Acceleration of the Diels-Alder Reaction between 9-Functionalized Anthracenes and C_{60}/C_{70} in the Cavity of a Water Soluble Subphthalocyanine Cage

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Abstract: Herein we report on the acceleration of the Diels-Alder reaction between a series of 9functionalized anthracenes and C_{60}/C_{70} encapsulated in a water-soluble metallo-organic Pd(II)-subphthalocyanine cage (**SubPc-cage**), which performs as a catalytic molecular reactor that provides a beneficial hydrophobic environment. Negatively and positively charged anthracenes do not react either with C_{60} or C_{70} , due to a favored solvation in water medium and/or to detrimental interactions with positively-charged Pd(II) corners of **SubPc-cage**. Experiments with C_{60} and C_{70} rendered parallel results, although C_{70} proved more reactive, leading to anthracene cycloadducts by reaction in the α bonds. All the results have been rationalized by theoretical calculations at the GFN2-xTB level.

Keywords: subphthalocyanine; metallo-organic cage; catalysis; water; fullerene

Introduction

Molecular cage-like containers can host a variety of guest molecules in their cavities by creating a suitable hydrophilic/hydrophobic environment in which stabilizing interactions take place.^[1] The central cavity of molecular capsules is reminiscent of an enzyme-active site, and, for that reason, they have been used as catalytic pockets to perform chemical reactions.^[2] The proximity and defined organization of substrates inside the confined spaces strongly reduce the entropy cost of the reaction, which results in a significant increase of the reaction rates.^[3] In this context, supramolecular coordination cages have drawn considerable attention as artificial

catalysts because they hold the advantage of structural robustness and easy preparation through modular approaches from metal ions and organic ligands.^[4]

Different types of transformations have been performed in the cavities of self-assembled coordination nanocages.^[2,5] Particularly relevant are those performed in eco-friendly aqueous media, using water-soluble molecular hosts that create a hydrophobic environment for the encapsulation of insoluble hydrophobic substrates.^[6] Recently we have reported a paradigmatic example of fullerene functionalization in aqueous media using a water-soluble, metallo-organic subphthalocyanine (SubPc) cage (**SubPc-cage** in Figure 1).^[7] SubPcs are bowl-shaped





Figure 1. Structure of SubPc-cage.

aromatic chromophores that render strong interactions with the spherical π -surface of C₆₀ and C₇₀ due to an excellent shape complementarity.^[8] SubPcbased coordination cages, prepared by Pd(II)-directed dimerization of a C₃-symmetry SubPc endowed with three peripheral 3-pyridyl units, form stable 1:1 host-guest complexes with fullerenes.^[9] These metallo-organic cavities have been used as photocatalytic molecular reactors to perform addition reactions over encapsulated \hat{C}_{60} ^[10] and as hydrophobic, confined microenvironments to realize Diels-Alder reactions over encapsulated C₆₀ dienophile and anthracene in water media^[7] that, indeed, did not take place in the absence of SubPc-cage. Noteworthy, optimized conditions for the Diels-Alder cycloaddition relied on the use of catalytic amounts of the SubPc container, which favored the co-encapsulation of insoluble C₆₀ and anthracene substrates. Importantly, catalytic turnover was facilitated by the lower stability of the host:guest complex of SubPc-cage with the resulting C_{60} cycloadduct, which assisted its displacement by pristine C_{60} . Although other molecular cavities had been previously used as containers to impact the reactivity of C_{60} ,^[11-13] the transformations occurred in organic solvents and, crucially, most of them required stoichiometric amounts of the cage.^[11,12]

In this work we aim to broaden the scope for the outstanding **SubPc-cage** catalyzed Diels-Alder reaction in water media to other anthracene derivatives. 9-Anthracenemethanol has been selected as synthon to prepare derivatives with different degree of hydrophilicity/hydrophobicity, which can have an impact on the progress of the reaction with C_{60} inside the hydrophobic **SubPc-cage**. Besides, the cavity-promoted reactivity of the larger homologue C_{70} is also explored, and the results are rationalized using theoretical calculations at the GFN2-xTB level.

