

Effect of Incarcerated HF on the Chemical Reactivity of Endohedral HF@C₆₀

Sara Vidal,^a Marta Izquierdo,^a Shamim Alom,^b Marc Garcia-Borràs,^{c,d} Salvatore Filippone,^a Sílvia Osuna,^d Miquel Solà,^{d*} Richard J. Whitby^{b*} and Nazario Martín^{a,c*}

^a *Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Avda. Complutense s/n E-28040 Madrid, Spain.* ^b *Chemistry, University of Southampton, Southampton, SO17 1BJ, U.K.* ^c *Department of Chemistry and Biochemistry, University of California Los Angeles, 607 Charles E Young Drive East, CA90095 Los Angeles, USA.* ^d *Institut de Química Computacional i Catàlisi and Departament de Química, Universitat de Girona, c/ Maria Aurèlia Capmany 6, 17003 Girona, Spain.* ^e *IMDEA-Nanociencia, C/ Faraday, 9, Campus de Cantoblanco, E-28049 Madrid, Spain.*

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ABSTRACT: The first chemical modification on the endohedral HF@C₆₀ is reported. In particular, the isomerization from optically pure (2*S*,5*S*)-*cis*-pyrrolidinofullerene **2b** to (2*S*,5*R*)-*trans*-pyrrolidinofullerene **2b** has been studied and compared with empty C₆₀ (**2a**) and endohedral H₂O@C₆₀ (**3**). Interestingly, the incarcerated HF molecule contributes to increase the isomerization rate through a H-bonding assistance involving weak hydrogen bonding without affecting the final *cis-trans* ratio or promoting the loss of enantioselective control through the retro-cycloaddition reaction. The comparative study shows a kinetic order for the isomerization process of H₂O@C₆₀ > HF@C₆₀ > C₆₀, thus confirming the effect of the incarcerated species on the zwitterionic intermediate stability.

Since the detection of endohedral fullerenes following the discovery of C₆₀,¹ many species such as metals, noble gases, clusters, atoms or molecules, have been encapsulated in the hollow fullerene cage. The main method to achieve endohedral fullerenes is based on the arc discharge of graphite rods containing metals. However, controlling the size of the carbon cage or the product distribution by using this methodology is not possible. “Molecular surgery” emerged as an alternative and suitable methodology to synthesize endohedral fullerenes in a controlled manner, and paved the way toward atoms or small molecules encapsulation, namely H₂@C₆₀,² He@C₆₀,³ and H₂O@C₆₀ (Figure 1).⁴

Because of their size, diatomic guest molecules are ideal candidates to be encapsulated inside C₆₀. Hydrogen fluoride (HF) is frequently used in a variety of organic synthetic protocols and has been extensively studied.⁵ HF molecules create hydrogen bonds between them forming aggregates; therefore, the study of isolated HF molecules is complicated. Recently, Krachmalnicoff *et al.*, have successfully isolated the HF molecule inside C₆₀ fullerene, thus forming the new endohedral HF@C₆₀ molecule.⁶ A single HF molecule trapped in a fullerene cage provides the opportunity to analyze its singular properties in an interaction free situation as well as in a well-defined environment. Furthermore, considering the polarity of the HF molecule, it is expected to have an impact on the exohedral reactivity of the [60]fullerene cage.

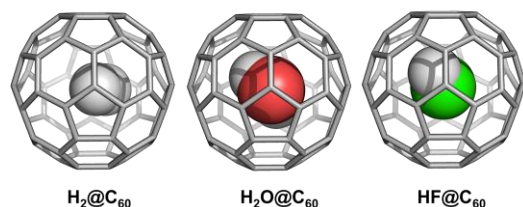


FIGURE 1. Endohedral [60]fullerenes bearing a neutral molecule in the inner cavity synthesized by molecular surgery.

