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A Computational Study of Tetrafluoro-[2.2]Cyclophanes

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A computational study of the isomers of tetrafluorinated [2.2]cyclophanes persubstituted in one ring, namely F_4-[2.2]paracyclophane (**4**), F_4-*anti*-[2.2]metacyclophane (**5a**), F_4-*syn*-[2.2]metacyclophane (**5b**), and F_4-[2.2]metaparacyclophane (**6a** and **6b**), was carried out. The effects of fluorination on the geometries, relative energies, local and global aromaticity, and strain energies of the bridges and rings were investigated. An analysis of the electron density by B3PW91/6-31+G(d,p), B3LYP/6-31+G(d,p), and MP2/6-31+G(d,p) was carried out using the natural bond orbitals (NBO), natural steric analysis (NSA), and atoms in molecules (AIM) methods. The analysis of frontier molecular orbitals (MOs) was also employed. The results indicated that the molecular structure of [2.2]paracyclophane is the most affected by the fluorination. Isodesmic reactions showed that the fluorinated rings are more strained than the nonfluorinated ones. The NICS, HOMA, and PDI criteria evidenced that the fluorination affects the aromaticity of both the fluorinated and the nonfluorinated rings. The NBO and NSA analyses gave an indication that the fluorination increases not only the number of through-space interactions but also their magnitude. The AIM analysis suggested that the through-space interactions are restricted to the F_4-[2.2]metacyclophanes. In addition, the atomic properties, computed over the atomic basins, gave evidence that not only the substitution, but also the position of the bridges could affect the atomic charges, the first atomic moments, and the atomic volumes.

1. Introduction

The [2.2]cyclophanes are the simplest class of [2_n]cyclophanes. They bear two benzene rings in their structure, and these rings are connected by *n*-ethano bridges, where $2 \leq n \leq 6$.[1] These cyclophanes are classified according to the position of their $-CH_2CH_2-$ bridges and the orientation of their benzene rings (anti and syn). Examples of such cyclophanes are [2.2](1.4)-cyclophane, also known as [2.2]paracyclophane (**1**); *anti*-[2.2]metacyclophane (**2a**); *syn*-[2.2]metacyclophane (**2b**); and [2.2]metaparacyclophane (**3**) (Figure 1a).

Cyclophanes have found applications in several different areas. Their use in the preparation of conducting polymers consisting of units that alternate a metal and the cyclophane is of particular interest.[2] Polymers prepared from cyclophanes by chemical deposition in the vapor phase (CVD)[3] can form biomimetic layers containing incorporated functional groups (proteins, antigens, cell receptors), which allow the control of interactions between biomaterials and organisms.[4] These compounds can also act as synthetic selective receptors of anions such as carboxylates and phosphates, which exhibit biological functions.[5] Literature data has revealed that cyclophane derivatives can be employed as catalysts for asymmetric syntheses.[6] As cyclophanes present host−guest interactions, it is possible to use them in supramolecular chemistry.[7,8] Also, there are some proposals to use them as molecular rotors.[9a−d]

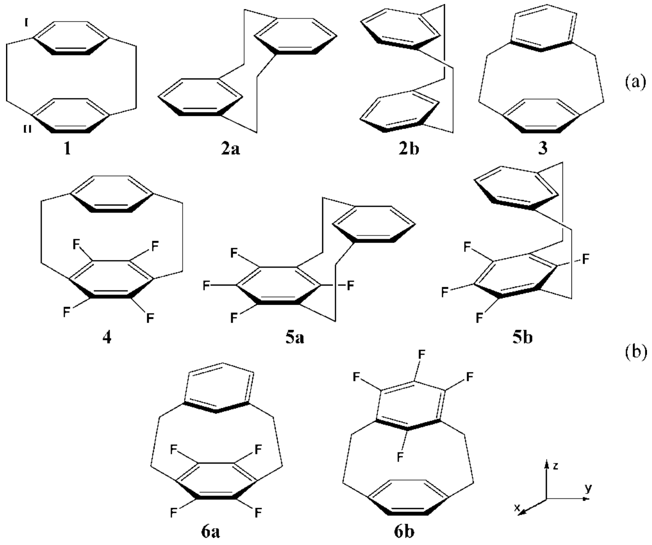

Figure 1. (a) [2.2] Cyclophanes (**1**−**3**) and (b) tetrafluoro-[2.2] cyclophanes (**4**−**6b**).

The chemistry of cyclophanes has been attracting a lot of research interest for many decades. This is because these compounds exhibit unique properties related to the transannular interactions taking place within their molecules. These interactions furnish a delocalized π electron system that stretches all over the molecule, as observed by photoelectron spectroscopy and electron spin resonance.[10,11] The preparation of polymers conjugated with [2.2]cyclophane or [3.3]cyclophane monomers shows that transannular interactions, through-space or the through-bond, lead to a π-conjugation extension through the polymer structure,[12] thus modifying such properties as electric conductivity, photoluminescence, electroluminescence, and fluorescence. The occurrence of transannular interactions in cyclophanes has been investigated since the pioneering work of Cram et al., [13a−k] with a view to explaining their behavior in several reactions. For instance, the benzene rings of [4.4]paracyclophane

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are close enough for a ring to affect the reactivity of the other in acylation and hydrogenation reactions.[13a,b] Other works by Cram, like the ultraviolet absorption studies regarding [*m*,*n*] paracyclophanes,[13c,e,f,h,i] as well as studies on acetylation and nitration rates as a function of substitution[13d,g] or even the determination of the acidity constant of heteroannular [2.2]paracyclophanes,[13k] leave no doubt as to the presence of transannular interactions in cyclophanes. However, despite their scientific and technological importance, the nature of these interactions has not yet been fully elucidated. Using a charge transport experiment in a metal−molecule−metal junction system, Seferos et al.[14] have recently proved that the through-space $\pi-\pi$ interactions between the benzene rings of [2.2]paracyclophane are the ones responsible for the high conductivity of the system, which is in agreement not only with spectroscopic measurements,[15a−d] but also with calculations using the DFT theory.[14]

Since their first synthesis,[16] the fluorinated derivatives of cyclophane, especially tetrafluoro-[2.2]paracyclophane (**4**) (Figure 1b), have attracted the attention of chemists because of their unusual characteristics. UV spectroscopy studies have confirmed the presence of attractive transannular interactions between the fluorinated and the nonfluorinated rings in **4**.[17] Literature reports have shown that the insertion of fluorine atoms into one of the rings of **1** leads to a decrease in the reactivity of the nonsubstituted ring in Friedel−Crafts acylation reactions, which indicates that there is a transannular interaction capable of withdrawing electrons from the nonsubstituted ring.[18] Additional tests gave evidence that **1** undergoes rearrangements under certain conditions ($AlCl_3$/HCl), as opposed to **4**, which is inert.[18] Attempts at acylating or brominating **4** also failed.[18] Experiments investigating hydrogen/deuterium exchange ($DCl/AlCl_3$) in **4** showed that only occasionally were all the hydrogen atoms exchanged for deuterium.[18] So it is clear that the presence of fluorine atoms in one of the rings of **1** affects the reactivity of the nonfluorinated ring.