Results and Discussion

Functionalized anthracenes have been widely used as dienes in cycloaddition reactions with C_{60} , but

reactions take place in harsh conditions such as liquid naphthalene as solvent^[14] solid state reactions^[15] or ultrasonication.^[16] Among the different substituted anthracenes, we have selected 9anthracenemethanol (Ant-2) and its derivatives with different hydrophilic or hydrophobic chains as dienes for the SubPc-cage catalyzed Diels-Alder reaction in water under mild conditions, to determine the role of the different substitution on the progress of the cavity-promoted reaction. C₆₀ cycloadducts from 9-substituted anthracenes have proved thermal lability,^[17] but we expect insolubility of the resulting cycloadduct in aqueous medium to minimize the cycloreversion. On this basis, compounds Ant-3-8 were prepared by O-alkylation of Ant-2 with different electrophiles to introduce either hydrophilic triethyleneglycol (Ant-3), alkylsulfonate (Ant-4^[18]) and bis-ammonium (Ant-5) chains, or hydrophobic hexyl (Ant-6), benzyl (Ant-7) and trityl (Ant-8) radicals (Figure 2 and Supporting Information).

The cavity-promoted Diels-Alder reaction between C₆₀ and the above-mentioned anthracene derivatives (Table 1) was tested in the presence of 10% mol of the hexacationic SubPc₂Pd₃ capsule (SubPc-cage) used in ground experiments. Please note that: i) the Diels-Alder reaction does not take place in the absence of the cage; and ii) rather than stoichiometric, using catalytic amounts of metallosupramolecular cage improves the performance of the reaction in aqueous media since it favors the coencapsulation of both reactants.^[7] The capsule was solubilized in water by injecting it from stock DMSO solutions to reach a final concentration of 1.0 mM in H₂O/1% DMSO. Although previous optimization studies concluded that excess anthracene (i.e., 10 equiv.) improved the conversion into the monoadduct, the evaluation of the influence of the hydrophilic/hydrophobic character of the anthracene derivatives on the progress of the reac-



Figure 2. Structure of anthracenes Ant-1–8 used for the SubPccage-catalyzed Diels-Alder reaction with fullerenes.

C ₆₀ or + Ant-n (1.0 equiv.) C ₇₀					R C ₆₀ -Ant-n		C ₇₀ -Ant-n Mixture of regioisomers			
C ₆₀	C ₆₀ -Ant-1	C ₆₀ -Ant-2	C ₆₀ -Ant-3	C ₆₀ -Ant-4	C ₆₀ -Ant-5	C ₆₀ -Ant-6	C ₆₀ -Ant-7	C ₆₀ -Ant-8		
Yield (%)	16 ^[a]	20 ± 4	6 ± 2	_	_	12 ± 1	27 ± 1	-		
C ₇₀	C ₇₀ -Ant-1	C ₇₀ -Ant-2	C ₇₀ -Ant-3	C ₇₀ -Ant-4	C ₇₀ -Ant-5	C ₇₀ -Ant-6	C ₇₀ -Ant-7	C ₇₀ -Ant-8		
Yield (%)	23 ± 2	38 ± 2	16 ± 2	_	_	20 ± 3	37 ± 1	_		

Table 1. Yields for the **SubPc-cage** catalyzed Diels-Alder reaction of pristine anthracene (**Ant-1**), and anthracenes **Ant-2–8** with C_{60}/C_{70} .

^[a] From ref [7]. Average of crude yields and standard deviation (all experiments were conducted in triplicate). Yields determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard (0.07 M, 10 μL, 0.0007 mmol).

tion was performed using a 1:1 ratio to avoid wasting the most elaborated anthracenes. The reactions were heated for three days at 80 °C and, to evaluate the conversion, reaction crudes were rapidly passed through silica to isolate the mixture of fullerene derivatives, namely pristine fullerene and the corresponding monoadducts. This mixture was then analyzed by ¹H-NMR using 1,3,5-trimethoxybenzene as internal standard to determine the yield in each compund (Table 1). Monoadducts were further isolated from pristine C₆₀ (which could be recovered) and structurally characterized by UV-vis, NMR and MS (MALDI) techniques. All adducts show a symmetric pattern in the aromatic region of the ¹H NMR, and a singlet between 5.5 and 5.9 ppm for the bridgehead proton. UV-vis spectra exhibit a low-intense absorption at 430 nm, which is the signature of 1,2-cycloadducts at the [6,6] bond of C₆₀.