It is known that the encapsulated molecules in endofullerenes can affect the exohedral reactivity of the fullerenes carbon cage.⁷ Dolgonos *et al.* reported a computational study of several diatomic molecules encapsulated into C₆₀.^{5b} They surmised that the dipole moment of the polar guest molecules trapped inside C₆₀ is decreased after the encapsulation, and specifically, the HF molecule exhibits the lowest interaction energy with the C₆₀ compared with other polar molecules investigated. Some of us have demonstrated the interaction of polar molecules inside fullerenes by reporting the *cis-trans* isomerization of enantiomerically pure H₂O@C₆₀ pyrrolidines, showing the existence of a hydrogen bonding assistance between the carbanion on the cage and the trapped water molecule.⁸

Herein, we report the first exohedral functionalization on the novel HF@C₆₀ using an efficient methodology to obtain enantiomerically enriched HF@C₆₀ pyrrolidines. A comparative study between pristine C₆₀, H₂O@C₆₀, and HF@C₆₀ on the *cis-trans* isomerization process is also discussed for a better understanding of the effect of the encapsulated molecule on the isomerization reaction. Furthermore, DFT calculations at the

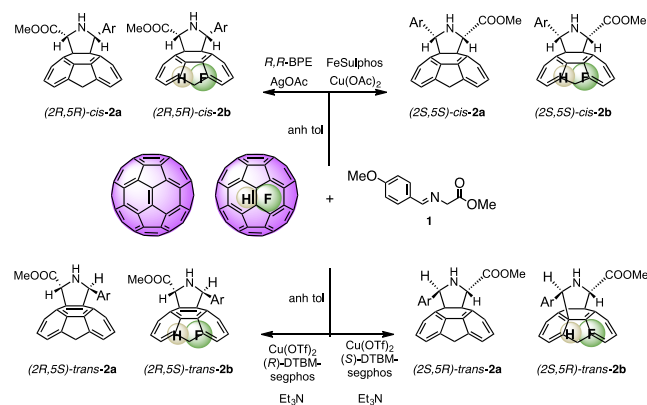
M06-2X/6-311++G(d,p)//OLYP/TZP level of theory nicely rationalize the experimental evidences.

Results and discussion

The synthesis of new enantiomerically enriched fulleropyrrolidines was carried out using the reported methodology involving a 1,3-dipolar cycloaddition of *N*-metalated azomethine ylide.⁹ In order to determine the difference in the chemical reactivity between empty C₆₀ and HF@C₆₀, the reaction was carried out with a mixture of both fullerenes in a ratio 12:88 (C₆₀:HF@C₆₀) under the same reaction crude, thus ensuring the same experimental conditions.

Following Scheme 1, the mixture of fullerenes reacted with iminoester **1** in the presence of the corresponding metal salt / chiral ligand pair to yield each one of the four enantiomers of the respective fulleropyrrolidines, namely the *cis*-**2a** and *cis*-**2b** and the *trans*-**2a** and *trans*-**2b** for the C₆₀ and HF@C₆₀, respectively, in good enantiomeric excesses.

Scheme 1. Synthesis of enantiomerically pure fulleropyrrolidines *cis*-**2a,b** and *trans*-**2a,b**.



Interestingly, despite the polarity of the HF molecule, we did not observe significant differences in terms of reactivity on the carbon cage of the HF@C₆₀ compared with C₆₀. Indeed, the ratio of the pristine cages before and after reacting remained unaltered, (C₆₀:HF@C₆₀ = 12:88), as well as the ratio of pyrrolidine-C₆₀ and pyrrolidine-HF@C₆₀. These experimental data, corroborated by theoretical calculations (see below) contradict *a priori* the expected higher reactivity for the HF@C₆₀ molecules as a result of an acidic/electrophilic LUMO activation of the cage double bonds.