We have already reported a computational study of the isomers of [2.2]cyclophanes, **1**−**3**, published in two different papers (Figure 1a).[19,20] In the first one[19] the changes in geometries, energetics, aromaticity, and NMR chemical shifts were analyzed, and the second one[20] presented a study about the electronic structure of these compounds by NBO (natural bond orbital) and AIM (atoms in molecules) methods. Apart from these studies there are few reports in literature about [2,2]cyclophanes. Grimme studied the para isomer, **1**, verified that the spin-component-scaled (SCS) MP2 method reproduces very well the experimental geometry, and concluded that the intraring interactions can be classified as overlap-dispersive ones.[21] Recently, Peloni, Lazzeretti and Zanasi built a spatial ring current model for **1** and concluded that ring models in a plane or a local single variable, as a local shielding value, are unable to represent the magnetropicity of a complex molecule, like **1**.[22] By comparing the ring current model, that is, the stagnation graph of **1** from that of the stacked dimer of benzene, it is possible to conclude that the presence of aliphatic bridges in **1** induces several changes in the magnetic behavior of the benzene dimer, as the reduction of the diatropicity. As part of our ongoing studies on this class of compounds, the purpose of the present work is to describe a computational study of the tetrafluorinated derivatives of [2.2]cyclophanes: F_4-[2.2]paracyclophane (**4**), F_4-anti-[2.2]meta-cyclophane (**5a**), F_4-sin-[2.2]metacyclophane (**5b**), and F_4-[2.2]metaparacyclophane (**6a** and **6b**). (Figure 1b). We have investigated not only the effects of fluorination on such properties as relative stabilities, the local and global aromaticity, and ring and bridge strains, but also the mechanisms of transannular interactions (through-bond or through-space) within the fluorinated isomers of [2.2] cyclophanes, **4**−**6b**.

2. Computational Methods

The geometries of the F_4-[2.2] cyclophane isomers were optimized and the vibrational frequencies were calculated using the B3PW91[23]/6-31+G(d,p)[24] model. Some molecules were optimized by MP2[25] method with the same basis set, to verify the reliability of the B3PW91 functional. The structures optimized by both models were superimposed by Vega ZZ 2.2.0 software.[26] The energies were corrected with spin-component scaled MP2[27] (SCS-MP2) and scaled opposite-spin MP2 (SOS-MP2).[28] All studied molecules are minima in the potential-energy surface. This model was employed in all calculations, except for the AIM analysis, for which the MP2/6-31+G(d.p) model was used. Local aromaticity was analyzed using the NICS[29] and HOMA[30] criteria. Global aromaticity was analyzed by the changes in the magnetic susceptibility. The strain on the aliphatic bridges and benzene rings was determined by means of isodesmic reactions.[31,32] The chemical shifts and the NICS aromaticity criterion were calculated using the GIAO method,[33] and magnetic susceptibilities were calculated by CSGT.[34] The NPA charges[35] were determined and compared with the AIM charges, obtained through integration over the atomic basins.[36] All these calculations were carried out using the Gaussian 98 program.[37] The electronic structure was investigated by means of the NBO,[38] NSA,[39] and AIM methods.[36] The frontier orbitals were also analyzed, to evaluate the occurrence of transannular interactions. The resonance structures of all the tetrafluorinated isomers were investigated by the NRT method.[40] The NBO, NSA, and NRT analyses were carried out using the NBO 5.0 program.[41] The Morphy98[42] and AIM2000[43] programs were used for the AIM analyses. The molecular orbitals were visualized using the Molekel 4.3 program.[44] The NBOs and the NLMOs were visualized by means of the NBOView 1.0 program.[45]

3. Results and Discussion

3.1. Geometries. The geometric parameters for F_4-[2.2]paracyclophane, (**4**), show that the C−C bond lengths of the fluorinated ring decrease compared to the bond lengths of the nonsubstituted ring in this same molecule. This indicates that there is a small increase in the *p* character of the C−C bonds of the substituted rings (Table S1, Support Information). The average length of the C−C bonds of the rings of the corresponding nonsubstituted isomer **1** is 1.46 Å,[19] whereas the C−C bond lengths of the fluorinated ring of **4** is 1.40 Å. The inter-ring distances C(2)−C(9) and C(1)−C(14) are smaller than those calculated for **1**. This indicates that the fluorination decreases the distance between rings. The same behavior was observed for the stacked interaction between benzene and fluorobenzene,[46a,b] or between benzene and hexafluorobenzene.[46c] The progressive substitution decreases the intermonomer distance and the increases the interaction energy.[46b] On the other hand, the bond lengths of the ethano bridges and the bond angles of the fluorinated and nonfluorinated rings of **4** are slightly different from those of **1**.[19] It is noteworthy that the dihedral angles of the ethano bridges in **4** are smaller than those of **1**, 8.7° and 6.4°, respectively. This decrease in the dihedral angle suggests that there is a smaller repulsion between the aromatic regions of the fluorinated isomer **4** compared to the corresponding nonsubstituted cyclophane, which characterizes the typical electron withdrawing effect of the fluorine atoms.