The analysis of the results indicates that hydrophilic anthracenes (Ant-3-5), and in particular the negatively and positively charged species, are less susceptible to reaction with C_{60} inside the SubPc cavity than the hydrophobic counterparts. The benzyloxy substituted anthracene Ant-7 proved the most reactive (together with Ant-2), while the adduct from the trityl derivative Ant-8 was not even observed in the reaction mixture, probably because its large steric volume inhibits the co-encapsulation with C₆₀ inside the cavity. To assess the role of SubPc-cage in the progress of the reaction, we heated C_{60} with the most reactive Ant-2 and Ant-7 under the same experimental conditions, but in the absence of the cage. As expected, the formation of the adducts was not observed in any of the experiments.

Previous theoretical calculations on the cagecatalyzed reactions of C₆₀ and non-functionalized anthracene (Ant-1)^[7] indicated that the latter occupy the hydrophobic pockets formed by the N, N, N', N'tetramethylethylenediamine ligands (see Figure 1) in the preformed SubPc-cage $\subset C_{60}$, leading to a preorganized complex that then underwent cycloaddition. To investigate whether the observed lack of reactivity with charged anthracene derivatives stems from complexation issues, we conducted a similar theoretical study, now extended to three different anthracenes: neutral (Ant-2), cationic (Ant-5) and anionic (Ant-4). Figure 3 illustrates the optimized structures of the complexes formed by SubPc-cage \subset C₆₀ and these anthracenes (SubPc-cage \subset C_{60} :2(4,5)) before the reaction, as well as the complexes with the corresponding monoadduct resulting from the cycloaddition (SubPc-cage \subset C_{60} -Ant-2(4,5)). From the structure of SubPc-cage \subset C₆₀:Ant-2, it can be inferred that neutral anthracene Ant-2 fits well within one of the pockets, displaying a similar orientation to that of pristine anthracene. The subsequent cycloaddition led to a monoadduct wherein the anthracene fragment is also oriented toward the pocket. In contrast, we observed that Ant-5, with its positive charge, tends to move away from the cage, plausibly due to repulsive interactions with the positively charged Pd(II) centers. Thus, SubPc-cage \subset C₆₀-Ant-5 displays the chain of the anthracene moiety outward-oriented and a positive relative stabilization energy of the complexation $(\Delta E_{\text{complex}})$.^[20] Conversely, in **SubPc-Cage** \subset C₆₀:Ant-4, the anthracene adopts a conformation that affords stabilizing ionic interactions between the sulfonate groups at the end of the chain and the positively charged Pd(II)-center at the longest

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Figure 3. Minimum-energy structures of a) SubPc-cage $\subset C_{60}$: Ant-2, b) SubPc-cage $\subset C_{60}$ -Ant-2 c) SubPc-cage $\subset C_{60}$ -Ant-5, d) SubPc-cage $\subset C_{60}$ -Ant-5, e) SubPc-cage $\subset C_{60}$ -Ant-4, and f) SubPc-cage $\subset C_{60}$ -Ant-4 calculated at the GFN2-xTB level. $\Delta E_{\text{complex}}$, $d_{\text{bowl-bowl}}$ and $d_{\text{Pd-Pd}}$, are indicated in each case.

possible distance. On the other hand, the corresponding monoadduct forms similar stabilizing ionic interactions but with the Pd(II) center closer to the anthracene. Importantly, the cycloaddition reaction is equally exothermic in the three cases. Based on these results, we could attribute the lack of reactivity observed for Ant-4 and Ant-5 to the poor capability of **SubPc-cage** to complex these species, which could be a result of their facilitated solvation in aqueous media and, in the case of Ant-5, to ionic repulsions with the cage.