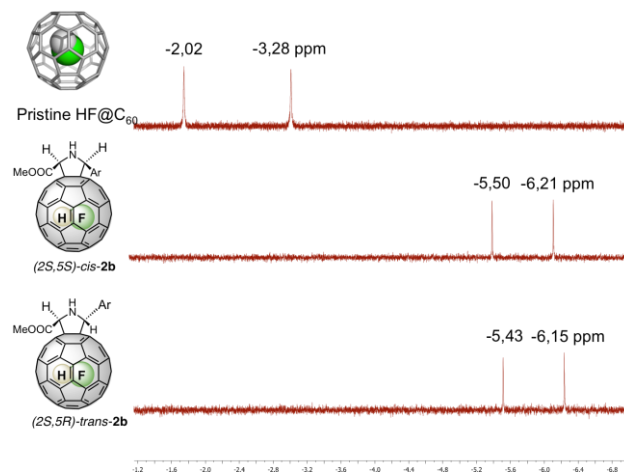


FIGURE 2. ¹H-NMR (700MHz, CDCl₃, 298K) spectra (-1,2 to -7 ppm) of compounds *cis*- and *trans*-**2b** and pristine HF@C₆₀.

The four new enantiomers *cis*- and *trans*-**2b** were fully characterized by NMR spectroscopy and mass spectrometry (S.I.). The signal for the inner proton of pristine HF@C₆₀ in the ¹H-NMR spectrum appears at -2.65 ppm (*J* = 505.6 Hz) as a doublet. However, if the carbon cage is functionalized that signal is shifted to -5.81 ppm (*J* = 505.8 Hz) for *cis*-**2b** and to -5.88 ppm (*J* = 506.0 Hz) for *trans*-**2b** (Figure 2 and S.I.).

Enantiospecific *cis/trans* isomerization: Anchimeric assistance of the inner molecule.

In order to get a better understanding of the HF behavior inside the carbon cage, we moved our attention to the isomerization process that involves the exohedral [60]fullerene functionalization. In this regard, the easy availability of optically active derivatives enables the use of chiral information as a powerful tool to shed light into the mechanism involved. Thus, analogously to a previous related work reported by some of us,⁸ we now study the isomerization process from the optically pure (2*S*,5*S*)-*cis*- to the (2*S*,5*R*)-*trans* pyrrolidinofullerene that proceeds with absolute enantiospecificity. This process can be accounted for by a stepwise mechanism with a configuration inversion at the pyrrolidine C5 carbon atom while the configuration at C2 is maintained without losing enantiomeric excess. This enantiospecificity is coherent with the formation of a zwitterionic intermediate by heterolytic pyrrolidine ring opening between the C5 and the cage (see Figure 3) that gives rise to a stable benzylic cation and a negative charge on the cage.

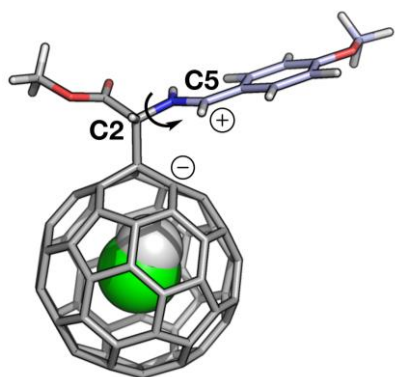


FIGURE 3. Zwitterionic intermediate formed by a carbanion on the C₆₀ cage and a benzylic cation on the former pyrrolidine ring.

The carbanion of the zwitterionic intermediate can interact with the inner species and determine its stability. The negative charge in the carbon atom of the [60]fullerene cage is stabilized by the H atom of the inner HF molecule, thus making the process faster. In a second step, the N-C2 bond of the intermediate rotates and is bonded back to the fullerene cage (Figure 3).

In addition to the study on the isomerization process from the optically pure (2*S*,5*S*)-*cis*-pyrrolidinofullerene **2b** to the (2*S*,5*R*)-*trans*-pyrrolidinofullerene **2b**, it has also been compared with those of the empty C₆₀ (**2a**) and endohedral H₂O@C₆₀ (**3**) (Figure 4). Thus, we can explore the influence of the hydrogen bonding –generated by the carbanion on the fullerene sphere and the hydrogen of the inner molecule (H₂O and HF)– on the racemization process. It is important to mention, however, that moderate temperatures have been used in order to avoid competitive cycles of retro-cycloaddition/cycloaddition reactions also leading to uncontrolled racemization processes. The selected system used for the isomerization experiment was the enantiomer (2*S*,5*S*)-*cis*-fulleropyrrolidine for all the cases with a *cis/trans* ratio of 98/2 for **2a** and **3** and 96/4 for **2b** (see SI). The experiments were performed in chlorobenzene/acetonitrile 1:1 as solvent mixture at three different temperatures (25°C, 30°C, and 40°C).

