Effect of Incarcerated HF on the Exohedral Chemical Reactivity of HF@C_{60}

Sara Vidal, a Marta Izquierdo, a Shamim Alom, b Marc García-Borràs, c,d Salvatore Filippone, a Silvia Osuna, a Miquel Solà, a,* Richard J. Whitby, a,* and Nazario Martin a,*

The first chemical modification on the brand new endohedral HF@C_{60} is reported. In particular, the isomerization from optically pure (25,5S)-cis-pyrrolidino[3,4;1,2][60]fullerene 2b to (25,5R)-trans-pyrrolidino[3,4;1,2][60]fullerene 2b has been studied and compared with empty C_{60} (2a) and endohedral H_{2}O@C_{60} (3). The comparative study shows a kinetic order for the isomerization process of H_{2}O@C_{60} > HF@C_{60} > C_{60}, thus confirming the effect of the incarcerated species on the zwitterionic intermediate stability.

Introduction

Since the detection of endohedral fullerenes following the discovery of C_{60}, 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 H_{2}@C_{60}, He@C_{60}, and H_{2}O@C_{60} (Figure 1).

Because of their size, diatomic guest molecules are ideal candidates to be encapsulated inside C_{60}. Hydrogen fluoride (HF) is frequently used in a variety of organic synthetic protocols and has been extensively studied. Recently, Krachmalnicoff et al., have successfully isolated the HF molecule inside C_{60} fullerene, thus forming the new endohedral HF@C_{60} molecule. 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 exochemical reactivity of the [60]fullerene cage.

It is known that some encapsulated molecules in endofullerenes can affect the exochemical reactivity of the fullerenes carbon cage.\(^a\)

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.\(^b\) In order to

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

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determine the difference in the chemical reactivity between empty 
C_{60} and HF@C_{60}, the reaction was carried out with a mixture of both 
fullerenes in a ratio 12:88 (C_{60}:HF@C_{60}) under the same reaction 
crude, thus ensuring the same experimental conditions. 

Following the Scheme 1, the mixture of fullerenes reacted with 
iminoster 1 in the presence of the corresponding metal salt / chiral 
ligand pair to yield each one of the four enantiomers of the 
respective pyrrolidino[60]fullerenes, namely the cis-2a and cis-2b 
and the trans-2a and trans-2b for the C_{60} and HF@C_{60}, respectively, 
in good enantiomeric excesses. It is important to note that the 
respective enantiomers shown in the Scheme 1 were obtained as a 
mixture of the respective empty and filled fullerene derivatives in 
the same ratio than the starting mixture.

The four new enantiomers cis-2b and trans-2b were fully 
characterized by NMR spectroscopy and mass spectrometry (S.I.). 
The signal for the inner proton of pristine HF@C_{60} 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 
−5.88 ppm (J = 506.0 Hz) for trans-2b (Figure 2) and to −5.81 ppm (J = 505.8 Hz) 
for cis-2b (see Figure 3).

Enantiospecific cis/trans isomerization: H-bonding 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. We now study the isomerization process 
from the optically pure (25,5S)-cis- to the (25,5R)-trans-
pyrrolidino[3,4,1,2][60]fullerene that proceeds with an absolute 
enantiospecificity. This process can be accounted for by a stepwise 
mechanism with a configurational inversion at the pyrrolidine C5 
carbon atom while the configuration at C2 is maintained without 
losing enantiospecific 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 [60]fullerene cage.

In addition to the study on the isomerization process from the 
optically pure (25,5S)-cis-pyrrolidino[60]fullerene 2b to the (25,5R)- 
trans-pyrrolidino[3,4,1,2][60]fullerene 2b, it has also been compared with 
those of the empty C_{60} (2a) and endohedral H_{2}O@C_{60} (3) (Figure 
S11). 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 (H_{2}O and HF)– on the isomerization 
process. The proposed mechanism for the isomerization (equilibrium reaction) 
follows a first-order rate law. However, competing reactions such as the previously reported retro-
cycloaddition^23 and the racemization might be also involved. 
Therefore, moderate temperatures have been used in order to 
avoid those competitive reactions. In all cases, the enantiomeric 
excesses of the trans derivatives remained unaltered demonstrating 
the enantiospecificity of the isomerization process (see SI).