TABLE 1: Relative Energies, Δ*E* (kcal.mol^{-1}) of the [2.2]cyclophanes 1−3 and 4−6b for B3PW91, MP2, SCS-MP2, and SOS-MP2 Methods

isomers	B3PW91	MP2	SCS-MP2	SOS-MP2
4	15.31	11.47	12.15	12.49
5a	0.00	0.00	0.00	0.00
5b	8.83	8.20	8.15	8.12
6a	8.26	4.45	4.99	5.26
6b	9.38	5.50	6.13	6.44
1	20.58	16.34	15.64	16.12
2a	0.00	0.00	0.00	0.00
2b	11.20	10.60	11.25	11.14
3	9.69	5.89	7.16	7.46

Asfor isomer **5a**, there are no significant variations in the bond lengths of the fluorinated ring compared to the bond lengths of the nonsubstituted ring or with regard to the bond lengths of the corresponding nonsubstituted cyclophane,[19] **2a** (Table S2, Supporting Information). Still concerning isomer **5a**, there are no significant changes in the inter-ring distances, C−C bond lengths of the ethano bridges, or bond lengths compared with isomer **2a**.[19] However, the dihedral angles of the ethano bridges of **5a** are slightly larger compared to the same angles in **2a**, 59.5° and 57.2°, respectively. Therefore, fluorination affects the geometry of **5a** to a lesser extent compared to the changes in the geometry of **4**.

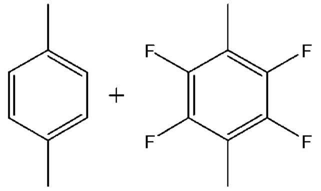
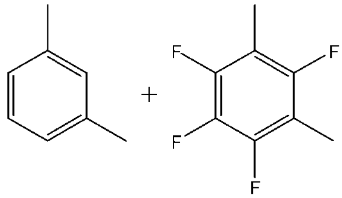
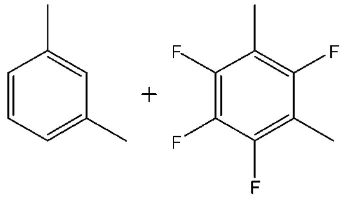
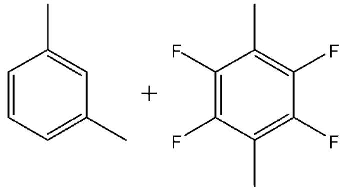
The C−C bond lengths of the aromatic rings of the fluorinated isomer **5b** are very similar to those of the corresponding nonsubstituted isomer **2b**: 1.4 Å (Table S3, Supporting Information). Similarly, substitution does not change the inter-ring distances, bridge lengths, or bond angles of **5b** compared to **2b**. As for the dihedral angles of the ethano bridges, a decrease in the angle of **5b** (20.0°) compared to **2b** (30.7°) is observed, which suggests that there is a reduction in the inter-ring repulsion. In the cases of **5b** and **2b**, it is possible to correlate the inter-ring repulsion with the dihedral angle of the bridges because the aromatic rings are in a syn-periplanar position (approximately superposed). Therefore, any variation in the electron density of the rings as a function of fluorination that affects the inter-ring electronic repulsion may be correlated with changes in the dihedral angles of the ethano bridges.

As for the fluorinated isomers **6a** and **6b**, there are no variations in their geometric parameters compared to the nonsubstituted analogue[19] **3** (Tables S4 and S5, Supporting Information). For the T-shaped conformation of benzene and fuorobenzenes that resembles the conformations of the rings in **6**, it was observed that the optimum distance between the monomers is constant.[46b,d] According to our results, the molecular structure of **1** is affected the most by the perfluorination of one of the aromatic rings. This can be attributed to the shorter distance between the aromatic rings within this compound.

Compounds **4** and **6a** were optimized by MP2/6-31+G(d,p) model, in order to verify the reliability of the B3PW91/6-31+G(d,p) model to describe the strong $\pi-\pi$ interactions between the aromatic rings. The superimposition of equivalent carbons of both molecules presents very small deviations, as indicated by the small rms, 0.098 for **4** and 0.072 for **6a**. For compound **4** the main differences observed between B3PW91 and MP2 geometries are the inter-ring distances, which decrease by 0.04 and 0.07 Å, and in the dihedral angle of the ethano bridges that increases by 13.8°. These changes are similar to those observed for **1** in one of our works[19] and also by Grimme.[21] A decrease of inter-ring distances and bridge bond angles was observed for **6a** as going from DFT to MP2, but in contrast to **4**, no changes were observed in the dihedral angles.

3.2. Energies. According to the results shown in Tables 1, S6 and S7, the stability order for the fluorinated isomers, **4−6b**,

TABLE 2: Isodesmic Reactions of F$_4$[2.2]cyclophanes

Isodesmic Reactions			SE(IR) (kcal/mol)	ΔSE(IR) (kcal/mol)
(**4**) + 4 CH_4 →		+ 2 C_2H_6	-26.40	-15.57
(**5a**) + 4 CH_4 →		+ 2 C_2H_6	-10.83	0.00
(**5b**) + 4 CH_4 →		+ 2 C_2H_6	-19.66	-8.83
(**6a**) + 4 CH_4 →		+ 2 C_2H_6	-19.42	-8.59

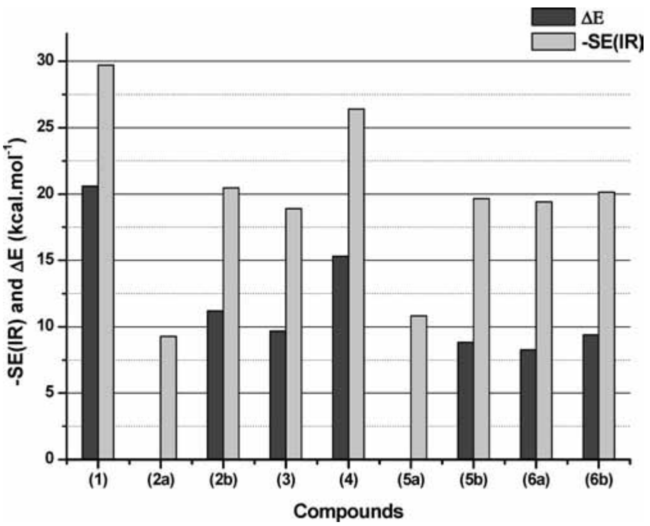


Figure 2. SE(IR) for the [2.2]cyclophanes (**1**−**3**) and the F_4[2.2]cyclophanes (**4**−**6b**) isomers.