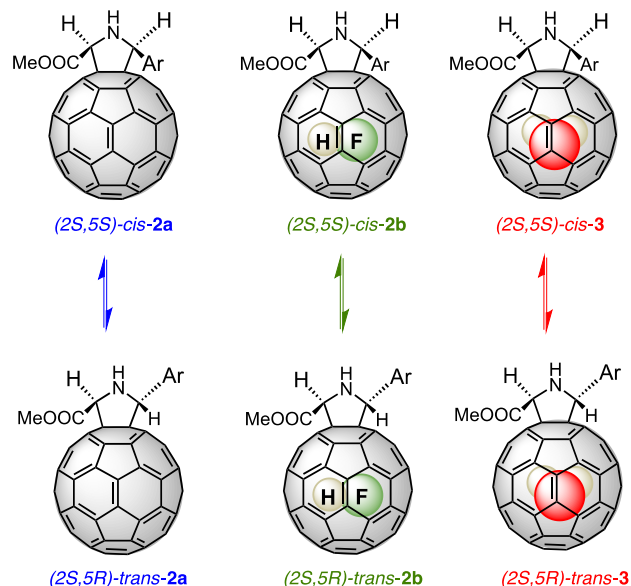
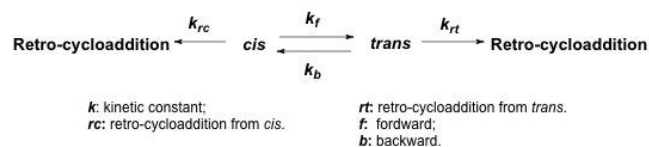


FIGURE 4. Isomerization process from the optically pure (2*S*,5*S*)-*cis*-pyrrolidino[60]fullerene to the (2*S*,5*R*)-*trans*-pyrrolidino[60]fullerene.

The reactions were monitored by HPLC until the equilibrium stages were reached (see Figure XX in the S.I.). Integration of the peak areas was used to determine the relative amount of the isomers at any time during the isomerization. These equilibrium stages and the time needed to reach them were different for each system and are summarized in Table 1. At 25°C, the equilibrium stage was 77/23 *cis:trans* while at 30°C and 40°C, the equilibrium stage *cis/trans* ratio changed significantly toward 59/41 and 55/45, respectively. In all cases, the enantiomeric excesses of the *trans* derivatives remained unaltered demonstrating the enantiospecificity of the isomerization process (see SI).

The proposed mechanism for the isomerization (equilibrium reaction) follows a first-order rate law. However, competing reactions such as the previously reported retro-cycloaddition (retro-Prato)¹⁰ and the racemization are also involved. This process could be outlined according to the following scheme:

Scheme 2. Representation of the reactions involved in the isomerization process.



If we ignore the retro-cycloaddition reaction contribution, the reaction rate would remain:

$$v = -\frac{d[\text{cis}]}{dt} = k_f[\text{cis}] - k_b[\text{trans}] \quad \text{equation (1)}$$

$$\ln \frac{(x-x_e)}{(x_0-x_e)} = -(k_f+k_b)t \quad \text{equation (2)}$$

$$K = k_f + k_b \quad \text{equation (3)}$$

Where x , x_e , and x_o are the concentrations of *cis* adduct at time t , at equilibrium, and at the starting point ($t = 0$), respectively, and k_f and k_b are the rate constants for the forward and backward *cis-trans* isomerization.

Table 1. Comparison of isomerization reaction rates of (2*S*,5*S*)-*cis*-**2a**, (2*S*,5*S*)-*cis*-**2b** and (2*S*,5*S*)-*cis*-**3** in chlorobenzene:acetonitrile 1:1 at 25 °C, 30 °C, and 40 °C.

