Journal Name

ARTICLE

Effect of Incarcerated HF on the Exohedral Chemical Reactivity of HF@C$_{60}$

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

The first chemical modification on the brand new endohedral HF@C$_{60}$ is reported. In particular, the isomerization from optically pure (2*S*,5*S*)-*cis*-pyrrolidino[3,4:1,2][60]fullerene **2b** to (2*S*,5*R*)-*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$_{60}$,[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 H$_2$@C$_{60}$,[2] He@C$_{60}$,[3] and H$_2$O@C$_{60}$[4] (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.[5] Recently, Krachmalnicoff *et al.*, have successfully isolated the HF molecule inside C$_{60}$ fullerene, thus forming the new endohedral HF@C$_{60}$ 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.

It is known that some encapsulated molecules in endofullerenes can affect the exohedral reactivity of the fullerenes carbon cage.[7]
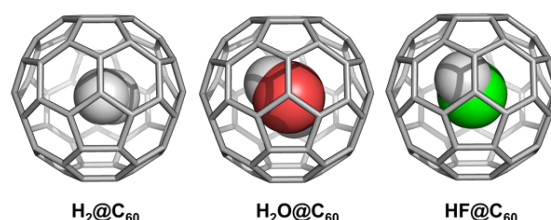

Figure 1 Endohedral [60]fullerenes bearing a neutral molecule in the inner cavity synthesized by molecular surgery.

Dolgonos *et al.* reported a computational study of several diatomic molecules encapsulated into C$_{60}$, including the HF molecule.[5b] Some of us have demonstrated the interaction of polar molecules inside fullerenes by reporting the *cis-trans* isomerization of enantiomerically pure H$_2$O@C$_{60}$ 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@C$_{60}$ using an efficient methodology to obtain enantiomerically enriched HF@C$_{60}$ pyrrolidines. A comparative study between pristine C$_{60}$, H$_2$O@C$_{60}$, and HF@C$_{60}$ on the *cis-trans* isomerization process is also discussed for a better understanding of the effect of the molecule inside on the isomerization reaction. Furthermore, DFT calculations at the M06-2X/6-311++G(d,p)//OLYP/TZP level of theory nicely underpin the experimental evidences. In contrast to that expected, the kinetics observed does not only depend on the inherent acidity of the incarcerated HF molecule.

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

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*

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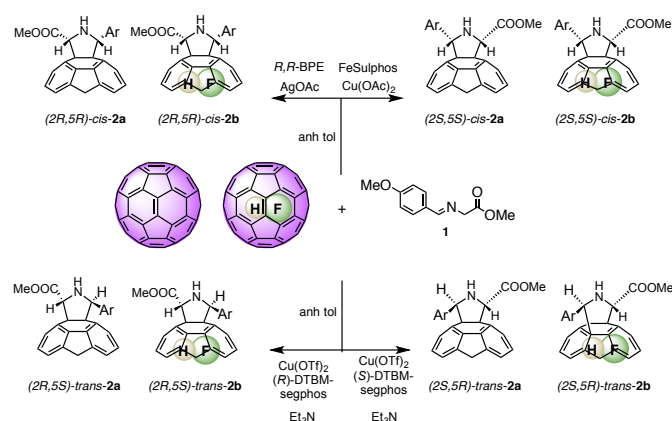
Scheme 1 Synthesis of enantiomerically pure fulleropyrrolidines *cis*-**2a,b** and *trans*-**2a,b**.

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@C_{60} compared with C_{60}. Indeed, the ratio of pristine cages before and after reacting remained unaltered, (C_{60}:HF@C_{60} = 12:88), as well as the ratio of pyrrolidine-C_{60} and pyrrolidine-HF@C_{60}. These experimental data, corroborated by theoretical calculations (see below), contradict *a priori* the expected higher reactivity for the HF@C_{60} molecules as result of an acidic/electrophilic LUMO activation of the cage double bonds.
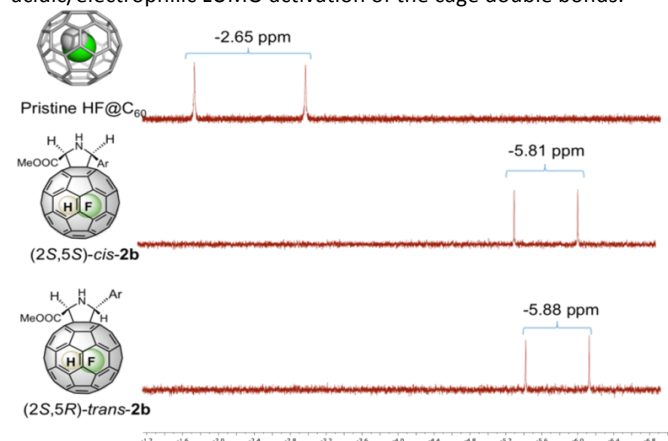

Figure 2 ^{1}H-NMR (700 MHz, CDCl$_3$, 298K) spectra (-1.2 to -7 ppm) of compounds *cis*-**2b** and *trans*-**2b** and ^{1}H-NMR (400 MHz, *o*-DCB-*d4*, 298K) spectrum of pristine HF@C_{60}.

