne and azide groups, along with the restricted motion of such reactants resulting from the encapsulation can be considered a *pre-organization* stage prior to the cycloaddition, which could lead to a greater reactivity as experimentally observed. The corresponding complexes (**8** and **9**) (Fig. 2) are more stable by −10.7 and −13.1 kcal mol^{-1} than the reactants for the 1,5- and 1,4-approaches, respectively (Fig. 3). This stabilization can be related directly to the van der Waals interactions of the reactants with the capsule walls, and indirectly to the trend of the particles to fill the empty space within the capsule. It is worth pointing out that the pre-reaction complex (**8**) which lead to the 1,5-regioisomer is also considerably more stable than the separate reactants. However, in this case the C–N distances are longer than those of **9**, 4.29 Å and 4.88 Å, and the relative orientation of the azide and alkyne groups is not so favorable for the cycloaddition as in **9**. While in complex **9** the C–C–N–N dihedral angle is 11.7°, the same angle in **8** is 67.4° and thus the reactive groups are not adequately oriented to achieve the 1,3-dipolar cycloaddition.

The azide–alkyne 1,3-dipolar cycloaddition starting from the complex **9** has an energy barrier of 19.3 kcal mol^{-1}, similar to that mentioned above for the uncatalyzed reaction (18.6 kcal mol^{-1}, Scheme 2). However, the relative energy of the transition structure (**11**) with respect to the separate reactants is only +10.2 kcal mol^{-1}. The whole system is stabilized because of the encapsulation of the reactants, thereby accounting for the significant increase in the reaction rate in the presence of **1**. This result reveals the influence of the non-covalent host–guest interactions in stabilizing the supramolecular arrangement, including the transition structure **11** on accelerating the reactions inside the capsule.

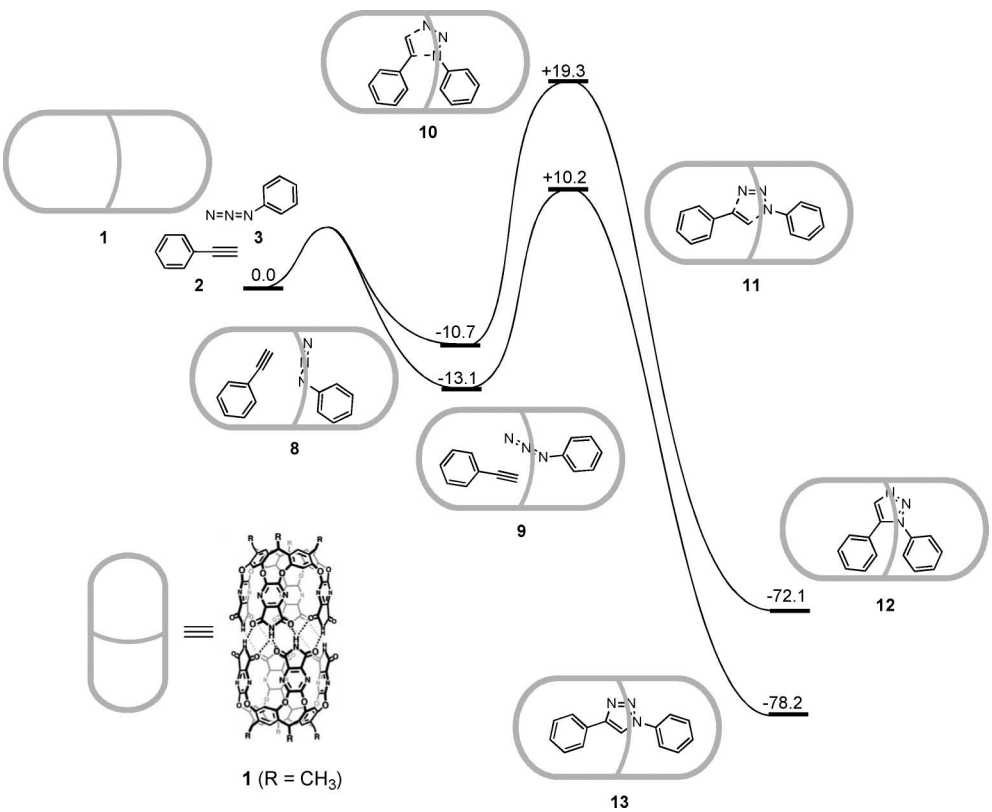


Fig. 3 Energy profile for the 1,3-dipolar cycloaddition of phenylacetylene (**2**) and phenylazide (**3**) assisted by the self-assembled molecular flask **1**.

In stark contrast, the 1,3-dipolar cycloaddition starting from the complex **8** (which leads to the 1,5-regioisomer) (Fig. 3) possesses an energy barrier of ~30 kcal mol^{-1}, even higher by more than 10 kcal mol^{-1} relative to the reaction without the assistance of any catalyst (see Scheme 2). The energy barrier with respect to the separated reactants is 19.3 kcal mol^{-1}, and therefore analogous to the uncatalyzed process. In this case, even though the host–guest complex is stabilized by –10.0 kcal mol^{-1}, the cycloaddition process is not accelerated. Fig. 4 shows the transition structures (**10** and **11**) corresponding to the 1,5- and 1,4-regioselectivities inside the molecular flask **1**.