is similar to that of the nonsubstituted ones **1**−**3**,[19] for all methods. In both cases, the most stable isomer is the one with the aromatic rings oriented in an antiperiplanar way (**5a** and **2a**). However, the least stable isomer is always the one with the ethano bridges bound in the para position, which poses higher tension to the molecule and leads to a larger repulsion between the π clouds of the aromatic rings, independent of the substitution. In this context, **4** and **1** are the most strained isomers, so they have the lowest relative stability. The stability order of **5b**, **6a**, and **6b** are slightly different compared to the stability order of the nonsubstituted isomers **2b** and **3**. As already reported, the relative energies of **3** and **2b** at B3PW91 level are closed, with **3** being more stable than **2b**. On the other hand, **3** and **2b** present a large stability energy difference at the MP2 level. On the other hand, B3PW91 results show that **5b** is more stable than **6b**, whereas **6a** is more stable than **5b** and **6b**, but for MP2 and its corrections, there is an inversion in the stability of **5b** and **6b**, because **6a** and **6b** are largely stabilized by these methods. As for the nonsubstituted isomers, **2b** is less stable than the isomer containing rings bound in the meta−para positions, **3**. This order is maintained after the perfluorination of one ring by the MP2 methods, in contrast with B3PW91, indicating that the ring interactions and the bridge tensions are the main factor in the determination of stability of [2,2]paracyclophanes, and they do not change significantly with perfluorination. A comparison of the relative energies of the fluorinated compounds with those of the nonfluorinated ones indicates that fluorination stabilizes **4**, **5b**, **6a**, and **6b** with respect to **5a**, and this stabilization occurs via a decrease in the electron density of the substituted ring due to the electron withdrawing effect of the fluorine atoms. For some isomers such as **1**, **3**, **4**, **6a**, and **6b**, but not **2b** and **5b**, MP2 methods give a larger stabilization in relative energies than B3PW91. This indicates that the MP2 stabilization is not only due to the change in the description of $\pi-\pi$ interaction, but also because **6b** and **2b** present a stacked geometry. It is possible to conclude that the qualitative order of relative energies is quite similar for B3PW91 and MP2, SCS-MP2, or SOS-MP2.

For the nonsubstituted cyclophanes, **1**−**3**, the stability order can be partially understood by considering the relative energies of the benzene dimers. Several calculations indicate that the parallel displaced (PD) and the T-shaped (T) conformations are almost isoenergetic, while the sandwich (S) geometry is a saddle point.[46a,47a−c] Two recent benchmark calculations indicate that T is marginally more stable than PD, and the stability order is: T ≥ PD > S, and S is ≈ 1.0 kcal/mol more unstable than T, in accordance with other studies.[47a,46a] Podeszwa, Bukowski, and Szalewicz explored the potential energy surface by using the SAPT(DFT) method.[47b] From the various minima (Mn) or saddle points (Sn), it is possible to classify the arrangement of the rings in **2a** as corresponding to M1, or PD in the most common nomenclature; **3** corresponds to M2, or T; **2b** to saddle point, S4; and **1** to S8. Except for the inversion of M1 and M2, the stability order, M2 ≥ M1 ≥ S4 > S8, is similar to that observed for [2.2]cyclophanes; M1, M2, and S4 are nearly isoenergetic. Similar results were obtained by Lee et al.[46a] indicating that the interaction between the aromatic rings are partially responsible for the observed stability of **1**−**3**. The large energy range spanned by [2.2]cyclophanes, compared to benzene dimers, can be associated to the strain of the bridges.

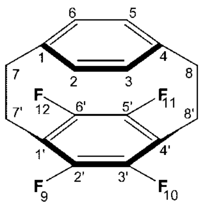
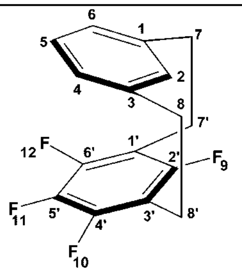
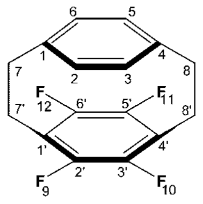
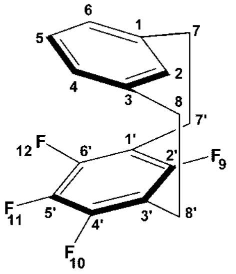
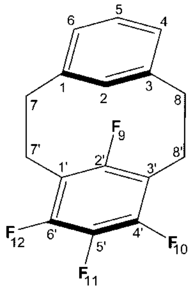
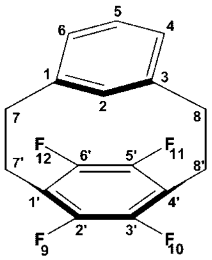
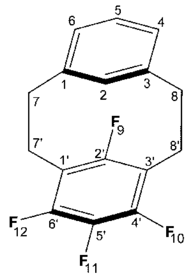
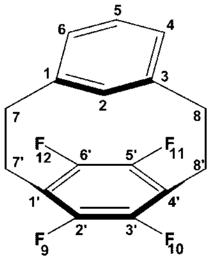
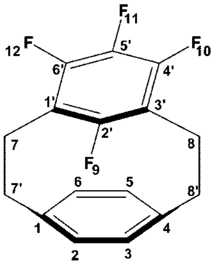
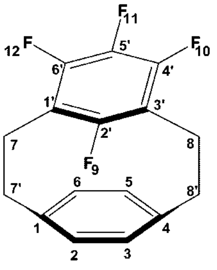
The analysis of the energetic changes in the benzene−fluorobenzene dimers can help to understand the results presented in Table 1. The monofluorination stabilizes the S, T, and PD conformers, but S is much more stabilized than T.[46a,47c,48] The gradual increase of the fluorination of one monomer leads to a stabilization of the S conformer, and this effect is addictive.[46b] In contrast, T is destabilized by progressive fluorination, with a nonlinear variation.[46b,d] The benzene−hexafluorobenzene PD heterodimer is much more stable than T, in contrast with the benzene homodimer, in which PD and T have nearly equal energies.[49] The same behavior was observed for the cyclophanes. The perfluorination stabilizes the S and PD, but destabilizes both T dimers.[49,46c] It is in contrast with the stability of cyclophanes, indicating that the interaction of aromatic dimers can partially explain the energetic order of cyclophanes and that the bridges provide an important contribution to the energetic stability of these systems.