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 ^{1}H-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 −5.81ppm (*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: 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 (2*S*,5*S*)-*cis*- to the (2*S*,5*R*)-*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 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 [60]fullerene cage.
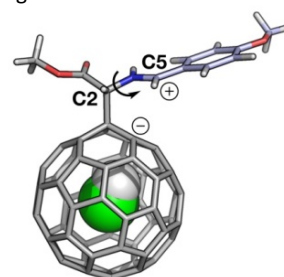

Figure 3 Zwitterionic intermediate formed by a carbanion on the C_{60} cage and a benzylic cation on C5 of the former pyrrolidine ring in the isomerization process.

In addition to the study on 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**, 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[10] 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 $k_{H2O@C60}$ > $k_{HF@C60}$ > k_{C60} (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 $H_2O@C_{60}$ 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 theory[11] including solvent effects to analyze the *cis-trans* isomerization in the $HF@C_{60}$ chiral pyrrolidino[60]fullerene (2*S*,5*S*)-*cis*-**2b** (see S.I. for a detailed description of the computational methods). Nitrogen inversion in pyrrolidino[60]fullerenes is fast[12] and consequently, for all computations, the most stable conformation of the pyrrolidino[60]fullerene was used. Moreover, different orientations of the HF unit inside C_{60} 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 (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 pyrrolidino[60]fullerene (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 25⁰C. 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 lower by 10 kcal/mol) than at C2 position because of the electron withdrawing character of the carboxylic group (see Figure 3).[13] 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 $HF@C_{60}$ than in hollow C_{60}. 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 $HF@C_{60}$ (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.
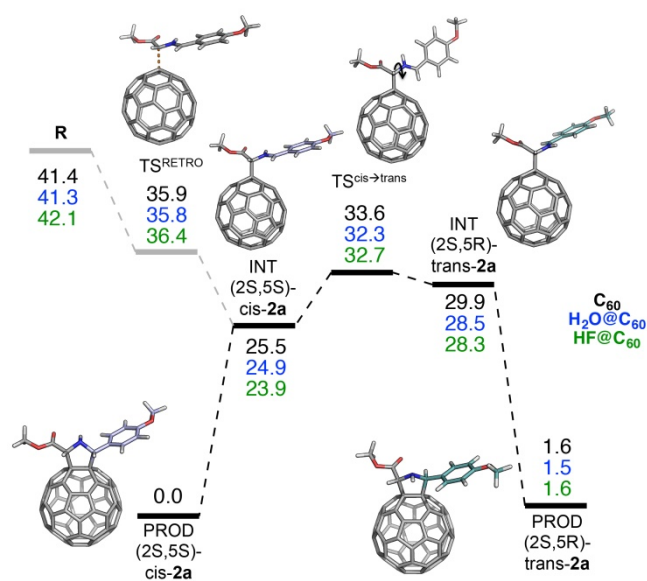

Figure 4 Relative M06-2X/6-311+G(d,p)//OLYP/TZP electronic energies for the *cis-trans* isomerization in **2a** (black values), **3** (blue values) and **2b** (green values). The retro-cycloaddition process is also included (in grey). All energies are in kcal/mol.

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-cycloaddition 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-cycloaddition 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-cycloaddition and isomerization process is substantially larger in the case of HF, as compared to free C_{60} and $H_2O@C_{60}$ (ca. 2.3 and 3.5 kcal/mol, respectively). Therefore, especially in the case of C_{60}, 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 $HF@C_{60}$ chiral pyrrolidino[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-(2*S*,5*S*)-*cis*-**2b**, and slightly longer in TS$^{cis\rightarrow trans}$ (ca. 2.7 Å) (Figure S31), indicating a disruption of the H-bonding in the TS$^{cis\rightarrow trans}$ due to a more delocalized negative charge on the pyrrolidino[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

acidic than H_2O, the H-bond in INT-HF@C_{60} is stronger than in INT-H_2O@C_{60} and this translates into a higher stabilization of the HF zwitterionic intermediate by about 1 kcal/mol (Figure 4). Since this H-bond is slightly "broken/disrupted" in the TS of the *cis-trans* rotation, partially breaking the stronger H-bond interaction in the HF system raises the rotational barrier by 0.4 kcal/mol as compared to H_2O (see detailed discussion in pages 25S-29S of the S.I.).

Although the activation barriers calculated are somehow high for a reaction that proceeds at room temperature, which is attributed to an overestimation of the Gibbs energy barrier to the M06-2X/6-311+G(d,p)//OLYP/TZP method used, they are reliable as confirmed by the experimental kinetic order for the isomerization process: H_2O@C_{60} > HF@C_{60} > C_{60}. Therefore, 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-cycloaddition reaction.

Conclusions

In summary, we have carried out the first chemical modification on the recently reported HF@C_{60} endohedral. 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 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} > HF@C_{60} > 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.