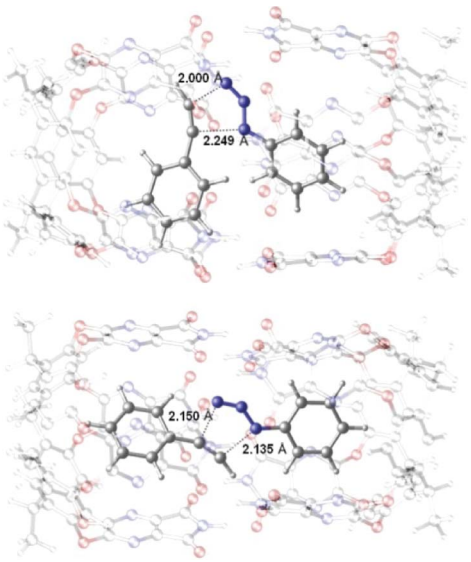


Fig. 4 Optimized structures of the transition structures **10** (top) and **11** (bottom).

As expected, the processes are considerably exothermic, and 78.2 and 72.1 kcal mol^{-1} are liberated during triazole formation for the 1,4- and the 1,5-approaches, respectively.

A further analysis of the structural parameters for the optimized transition structures, both isolated and within **1**, reveals the reasons for the different energy barriers occurring during the formation of the triazole moiety and thus the increase of the reaction rate. In the transition states leading to the 1,4-isomer (**5** and **11**) there are not important changes in the C–N distances (Fig. 5). It is only worth noting the increase in the coplanarity of the aromatic ring of phenylazide and the emerging triazole in the encapsulated transition state, with a dihedral angle of only 5.7° (Fig. 5). Conversely, in the case of the 1,5-regioisomer the change in the dihedral angle is more important. When the reaction takes place outside the molecular flask, the transition structure is stabilized by a T-shaped aromatic interaction between the phenyl groups (Fig. 5c). While the phenyl group from the azide remains coplanar to the triazole, the aromatic ring corresponding to the alkyne gets a C–C–C–C dihedral angle of 91.4°. However and due likely to the steric hindrance caused by the capsule walls, the phenyl group in **10** cannot adopt this orientation (Fig. 5d) and the stabilization of the transition state by aromatic stacking is not possible.

Once the 1,3-dipolar cycloaddition assisted by **1** is over, the capsule needs to be recovered to complete the catalytic cycle.

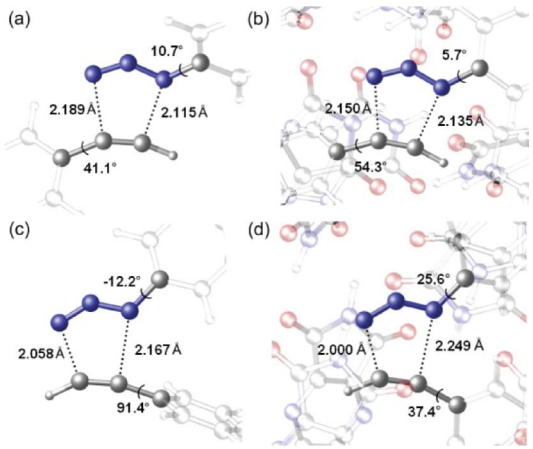


Fig. 5 Significant bond lengths and dihedral angles for the transition structures (a) **5**, (b) **11**, (c) **6**, and (d) **10**. The atoms corresponding to the triazole moiety are highlighted.

The recovery of **1** would take place through the equilibrium between the host–guest complexes. In this way, the host–guest complex **13** should be equilibrated with the initial pre-reaction complex **9**, so the reactants (**2** + **3**) displace the triazole **4** from the capsule. However, product inhibition has been experimentally observed for this reaction.[9] In principle, the host–guest complex comprising **1** and the 1,4-triazole must be the most stable species. As a consequence, the catalyst is filled with the product as the reaction progresses, which slows down and halts ultimately the overall cycloaddition.[9]

The energy balance shown in Fig. 6 determines the ability with which compounds **2** and **3** can release **4** from the capsule, thus recovering the catalyst. The encapsulated triazole (**13**) and the separate reactants are more stable by 1.6 kcal mol^{-1} than the pre-reaction complex (**9**) and the isolated triazole (**4**). Although these energetics cannot quantitatively explain the observed product inhibition, the ONIOM method provides a good qualitative approach to the relative stability of the host–guest complexes.

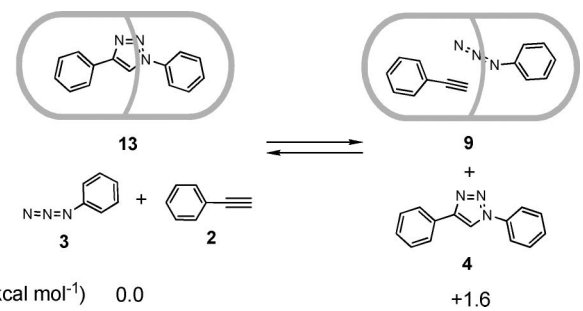


Fig. 6 Relative energies of the encapsulated 1,4-triazole (**13**) and the pre-reaction complex **9**.

In summary, the ONIOM method has been employed to model the 1,3-dipolar cycloaddition of phenylazide with phenylacetylene assisted by the molecular flask (**1**) developed by Rebek and associates. The reactants have been treated at the DFT level, whereas the capsule has been modeled at the semiempirical PM6 level. Both the structural parameters for the pre-reaction complexes and the transition states, and the energetics for the transformation accounts satisfactorily for the rate enhancement

and the complete regioselectivity of the transformation in the presence of **1**. In short, the ability of the ONIOM approach to simulate the essential features provided by molecular flasks as innovative reaction media and catalysts should stimulate further pursuits in the computational evaluation of large molecular and supramolecular systems.

Acknowledgements

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