Next, we turned to explore the cavity-promoted reaction between these anthracene derivatives and C₇₀. The decreased symmetry of this fullerene derives in four different types of reactive sites (α -, β -, γ -, and δ -site), which means that even monoadducts of C_{70} can be obtained as mixture of (regio)isomers,^[19] although α position has been generally found to be the most reactive.^[21,22] Initially. we undertook the reaction with pristine anthracene. As expected, the conversion to the C₇₀-Ant-1 adduct ocurred in higher yields than for the C₆₀ counterpart, as a result of the higher strain of the C₇₀ double bonds. The ¹H NMR spectrum in a mixture of CS₂: $CDCl_3$ (3:2) (Figure 4 top) shows two doublets (7.73) and 7.48 ppm) and two triplets (7.40 and 7.33 ppm) in the aromatic region, and two singlets (5.65 and 5.11 ppm) for the bridgehead hydrogens, this splitting reflecting the lower symmetry of this adduct. The comparison with reported data for C₇₀-Ant-1 in the same solvent (Figure S30)^[22a] indicates that the reaction takes place at one the α -bonds. Therefore, SubPc-cage accelerates the reaction but does not have an impact on the site-selectivity, which is



Figure 4. ¹H NMR of C_{70} -Ant-1 (top) and C_{70} -Ant-2 (mixture of regioisomers) (bottom) in CS_2 :CDCl₃ (3:2).

directed by the reactivity of the specific double bonds.

In order to gain insights into the cage-catalyzed transformation of C_{70} , we also computationally studied the species involved in the cycloaddition. The optimized structures of **SubPc-cage** $\subset C_{70}$ and the complex with the corresponding monoadduct (**SubPc-cage** $\subset C_{70}$ -Ant-1), as well as the preorganized complex with pristine anthracene (**SubPc-cage** $\subset C_{70}$ -Ant-1), are depicted in Figure 5. As in the case of C_{60} , **SubPc-cage** undergoes axial elongation ($d_{bowl-bowl}$) and equatorial contraction (d_{Pd-Pd}) upon C_{70} complexation. It should be noted that, although the contraction takes place to a similar extent, the axial elongation with C_{70} is more

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Figure 5. Minimum-energy structures of a) SubPc-cage, b) SubPc-cage $\subset C_{70}$, c) SubPc-cage $\subset C_{70}$:Ant-1 and d) SubPc-cage $\subset C_{70}$ -Ant-1 calculated at the GFN2-xTB level. Relative stabilization energies, $d_{\text{bowl-bowl}}$ and $d_{\text{Pd-Pd}}$, are indicated in each case.

pronounced than with C_{60} (14.53 vs 12.48 Å).^[7] This stronger distortion would involve an additional energy penalty during the complexation, which may be responsible for the fourfold $\Delta E_{complex}$ of C_{60} compared to that of C_{70} . In the pre-organized complex **SubPc-cage** $\subset C_{70}$:**Ant-1**, the anthracene molecule displays the expected location (i.e., at one of the hydrophobic pockets). The subsequent Diels-Alder reaction, which is exothermic also in this case, would give rise to **SubPc-cage** $\subset C_{70}$ -**Ant-1**, presenting a similar host:guest geometry to that of the C_{60} counterpart. Importantly, the $\Delta E_{complex}$ of **SubPc-cage** $\subset C_{70}$ -**Ant-1** is approximately three times lower than that for pristine C_{70} , which is line with the observed catalytic behavior of the cage.

Next, SubPc-cage catalyzed Diels-Alder reaction was tested with anthracenes Ant-2-8. As observed for pristine anthracene, all the reactions rendered better yields in the corresponding adducts than those with C_{60} . The reactivity trend among the members of the series was also the same than for C₆₀, with hydrophobic anthracenes reacting better than hydrophilic derivatives, and with anthracenes Ant-2 and Ant-7 standing as the most reactive of the series. The signal distribution in the ¹H NMR spectra matches with the formation of the α -adducts in all cases (Supporting Information). Figure 4 shows a comparison between the ¹H NMR signals of C₇₀-Ant-1 and C₇₀-Ant-2. Considering that C₇₀ fullerene does not present a symmetry plane perpendicular to the involved α -bond, the lower symmetry of the 9functionalized anthracene Ant-2 derives in the appearance of two signals for the single bridgehead hydrogen in C70-Ant-2, which correspond to the presence of two possible regioisomers. This splitting

for the bridgehead hydrogen consistently appears in the spectra of all the C_{70} -Ant-n adducts, together with the splitting of the aromatic signals of the corresponding benzene rings (Supporting Information). HPLC analysis of C_{70} -Ant-2 confirms the presence of two regioisomers (Figure S41).