Comparing the experimental findings of the three systems, the two 
endohedral fullerenes show the highest isomerization rates k_{H_{2}O@C_{60}} > k_{H@C_{60}} > k_{C_{60}} (see Table S1). This confirms that the encapsulated 
molecule plays a significant role in the zwitterionic intermediate 
stability. In view of the aforementioned results, the H-bonding
assistance is stronger for the H₂O@C₆₀ 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 theory including solvent effects to analyze the cis-trans isomerization in the HF@C₆₀ chiral pyrroldino[60]fullerene (25,55)-cis-2b (see S.I. for a detailed description of the computational methods). Nitrogen inversion in pyrroldino[60]fullerenes is fast and consequently, for all computations, the most stable conformation of the pyrroldino[60]fullerene was used. Moreover, different orientations of the HF unit inside C₆₀ for reactants, intermediates, and products have been studied and the most stable orientation has been considered in all cases (see S.I.).

Figure 4 provides the computed reaction path for the cis-trans isomerization and the retro-cycloaddition process for (25,55)-cis-2b. For comparison purposes, it also includes the values for the analogous empty pyrroldino[60]fullerene (25,55)-cis-2a and water-incarcerated endohedral pyrroldino[60]fullerene (25,55)-cis-3 taken from our previous study. As found in 2a and 3 and in agreement with experimental observations, PROD-(25,55)-cis-2b is more stable by 1.6 kcal/mol than PROD-(25,5R)-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-(25,5S)-cis-2b and INT-(25,5R)-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. The heterolytic dissociation of the C=C bond to form the zwitterionic intermediate is much easier at C5 (with an energy barrier lower by 10 kcal/mol) than at C2 position because of the electron withdrawing character of the carboxylic group (see Figure 3). This result is in concordance with 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 HF@C₆₀ than in hollow C₆₀. The reason of 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 S31). The H–F distance in cis and trans intermediates is 0.931 Å, somewhat elongated as compared to that of HF@C₆₀ (0.929 Å), but less than that found in the hydrogen bonded (HF) dimer (0.937 Å). Therefore, this H–C interaction in the zwitterionic intermediate can be classified as a weak hydrogen bond.

From the zwitterionic INT-(25,5S)-cis-2b, the system can evolve through two different pathways: i) cis-trans isomerization to produce INT-(25,5R)-trans-2b or ii) retro-cycloaddition reaction to recover the initial reactants. Isomerization occurs through rotation around the C2–N bond of INT-(25,5S)-cis-2b to yield INT-(25,5R)-trans-2b, which evolves to PROD-(25,5R)-trans-2b in an almost barrierless process. The retro-cycloaddition reaction from INT-(25,5S)-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 barriers for the retro-cycloaddition and isomerization processes 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-cycloaddition 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 pyrroldino[60]fullerene. The encapsulated HF molecule assists the isomerization process by stabilizing the formed fullerene anion intermediate, where the hydrogen atom of HF is directly pointing to the negatively charged carbon atom on fullerene surface. This distance is ca. 2.6 Å in INT-(25,5S)-cis-2b, and slightly longer in TS cis-trans (ca. 2.7 Å) (Figure S31), indicating a disruption of the H-bonding in the TS cis-trans due to a more delocalized negative charge on the pyrroldino[60]fullerene in the TS structure. 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 S1). Because HF is more
Conclusions

In summary, we have carried out the first chemical modification on pyrrolidino[60]fullerene \( O@C \). Although the activation barriers calculated are somehow high for a rotation, partially by about 1 kcal/mol (Figure 15a). This journal is more endohedral. In this work, we have studied the isomerization process from \( \text{cis} \)-pyrrolidino[60] fullerene \( 2b \) to the \( \text{trans} \)-pyrrolidino[60] fullerene \( 2b \) and it has been compared with the empty \( C_60 \) (2a) and \( H_2O@C_{60} \) (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.

As a whole, the experimental findings reveal that the two endohedral fullerenes present the highest isomerization rates, \( H_2O@C_{60} \rightarrow HF@C_{60} \rightarrow C_{60} \), 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 study paves the way to a variety of reactions where the presence of the inner HF molecule can influence or decide the outcome of the molecular chemical reactivity.

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Notes and references