3.3. Isodesmic Reactions. The effects of fluorination on the energy of the ethano bridges cleavage were determined by isodesmic reactions with the B3PW91/6-31+G(d,p) model (Table 2).[31] These reactions indicate that the order of the strain

TABLE 3: Strain Energies and Component Partitioning (kcal·mol^{-1})

			anti				eclipsed			
compd	SE(IR)	SE(bb)	SE(br-a)	SE(rep-a)	SE(sum-a)	SE(bb)/SE(sum-a)	SE(br-e)	SE(rep-e)	SE(sum-e)	SE(bb)/SE(sum-e)
1	29.72	17.85	25.90	14.03	43.75	0.408	14.54	2.67	32.39	0.551
2a	9.27	5.88	16.74	13.35	22.62	0.260	5.26	1.87	11.14	0.528
2b	20.46	6.40	21.05	7.00	27.45	0.233	9.56	−4.50	15.96	0.401
3	18.90	9.83	20.53	11.46	30.36	0.323	9.05	−0.02	18.88	0.521
4	26.40	15.89	22.05	11.54	37.94	0.419	10.57	0.06	26.46	0.601
5a	10.83	8.32	16.48	13.97	24.80	0.335	5.00	2.49	13.32	0.624
5b	19.66	9.37	22.62	12.33	31.99	0.293	11.14	0.85	20.51	0.456
6a	19.42	10.96	21.41	12.95	32.37	0.339	9.93	1.47	20.89	0.524
6b	20.14	12.27	22.13	14.26	34.40	0.356	10.65	2.78	22.92	0.535

TABLE 4: NRT Analysis for the Isomers 4−6b Showing the Weight of the RS, W_α (%), and Degenerescences (deg)

Comp.	*Structure α*	*deg*	*W_α (%)*	*Comp.*	*Structure α*	*deg*	*W_α (%)*
4	 **4A**	2	27.67	**5b**	 **5B**	2	19.40
	 **4A'**	2	8.20		 **5B'**	2	19.39
5a	 **5A**	2	19.28	**6a**	 **6A**	2	29.82
	 **5A'**	2	19.23		 **6A'**	2	7.62
6b	 **6B**	1	35.73		 **6B'**	1	34.55

energies over the ethano bridges, SE(IR), is the same for both the fluorinated and nonsubstituted cyclophanes. Isomer **4** is the most strained, isomer **5a** is the least strained, and isomers **5b**, **6a**, and **6b** have intermediate strain energies. A comparison between the SE(IR) and Δ*E* values of **4** and **1** shows that the presence of the fluorine atoms in one of the aromatic rings of **4** leads to a decrease in both SE(IR) and Δ*E* (Figure 2). As for the other fluorinated isomers, the Δ*E* values decrease more sharply than SE(IR), compared to the nonsubstituted cyclophanes. It is noteworthy that the SE(IR) values relative to the isodesmic reaction of **5a** are similar to the Δ*E* ones, which suggests that both energies are affected by the same destabilizing effects, especially the repulsion between the aromatic rings. However, one has to bear in mind that the strain of the ethano bridges is also important in this case.

The results from the isodesmic reactions show the same inversion in the relative energy order as the one observed for the relative energies of **5b**, **6a**, and **6b**, being **5b** slightly more

TABLE 5: Second-Order Stabilization Energies, $\Delta E^{(2)}$, for the Main Resonance Structures of the Fluorinated [2.2]Cyclophanes[a]

	$\Delta E^{(2)}$ (kcal/mol)									
interactions	**4A**	**4A′**	**5A**	**5A′**	**5B**	**5B′**	**6A**	**6A′**	**6B**	**6B′**
$\pi_{C(1)-C(2)} \rightarrow \pi^*_{C(1')-C(2')}$	-	-	-	-	-	-	-	-	**0.54**	-
$\pi_{C(1')-C(2')} \rightarrow \pi^*_{C(1)-C(6)}$	-	**1.11**	-	-	-	**0.80**	-	-	-	**0.76**
$\pi_{C(1')-C(2')} \rightarrow \pi^*_{C(2)-C(3)}$	-	-	-	**2.40**	-	**1.84**	-	-	-	-
$\pi_{C(1)-C(2)} \rightarrow \pi^*_{C(3)-C(4)}$	-	-	-	-	-	-	19.43	21.28	22.53	-
$\pi_{C(1)-C(2)} \rightarrow \pi^*_{C(5)-C(6)}$	-	-	-	-	-	-	21.28	19.44	19.04	-
$\pi_{C(1)-C(2)} \rightarrow \sigma^*_{C(7)-C(7')}$	-	-	-	-	-	-	*3.95*	*3.94*	*3.83*	-
$\pi_{C(1')-C(2')} \rightarrow \sigma^*_{C(7)-C(7')}$	-	*3.66*	-	*3.34*	-	*3.71*	*3.30*	-	*3.61*	*3.61*
$\pi_{C(1)-C(6)} \rightarrow \pi^*_{C(1')-C(2')}$	-	**1.12**	-	-	-	**0.57**	-	-	-	-
$\pi_{C(1)-C(6)} \rightarrow \pi^*_{C(5')-C(6')}$	-	**0.65**	-	-	-	-	-	-	-	-
$\pi_{C(1')-C(6')} \rightarrow \pi^*_{C(1)-C(6)}$	-	-	-	-	**0.54**	-	-	-	-	-
$\pi_{C(1)-C(6)} \rightarrow \pi^*_{C(2)-C(3)}$	19.21	19.12	18.99	18.87	19.04	18.94	-	-	-	18.35
$\pi_{C(1)-C(6)} \rightarrow \pi^*_{C(4)-C(5)}$	21.66	21.10	21.23	21.16	21.13	21.05	-	-	-	21.13
$\pi_{C(1)-C(6)} \rightarrow \sigma^*_{C(7)-C(7')}$	*4.10*	*4.10*	*3.32*	*3.34*	*3.28*	*3.29*	-	-	-	*3.10*
$\pi_{C(1')-C(6')} \rightarrow \sigma^*_{C(7)-C(7')}$	*3.77*	-	*3.00*	-	*3.36*	-	-	*2.67*	-	-
$\pi_{C(2)-C(3)} \rightarrow \pi^*_{C(1')-C(2')}$	-	**0.56**	-	**2.23**	-	**1.73**	-	-	-	-
$\pi_{C(2)-C(3)} \rightarrow \pi^*_{C(2')-C(3')}$	-	-	**1.36**	-	-	-	-	-	-	-
$\pi_{C(2')-C(3')} \rightarrow \pi^*_{C(2)-C(3)}$	-	-	**1.53**	-	-	-	-	-	-	-
$\pi_{C(2)-C(3)} \rightarrow \pi^*_{C(3')-C(4')}$	-	**0.58**	-	-	-	**1.02**	-	-	-	-
$\pi_{C(2)-C3)} \rightarrow \sigma^*_{C(8)-C8')}$	-	-	*3.47*	*3.48*	*4.15*	*4.14*	-	-	-	-
$\pi_{C(3)-C(4)} \rightarrow \pi^*_{C(2')-C(3')}$	-	-	-	-	-	-	-	**0.55**	-	-
$\pi_{C\ (3')-C(4')} \rightarrow \pi^*_{C(2)-C(3)}$	-	-	-	-	-	**0.57**	-	-	-	**0.67**
$\pi_{C(3)-C(4)} \rightarrow \pi^*_{C(3')-C(4')}$	-	-	-	-	-	-	-	-	**1.06**	-
$\pi_{C\ (3')-C(4')} \rightarrow \pi^*_{C(3)-C(4)}$	-	-	-	-	-	-	**1.09**	-	-	-
$\pi_{C(3')-C(4')} \rightarrow \pi^*_{C(4)-C(5)}$	-	**1.06**	-	-	-	-	-	-	-	-
$\pi_{C(4)-C(5)} \rightarrow \pi^*_{C(1')-C(2')}$	-	-	-	-	-	-	-	-	-	**0.72**
$\pi_{C(4)-C(5)} \rightarrow \pi^*_{C(3')-C(4')}$	-	**1.09**	-	-	-	-	-	-	-	**0.82**
$\pi_{C(4)-C(5)} \rightarrow \sigma^*_{C(8)-C(8')}$	*4.25*	*4.25*	-	-	-	-	-	-	-	*3.10*
$\pi_{C(5)-C(6)} \rightarrow \pi^*_{C(1')-C(2')}$	-	-	-	-	-	-	-	-	**0.65**	-
$\sigma_{C(7)-C(7')} \rightarrow \pi^*_{C(1')-C(2')}$	-	*3.93*	-	*4.13*	-	*3.85*	*5.19*	-	*3.59*	*3.59*
$\sigma_{C(7)-C(7')} \rightarrow \pi^*_{C(1)-C(2)}$	-	-	-	-	-	-	*3.12*	*3.16*	*4.57*	-
$\sigma_{C(7)-C(7')} \rightarrow \pi^*_{C(1')-C(6')}$	*4.07*	-	*4.38*	-	*3.92*	-	-	*4.48*	-	-
$\sigma_{C(7)-C(7')} \rightarrow \pi^*_{C(1)-C(6)}$	*3.53*	*3.52*	*3.79*	*3.69*	*2.61*	*2.55*	-	-	-	*4.09*
$n_{F(9)p\pi} \rightarrow \pi^*_{C(1')-C(2')}$	-	18.42	-	19.84	-	18.31	18.86	-	18.83	18.85
$n_{F(9)p\pi} \rightarrow \pi^*_{C(2')-C(3')}$	18.57	-	19.81	-	18.05	-	-	18.85	-	-
$n_{F(11)p\pi} \rightarrow \pi^*_{C(4')-C(5')}$	18.42	-	18.92	-	18.86	-	-	18.40	-	-
$n_{F(11)p\pi} \rightarrow \pi^*_{C(5')-C(6')}$	-	18.58	-	18.92	-	18.95	18.45	-	18.80	18.80
$n_{F(11)p\pi'} \rightarrow \sigma^*_{C(5')-C(6')}$	7.39	7.39	7.69	7.69	7.63	7.63	7.35	7.35	7.62	7.62