With Ant-2 and Ant-7 recognized as the most reactive members of the series, we turned to test the cavity-promoted reactions with these two derivatives using the conditions optimized in the previous work,^[7] namely, 10 equiv. of anthracene with respect to the fullerene. Therein, this excess contributed to the major formation of C_{60} -Ant-1 adduct, but also afforded a notable amount of the trans-3 bis-adduct in a site-selective way. As C₇₀ could give rise to a more complicated mixture of addition compounds, C_{60} was selected as the fullerene species to perform the reaction under these conditions. In the case of Ant-7, the reaction led to a complicated mixture of compounds, probably derived from secondary reactions of the anthracene derivative, and only a minor amount of C_{60} -Ant-7 was isolated. For the reaction with Ant-2, monoadduct C_{60} -Ant-2 was obtained in an improved 38% yield. To our surprise, no traces of trans-3 bis-adduct were observed.^[23]

This unexpected result could be in principle attributed to a low affinity of SubPc-cage for the C₆₀-Ant-2 monoadduct, which would thus be released from the cavity prior to the second cycloaddition. However, the calculated difference in complexation energy ($\Delta E_{\text{complex}}$) for SubPc-cage $\subset C_{60}$ -Ant-1 and SubPc-cage $\subset C_{60}$ -Ant-2 with respect to SubPc-cage $\subset C_{60}$ (-0.31)^[7] is similar, which discredits this hypothesis. It should be noted that the second cycloaddition over the fullerene in **SubPc-cage** \subset C₆₀-Ant-2 is expected to occur only if anthracene molecules occupy at least one of the two non-occupied hydrophobic pockets of the cage. Thus, another plausible explanation is that the multiaddition is not observed because the complexation of Ant-2 (i.e., formation of SubPc-cage $\subset C_{60}$ -Ant-2: Ant-2) is not as favored as in the case of pristine anthracene. Since the $\Delta E_{\text{complex}}$ of **Ant-2** is similar to that of anthracene (Figure 3), the poorer capability must arise from entropic factors, rather than enthalpic, which is reasonable as substituted anthracenes have more orientational restrictions to fit within the pocket.

Conclusion

In this work, we have extended the application of the **SubPc-cage** catalyzed Diels-Alder reaction between C_{60} and anthracene in water to functionalized anthracenes holding either hydrophilic or hydrophobic chains, and to C_{70} fullerene. From the results, it could be concluded that hydrophilic anthracenes

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are less prone to react with fullerenes inside the molecular cavity, which is particularly manifest for the ionic species containing either sulfonate or ammonium groups that did not rendered the cycloaddition reaction. As supported by theoretical calculations, this must be due to a better solvation of charged anthracenes in aqueous medium, and in the case of cationic derivatives, to additional ionic repulsive interactions with positively-charged Pd(II) corners at the SubPc-cage. However, 9-anthracenemethanol Ant-2 and the corresponding benzyloxy derivative Ant-7 rendered 20-30% yields for reactions with C_{60} , demonstrating that catalytic turnover is taking place in this case. When using excess anthracenes Ant-2 and Ant-7 to improve the conversion, only reaction with Ant-2 underwent a yield increase (i.e., 38%). Remarkably, unlike in reactions between C₆₀ and pristine anthracene,^[7] bis-addition to the trans-3 position was not observed. Based on theoretical calculations, a plausible explanation would be that the necessary accommodation of substituted anthracene Ant-2 in the hydrophobic pocket of SubPc-cage \subset C₆₀-Ant-2 complexes is hampered by orientational restrictions, which are higher than in the case for reactions with pristine anthracene.