Compound	T (°C)	<i>cis/trans</i> eq	K (h ⁻¹)
2a	25	77/23	$5,29 \times 10^{-3} \pm 1,90 \times 10^{-4}$
2b	25	77/23	$9,03 \times 10^{-3} \pm 3,92 \times 10^{-4}$
3	25	77/23	$10,95 \times 10^{-3} \pm 1,08 \times 10^{-3}$
2a	30	59/41	$8,50 \times 10^{-3} \pm 2,88 \times 10^{-4}$
2b	30	59/41	$10,26 \times 10^{-3} \pm 4,01 \times 10^{-4}$
3	30	59/41	$12,90 \times 10^{-3} \pm 5,99 \times 10^{-4}$
2a	40	55/45	$11,80 \times 10^{-3} \pm 6,34 \times 10^{-4}$
2b	40	55/45	$12,10 \times 10^{-3} \pm 5,54 \times 10^{-4}$
3	40	55/45	$13,99 \times 10^{-3} \pm 6,40 \times 10^{-4}$

Comparing the experimental findings of three systems, the two endohedral fullerenes have the highest isomerization rates $K_{\text{H}_2\text{O}@C_{60}} > K_{\text{HF}@C_{60}} > K_{C_{60}}$ (see Table 1). This confirms that the encapsulated molecule plays an important role in the zwitterionic intermediate stability. In view of the aforementioned results, the H-bonding assistance is stronger for the $\text{H}_2\text{O}@C_{60}$ system according to the kinetic constants.

These experimental results are in good agreement with that predicted by theoretical calculations (see below).

Mechanism for the enantiospecific *cis/trans* isomerization process.

We have carried out density functional theory calculations at the M06-2X/6-311++G(d,p)//OLYP/TZP level of theory¹¹ including solvent effects (acetonitrile) to analyze the *cis-trans* isomerization in the $\text{HF}@C_{60}$ chiral fulleropyrrolidine (2*S*,5*S*)-*cis*-**2b** (see S.I. for a detailed description of the computational methods). Nitrogen inversion in fulleropyrrolidines is fast¹² and, consequently, we have done all our computations using the most stable conformation of the fulleropyrrolidine. Moreover, we have studied different orientations of the HF unit inside C_{60} for reactants, intermediates, and products and we have considered the most stable orientation in all cases (see S.I.).

Figure 5 provides the computed reaction path for the *cis-trans* isomerization and the retro-cycloaddition process for (2*S*,5*S*)-*cis*-**2b**. For comparison purposes, it also includes the values for the analogous empty pyrrolidino[60]fullerene (2*S*,5*S*)-*cis*-

2a and water-incarcerated endohedral fulleropyrrolidine (2*S*,5*S*)-*cis*-**3** taken from our previous study.⁸ As found in **2a** and **3** and in agreement with experimental observations, PROD-(2*S*,5*S*)-*cis*-**2b** is more stable by 1.6 kcal/mol than PROD-(2*S*,5*R*)-*trans*-**2b**. This value is not far from the experimental 0.7 kcal/mol determined from the observed 77:23 ratio of products at 25 °C. The *cis-trans* isomerization occurs through a stepwise mechanism with the formation of zwitterionic intermediates referred as INT-(2*S*,5*S*)-*cis*-**2b** and INT-(2*S*,5*R*)-*trans*-**2b** in Figure 4. Zwitterionic intermediates of this type are not exceptional and, for instance, they were also found in 1,3-dipolar isomerizations on endohedral metallofullerenes.¹³ The heterolytic dissociation of the C–C bond to form the zwitterionic intermediate is much easier at C5 (with an energy barrier less than 1 kcal/mol) than at C2 position because of the electron withdrawing character of the carboxylic group (see Figure 2). **Error! Marcador no definido.** This result explains the experimental observation that the C2 configuration is preserved along the whole isomerization process. After dissociation, the negative charge is located on the cage and the positive one in the benzylic cation. As compared to separated reactants, zwitterionic intermediates are about 1.5 kcal/mol more stable in $\text{HF}@C_{60}$ than in hollow C_{60} . The reason for this stabilization is the formation of an interaction between the H of the HF unit and the negatively charged C atom on the fullerene cage. The distance between the H atom of HF and C5 in the zwitterionic intermediate is *ca.* 2.6 Å (see Figure 6). The H–F distance in *cis* and *trans* intermediates is 0.931 Å, somewhat elongated as compared to that of $\text{HF}@C_{60}$ (0.929 Å), but less than that found in the hydrogen bonded (HF)₂ dimer (0.937 Å). Therefore, this H...C interaction in the zwitterionic intermediate can be classified as a weak hydrogen bond. Nevertheless, the higher stability of zwitterion INT-(2*S*,5*S*)-*cis*-**2b** with respect to INT-(2*S*,5*S*)-*cis*-**3** (*i.e.* 1 kcal/mol) is in line with the fact of HF being a better H-bond acceptor than H₂O.