[a] Through-space and through-bond interactions are depicted in bold and in italics, respectively.

stable than **6b** (Figure 2). Generally, the isodesmic reactions demonstrate that the fluorine atoms significantly affect the energy of the ethano bridges cleavage in the case of compounds **4**−**6b**, causing a reduction in the absolute values of the relative energies of these isomers, even though the stability order is analogous to that of the nonsubstituted isomers **1**−**3**.

To separate the deformations in the bond lengths from the nonbonded interactions affecting the strain energies in the frontal approximation, a partitioned treatment of the strain energies was applied,[32] using a the same procedure employed for the nonsubstituted isomers.[19] The SE(bb) values for **4** are slightly lower than the respective values obtained for **1** (Table 3). As for **5a**−**6b**, they have higher SE(bb) values. Although the geometric parameters do not give evidence of significant changes in the geometry as a function of the substitution, the SE(bb) values show that the aromatic rings become more strained upon substitution.

The SE(br) values obtained for the fluorinated derivatives are relatively high, if the anti conformation (*a*) of *n*-butane is considered. The SE(br-a) values of the fluorinated compounds are very close to those of the nonsubstituted isomers. However, the SE(br-e) values are twice or three times lower than those of SE(br-a), if we consider the eclipsed conformation of *n*-butane. Furthermore, the SE(br-e) values of the fluorinated and the nonsubstituted isomers are very similar, with a decrease for **4** compared to **1** and an increase for the others. As for the terms involving the repulsion between rings and bridges (SE-rep), **4** and **6b** have the lowest and highest SE(rep-a) values, respectively. The same is observed in the case of the SE(rep-e) values; that is, the bridge-ring repulsion is more intense in the case of **6b**. However, the opposite trend is observed for the nonsubstituted isomers: **1** is the isomer with the highest SE(rep-a) and SE(rep-e) values. As for the SE(bb)/SE(sum) values, the rings of isomer **4** are the most strained ones when the conformer (*a*) of butane is considered. Nevertheless, when the eclipsed conformer (*e*) is considered, the most strained rings are those of isomer **5a**. In general terms, the aromatic rings of the fluorinated isomers are more strained than those of the non-substituted cyclophanes, as can be seen from the SE(bb)/SE(sum-a) and SE(bb)/SE(sum-e) values. This is in contrast with the conclusion obtained from the comparison between the ΔE and ΔS E(IR) values (Tables 1 and 2).

3.4. Chemical Shifts. The calculated chemical shifts are in good agreement with the experimental values.[50,51] Comparisons were carried out for isomers **4** and **6a** only, because of the data found in the literature. As in the case of the nonsubstituted isomers,[19] tetramethylsilane (TMS) was used as the internal standard in the calculations. The numbering adopted herein is the same as that employed for the geometry description (Support information).