On the other hand, C_{70} showed a similar reactivity trend than its lower homolog towards the tested anthracenes, but proved more reactive (i.e., ca. 40% conversion for reaction with either **Ant-2** or **Ant-7** and C_{70} in a 1:1 ratio). In this case, the Diels-Alder cycloaddition selectively took place in the [6,6]- α bond, as usually occurs in [4+2] addition reactions over C_{70} dienophile in high boiling organic solvents. As in the case of C_{60} , theoretical calculations revealed that **SubPc-cage** displays a higher host: guest affinity for C_{70} than for its mono-adduct, which is in line with the catalytic nature of the process.

These results validate **SubPc-cage** as a nanoreactor to perform reactions over fullerenes to obtain derivatives that can be key components in state-ofthe-art technologies.

Experimental Section

General Experimental Details

All reactions were performed in standard glassware, except for Diels Alder reactions that were carried out in microwave reaction vials, which were capped with a Supelco aluminum stopper with septum (PTFE/butyl). The monitoring of the reactions has been carried out by thin layer chromatography (TLC), employing aluminum sheets coated with silica gel type 60 F254 (0.2 mm thick, E. Merck). Purification of the synthesized products was performed by column chromatography, using silica gel (230–400 mesh, 0.040–0.063 mm, Merck) or preparative TLC (PLC Silica gel 60 F ₂₅₄, 0.5 mm, Merck). Mass Spectrometry (MS) and High-Resolution Mass spectra (HRMS) were recorded employing Electrospray Ionization (ESI TOF MS) using an API Q-Star Pulsar from Sciex, or Matrix Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) using a Bruker Ultraflex III TOF/ TOF spectrometer, with a nitrogen laser operating at 337 nm or with a NdYAG laser operating at 335 nm; or Atmospheric Pressure Chemical Ionization (APCI) using a Bruker MAXIS II with a high resolution Q-TOF analyzer. All MS experiments were carried out at the Servicio Interdepartmental de Investigación (SIdI) of the Universidad Autónoma de Madrid. NMR spectra (¹H NMR, ¹³C NMR) were recorded on a Bruker AC-300 (300 MHz) instrument or a Bruker XRD500 (500 MHz). Deuterated solvents employed are indicated in each spectrum. UV-vis spectra were recorded on a JASCO-V660 spectrophotometer using spectroscopic grade solvents and 1 cm quartz cuvettes. HPLC data were collected on Agilent 1200 equipment with a semi-preparative Daicel Chiralpak IC column (10 mm ø×20 mmL).

General Procedure for the SubPc-Cage Catalyzed Diels Alder Reaction with Fullerenes

Fullerene C_{60}/C_{70} (0.004 mmol, 1 eq.), pristine anthracene (Ant-1) or anthracene derivatives Ant-2-8 (0.004 mmol, 1 eq.) and SubPc-cage (0.0004 mmol, 1.0 mg) were suspended in a mixture of H₂O (1% DMSO) (0.5 mL). Argon was purged in the solutions for 15 minutes and the mixture sonicated for 30 minutes. The resulting purple solutions were stirred under argon atmosphere at 80 °C for 3 days in dark. After that, the solvent was removed under vacuum without heating to give the crude reaction which was rapidly passed through a silica plug in CS_2 :EtOAc (5%). After removal of the solvent, the mixture of fullerenes was then redissolved in CS_2 (0.3 mL), and a stock solution containing 1, 3, 5trimethoxybenzene internal standard (0.07 M, 10 µL, 0.0007 mmol) in 0.3 mL of acetone-d₆ was added. Finally, the suspension was filtered in a pipette through cotton wool and transferred into an NMR tube for quantitative analysis. In the last step, the adducts were purified through preparative TLC using appropriate eluents (see Supporting Information).

Computational Studies

All reported structures were optimized at semiempirical GFN2-xTB^[24] level in the presence of solvent (water) with the GBSA solvent model (Generalized Born (GB) model and solvent accessible surface area, (SA)). All the calculations were carried out by the methods implemented in Gaussian 16 package.^[25]

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