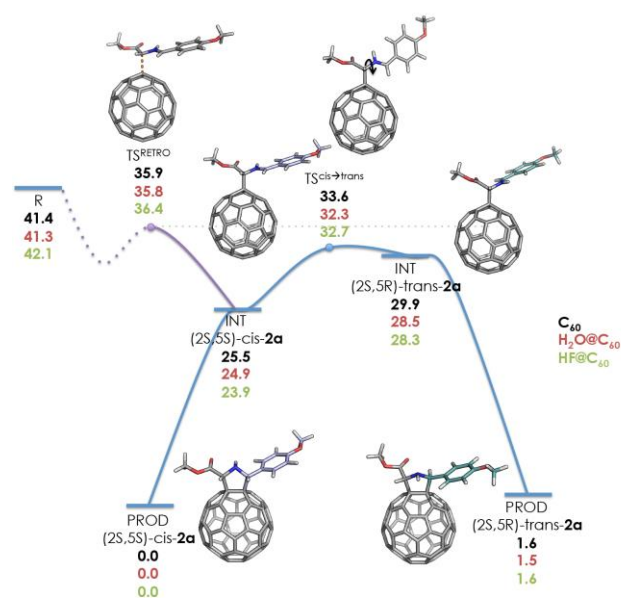


FIGURE 5. Relative M06-2X/6-311++G(d,p)//OLYP/TZP electronic energies for the *cis-trans* isomerization in **2a** (black values), **3** (red values) and **2b** (green values). The retro-Prato

process is also included (in purple). All energies are in kcal/mol.

From the zwitterionic INT-(2*S*,5*S*)-*cis*-**2b**, the system can evolve through two different pathways: i) *cis*-*trans* isomerization to produce INT-(2*S*,5*R*)-*trans*-**2b** or ii) retro-Prato reaction to recover the initial reactants. Isomerization occurs through rotation around the C2–N bond of INT-(2*S*,5*S*)-*cis*-**2b** to yield INT-(2*S*,5*R*)-*trans*-**2b**, which evolves to PROD-(2*S*,5*R*)-*trans*-**2b** in an almost barrierless process. The retro-Prato reaction from INT-(2*S*,5*S*)-*cis*-**2b** is also possible, but it has a barrier that is about 3.7 kcal/mol higher than the *cis*-*trans* isomerization process. This difference between the activation barrier for the retro-Prato and isomerization process is substantially larger in the case of HF, as compared to free C₆₀ and H₂O@C₆₀ (ca. 2.3 and 3.5 kcal/mol, respectively). Therefore, especially in the case of C₆₀, the retro-Prato pathway can compete with the isomerization process at high temperatures.