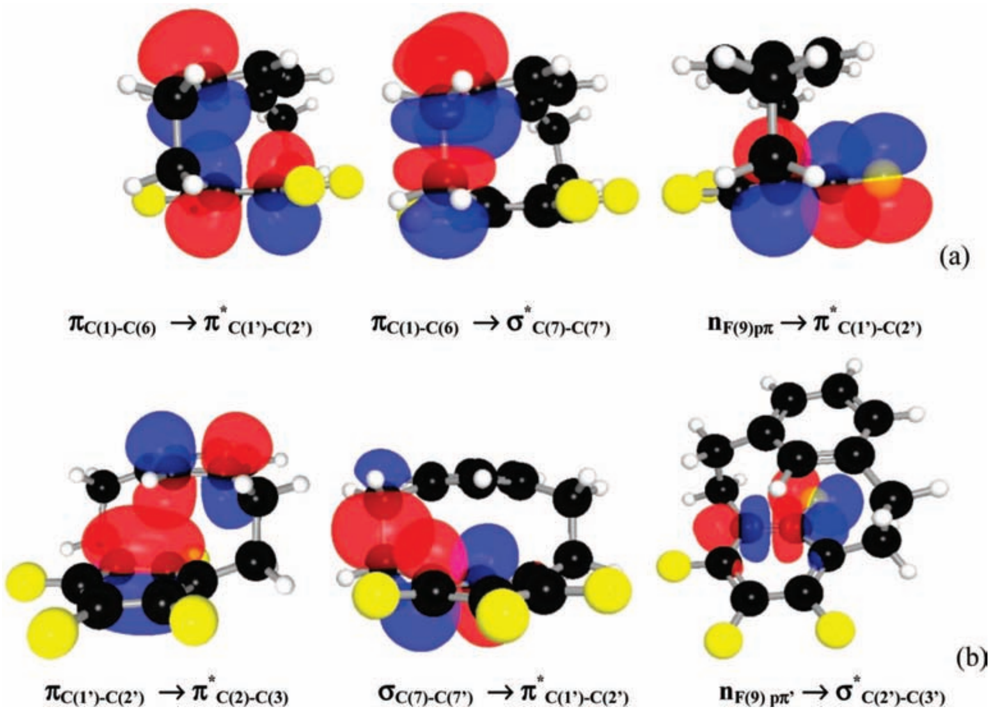


Figure 3. Through-space and through-bond interactions, and interactions involving the fluorine lone pairs in the case of the RS **4A′** (a) and **5A′** (b).

Comparing the chemical shifts of the hydrogens located in the aromatic ring of the fluorinated isomer **4** with those of the nonsubstituted isomer **1**, the chemical shifts of H(25), H(26), H(27), and H(28) (Table S8) in the former are around 7.2 ppm, while in the latter the same hydrogens have chemical shifts of 6.8 ppm. This indicates that the fluorine atoms decrease the deshielding of the aromatic protons, thus suggesting the presence of a transannular transfer of π electrons from ring I to the perfluorinated ring II. This effect shows that the electron density of the whole molecule is affected by the substitution. On the other hand, the chemical shifts of the hydrogens on the ethano bridges of **4** are not significantly different from those of **1**. As for the chemical shift of the carbon atoms (Table S9), the chemical shifts of the carbons in the ethano bridge of **4** are different depending on their location, while all the carbons in the bridge of **1** have a chemical shift of 39.3 ppm. The chemical shift of the ethano bridge carbons bonded to the fluorinated ring of **4** is 25.6 ppm, while the chemical shift of the ethano carbons bonded to the nonsubstituted ring is 37.1 ppm; that is, both carbons are more shielded compared to the shifts of the corresponding carbons in **1**. The shielding is more effective in the case of the carbons bonded to ring II because of the hyperconjugation of the bridge CH_2. Moreover, the chemical shifts of the carbons in ring II of molecule **4** (145 ppm) are always higher than those of **1** (129−138 ppm), which is also attributed to the high electronegativity of the fluorine atoms. On the other hand, the carbons of ring II that are bonded to the bridge also have lower chemical shifts (118.3 ppm), which is also explained by the hyperconjugation of the CH_2 groups.

The chemical shifts of the hydrogens in the fluorinated isomer **5a** are not significantly different from the chemical shifts of the hydrogens in the nonsubstituted **2a**. Only H(30), which is in the same direction as the substituted ring, is more deshielded (4.6 ppm) than the corresponding hydrogen in compound **2a** (4.3 ppm). This must be due to the effects of the fluorine atoms on the anisotropy of the fluorinated ring. Similarly, the carbons bonded to the halogens are more deshielded than the others, so their chemical shifts are higher, as observed in the case of **4**. As for the other carbons, the same differences between **4** and **1** are also observed in the case of **5a** and **2a**. However, the hydrogens lying in the same direction as the substituted ring in **5b**, H(17), H(18), and H(19), are more shielded than the hydrogens H(27), H(28), and H(29) in **5a**. The remaining hydrogen atoms of **5b** and **5a** have slightly different chemical shifts. The observed differences may be attributed not only to the substitution, but also to the differences in the disposition of the aromatic rings, which leads to changes in the diamagnetic anisotropy. On the other hand, the ethano carbon atoms bonded to the fluorinated ring are more shielded, due to the hyperconjugation of the bridges with the rings. Comparing the remaining carbon atoms of **5a** and **5b**, there were only slight variations between their chemical shifts.

Analysis of the shifts of the atoms of the fluorinated isomer **6a** shows there is a considerable variation in the chemical shift of the hydrogen directed toward the fluorinated ring, H(22), whose chemical shift is 6.3 ppm, while the chemical shift of the corresponding atom in the nonsubstituted isomer **3** is 5.7 ppm. The ethano carbons directly bonded to the fluorinated ring, C(8) and C(15), are more shielded, $\delta = 29.4-29.0$ ppm, whereas the ethano carbons bonded to the nonsubstituted ring are less shielded, $\delta = 36.2-36.6$ ppm. However, the corresponding carbons in **3** are less shielded ($\delta = 40.0$ ppm). With respect to the carbons bonded directly to the fluorine atoms, C(10) and C(11) are more shielded than C(13) and C(14). This difference may be attributed to their spatial disposition, which causes them to be more affected by the anisotropies of the nonsubstituted ring. The behavior of the chemical shifts in the case of isomer **6b** is very similar to the one observed for **6a**.

3.5. Attractive Interactions between the NBOs. Natural bond orbital analysis, NBO, was applied to the main resonance structures, RS, of the F_4[2.2]cyclophane isomers, **4A−6B′** (Table 4).