Acknowledgements

Notes and references

1 J. R. Heath, S. C. O'Brien, Q. Zhang, Y. Liu, R. F. Curl, F. K. Tittel and R. E. Smalley, *J. Am. Chem. Soc.*, 1985, **107**, 7779–7780.
2 a) Y. Murata, M. Murata and K. Komatsu, *J. Am. Chem. Soc.,* 2003, **125**, 7152-7153. b) K. Komatsu, M. Murata and Y. Murata, *Science,* 2005, **307**, 238–240.
3 Y. Morinaka, F. Tanabe, M. Murata, Y. Murata and K. Komatsu, *Chem. Commun.*, 2010, **46**, 4532-4534.
4 a) K. Kurotobi and Y. Murata, *Science,* 2011, **333**, 613-616. b) Y. Hashikawa, M. Murata, A. Wakamiya and Y. Murata, *Angew. Chem. Int. Ed.,* 2016, **55**, 13109-13113.
5 a) D. Feller and K. A. Peterson, *Theochem.*, 1997, ***400***, 69-70. b) G. A. Dolgonos and G. H. Peslherbe, *Phys. Chem. Chem. Phys.*, 2014, **16**, 26294-26305.
6 A. Krachmalnicoff, R. Bounds, S. Mamone, S. Alom, M. Concistrè, B. Meier, K. Kouřil, M. E. Light, M. R. Johnson, S. Rols, A. J. Horsewill, A. Shugai, U. Nagel, T. Room, M. Carravetta, M. H. Levitt and R. J. Whitby, *Nat. Chem.*, 2016, **8**, 953–957.
7 a) M. R. Cerón, M. Izquierdo, M. Garcia-Borràs, S. S. Lee, S. Stevenson, S. Osuna and L. Echegoyen, *J. Am. Chem. Soc.,* 2015, **137**, 11775–11782. b) M. Yamada, M. Okamura, S. Sato, C. I. Someya, N. Mizorogi, T. Tsuchiya, T. Akasaka, T. Kato and S. Nagase, *Chem. Eur. J.*, 2009, **15**, 10533-10542. c) M. Izquierdo, M. R. Cerón, M. M. Olmstead, A. L. Balch and L. Echegoyen, *Angew. Chem. Int. Ed.*, 2013, **52**, 11826–11830. d) M. Garcia-Borràs, S. Osuna, J. M. Luis, M. Swart and M. Solà, *Chem. Eur. J.,* 2013, **19**, 14931–14940. e) M. Murata, S. Maeda, Y. Morinaka, Y. Murata and K. Komatsu, *J. Am. Chem. Soc.*, 2008, **130**, 15800-15801.
8 E. E. Maroto, J. Mateos, M. Garcia-Borràs, S. Osuna, S. Filippone, M. A. Herranz, Y. Murata, M. Solà and N. Martín, *J. Am. Chem. Soc.,* 2015, **137**, 1190–1197.
9 a) S. Filippone, E. E. Maroto, A. Martín-Domenech, M. Suárez and N. Martín, *Nat. Chem.*, 2009, **1**, 578-582. b) J. Marco-Martínez, S. Reboredo, M. Izquierdo, V. Marcos, J. L. López, S. Filippone and N. Martín, *J. Am. Chem. Soc.*, 2014, **136**, 2897-2904. c) E. E. Maroto, M. Izquierdo, M. Murata, S. Filippone, K. Komatsu, Y. Murata and N. Martín, *Chem. Commun.*, 2014, **50**, 740-742. d) K. Sawai, Y. Takano, M. Izquierdo, S. Filipone, N. Martín, Z. Slanina, N. Mizorogi, M. Waelchli, T. Tsuchiya, T. Akasaka and S. Nagase, *J. Am. Chem. Soc.,* 2011, **133**, 17746–17752. e) E. E. Maroto, J. Marco-Martínez, M. Izquierdo, S. Reboredo, S. Filippone and N. Martín, *Acc. Chem. Res.,* 2014, **47**, 2660–2670.
10 a) S. Filippone, M. Izquierdo, A. Martín-Domenech, S. Osuna, M. Solà and N. Martín, *Chem. Eur. J.*, 2008, **14**, 5198-5206. b) N. Martín, M. Altable, S. Filippone, A. Martín-Domenech, L. Echegoyen and C. M. Cardona, *Angew. Chem. Int. Ed.*, 2006, **45**, 110–114. c) O. Lukoyanova, C. M. Cardona, M. Altable, S. Filippone, N. Martín and L. Echegoyen, *Angew. Chem. Int. Ed.*, 2006, **45**, 7430-7433.
11 a) N. C. Handy and A. J. Cohen, *Mol. Phys.,* 2011, **99**, 403-412. b) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1992, ***45***, 13244- 13249. c) J. Baker and P. Pulay, *J. Chem. Phys.,* 2002, **117**, 1441-1449. d) Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215-241.
12 O. Lukoyanova, A. Kitaygorodskiy, C. M. Cardona and L. Echegoyen, *Chem. Eur. J.,* 2007, **13**, 8294-8301.
13 S. Aroua, M. Garcia-Borràs, S. Osuna and Y. Yamakoshi, *Chem. Eur. J.,* 2014, **20**, 14032-14039.