It is worth noting that the presence of the inner HF molecule does not affect the final relative stability of the *cis* and *trans* products. However, it has an important effect on the retro-reaction pathway and, especially, it has a significant influence on the energy barrier of the *cis*-*trans* isomerization process. The activation barrier is considerably lower in **2b** (32.7 kcal/mol with respect to the lowest energy *cis* product) as compared to **2a** (33.6 kcal/mol). This ca. 1 kcal/mol difference is in agreement with the improved stereochemical outcome observed experimentally for the HF@C₆₀ chiral fulleropyrrolidine. The encapsulated HF molecule assists the isomerization process by stabilizing the formed fullerene anion, where the hydrogen atom of HF is directly pointing to the negatively charged carbon atom on the fullerene surface. This distance is ca. 2.6 Å in INT-(2*S*,5*S*)-*cis*-**2b**, and slightly longer in TS^{cis→trans} (ca. 2.7 Å) (Figure 6), indicating that a small disruption of this H-bond interaction occurs at the transition state. The slightly smaller energy barrier (by 0.4 kcal/mol) for the *cis*-*trans* isomerization process in **3** as compared to **2b** also concurs with the experimental rate constants (see Table 1). The latter may be due to the slightly weaker H-bond interaction between the carbon atom at the fullerene cage and the H₂O molecule. This leads to a smaller energy penalty to achieve the TS^{cis→trans} as compared to the HF case.

Our findings indicate the incarcerated HF molecule contributes to increase the isomerization rate without affecting the final *cis*-*trans* ratio or promoting the loss of enantioselective control through the retro-Prato reaction.

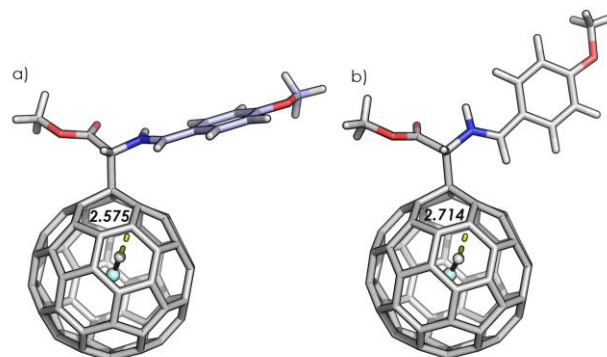


FIGURE 6. Optimized geometries at OLYP/TZP level of theory of a) INT-(2*S*,5*S*)-*cis*-**2b** and b) TS^{cis→trans} for HF@C₆₀. Distances are in Å.

Conclusions

In summary, we have carried out the first chemical modification on the recently reported HF@C₆₀ endohedral by 1,3-dipolar cycloaddition on the fullerene cage. In this work, we have studied the isomerization process from the optically pure (2*S*,5*S*)-*cis*-pyrrolidino[60]fullerene **2b** to the (2*S*,5*R*)-*trans*-pyrrolidino[60]fullerene **2b** and it has been compared with the empty C₆₀ (**2a**) and H₂O@C₆₀ (**3**) related fullerenes. This study has been carried out at moderate temperatures to avoid the competitive retro-cycloaddition process occurring at higher temperatures. It is worth mentioning that the easy availability of these optically active fullerenes enables the use of chiral information as a straightforward and powerful tool to shed light into the effect of the incarcerated molecule on the mechanism involved.

Interestingly, the incarcerated HF molecule contributes to increase the isomerization rate through a weak hydrogen bonding assistance without affecting the final *cis*-*trans* ratio or promoting the loss of enantioselective control through the retro-cycloaddition reaction.

As a whole, the experimental findings reveal that the two endohedral fullerenes present the highest isomerization rates H₂O@C₆₀ > HF@C₆₀ > C₆₀, which confirms that the encapsulated molecule plays a significant role in the zwitterionic intermediate stability and, therefore, in the kinetics of the process. Actually, this first evidence of the assistance of the incarcerated HF molecule in the new HF@C₆₀ paves the way to the study of a variety of reactions where the presence of the inner HF molecule can influence or determine the outcome of the chemical reactivity.

ASSOCIATED CONTENT

Supporting Information

General methods, synthesis of starting materials, spectroscopical data, computational methods, Relative stabilities of different HF orientations inside C₆₀ for products and intermediates, and Cartesian coordinates of all stationary points located. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

- Nazario Martín: nazmar@ucm.es
- Richard J. Whitby: R.J.Whitby@soton.ac.uk
- Miquel Solà: miquel.sola@udg.edu

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