Table 5 presents the values of through-space (in bold) and through-bond (in italics) interactions. For all the RS, **4A−6B′**, the most stabilizing interactions are those taking place between the neighboring π orbitals of a given ring, such as the $\pi_{C(1)C(6)} \rightarrow \pi^*_{C(4)C(5)}$ and $\pi_{C(1)C(2)} \rightarrow \pi^*_{C(5)C(6)}$ interactions, whose stabilization energies are around 20 kcal·mol^{-1}. These interactions give an indication of the resonance of the benzene rings. Another important group of interactions is the one involving the π orbitals of the aromatic rings and the σ^* orbitals of the ethano bridges, or the σ orbitals of the ethano bridges and the π^* orbitals of the aromatic rings, which are part of the through-bond electron density transfer between the rings. The stabilization energies of these interactions lie between 2.5 and 5.2 kcal·mol^{-1}. It is noteworthy that the substitution does not affect the magnitude of the various interactions; that is, the values of the main interactions in **4** are very similar to those of the corresponding interactions in **1**. Furthermore, substitution by fluorine promotes the very intense stabilizing interactions, corresponding to the electron density donation from the lone pairs, p_π and $p_{\pi'}$, of the fluorine atoms to the σ^* and π^* orbitals of the C−C bonds in the ring. The most intense interactions occur between the fluorine lone pairs and the π^* orbitals, which are around 19.0 kcal·mol^{-1}, ($n_{F(11)\ p(\pi)} \rightarrow \pi^*_{C(4')C(5')}$; $n_{F(11)\ p(\pi)} \rightarrow \pi^*_{C(5')C(6')}$). As for the interactions involving the fluorine lone pairs and the σ^* orbitals, their values are around 6.4 or 7.7 kcal·mol^{-1} ($n_{F(11)p(\pi)} \rightarrow \sigma^*_{C(5')C(6')}$).

Despite these various interaction types, no through-space interactions were observed for the RS **4A**. Nevertheless, the RS **4A′** has many through-space interactions with magnitudes varying between 0.6 and 1.1 kcal·mol^{-1}. As for the other interactions, their values are very close to those of RS **4A**. In the case of **4**, results show that, compared to the other interactions, the through-space interactions contribute very little to the stabilization of the system, and they occur only in RS **4A′**. As for compound **5a**, the number of through-space interactions is smaller than in the case of **4**. However, these interactions are more intense and take place in the two RS, **5A** and **5A′**, with stabilization energies ranging from 1.4 to 2.4 kcal·mol^{-1}. Compared to **4**, the remaining interactions in **5a** do not vary. Compound **5b** also displays a reasonable number of through-space interactions, with magnitudes varying from 0.7 to 1.1 kcal·mol^{-1}, and they predominate in the RS **5B′**. Compound **6a** is the one with the smallest number of through-space interactions, only one for each RS. The through-space interactions do not occur in one specific direction for some resonance structures; that is, there may be interactions involving the π orbitals of the nonsubstituted ring and the π^* orbitals of the fluorinated ring, and vice-versa. For instance, the main through-space interactions in the RS **4A′**, **5B**, **6B**, and **6B′** involve the π orbitals of the nonsubstituted ring and the π^* orbitals of the fluorinated ring. As for the RS **6A** and **6A′**, there are interactions between the π and π^* orbitals of the fluorinated and the nonsubstituted rings, respectively. In the case of **5A** and **5A′**, these numbers are equivalent. In general, the NBO analysis revealed that the various stabilizing interactions are maintained despite the fluorination, and this substitution leads to a considerable increase in the number of *through-space* interactions, even though the stabilization energies are not large. Some of the most important stabilizing interactions of the F$_4$[2.2]cyclophane isomers are depicted in Figure 3.

TABLE 6: Second-Order Stabilization Energies, $\Delta E^{(2)}$ (kcal·mol^{-1}), Energy Difference between the Acceptor and Donor Orbitals, $\varepsilon_j - \varepsilon_i$, and Fock, $F(i,j)$, (hartree) Matrix Elements

interactions	ER	$\Delta E^{(2)}$	$\varepsilon(i) - \varepsilon(j)$	$F(i,j)$
$\pi_{C(1)-C(6)} \rightarrow \pi^*_{C(4)-C(5)}$	**4A**	21.66	0.28	0.069
	4A′	21.10	0.28	0.067
	5A	21.23	0.28	0.069
	5A′	21.16	0.28	0.069
	5B	21.13	0.28	0.069
	5B′	21.05	0.28	0.069
	6B′	21.13	0.28	0.069
$\pi_{C(1)-C(2)} \rightarrow \pi^*_{C(5)-C(6)}$	**6A**	21.28	0.28	0.069
	6A′	19.44	0.28	0.066
	6B	19.04	0.28	0.066
$\pi_{C(1)-C(6)} \rightarrow \pi^*_{C(1')\text{-}C(2')}$	**4A′**	1.12	0.25	0.015
$\pi_{C(2')\text{-}C(3')} \rightarrow \pi^*_{C(2)-C(3)}$	**5A**	1.53	0.32	0.020
$\pi_{C(1')\text{-}C(2')} \rightarrow \pi^*_{C(2)-C(3)}$	**5A′**	2.40	0.32	0.025
$\pi_{C(1')\text{-}C(6')} \rightarrow \pi^*_{C(1)-C(6)}$	**5B**	0.54	0.32	0.012
$\pi_{C(1')\text{-}C(2')} \rightarrow \pi^*_{C(2)-C(3)}$	**5B′**	1.84	0.32	0.022
$\pi_{C(3')\text{-}C(4')} \rightarrow \pi^*_{C(3)-C(4)}$	**6A**	1.09	0.32	0.017
$\pi_{C(3)-C(4)} \rightarrow \pi^*_{C(2')\text{-}C(3')}$	**6A′**	0.55	0.25	0.011
$\pi_{C(3)-C(4)} \rightarrow \pi^*_{C(3')\text{-}C(4')}$	**6B**	1.06	0.25	0.015
$\pi_{C(4)-C(5)} \rightarrow \pi^*_{C(3')\text{-}C(4')}$	**6B′**	0.82	0.25	0.013
$n_{F(11)p\pi} \rightarrow \sigma^*_{C(5')\text{-}C(6')}$	**4A**	7.39	0.96	0.075
	5A	7.69	0.95	0.076
	5B	7.63	0.96	0.076
	6A	7.35	0.95	0.075
	6B	7.62	0.96	0.076
$\pi_{C(1)-C(6)} \rightarrow \sigma^*_{C(7)\text{-}C(7')}$	**4A**	4.10	0.56	0.047
	4A′	4.10	0.56	0.047
	5A	3.32	0.58	0.043
	5A′	3.34	0.58	0.043
	5B	3.28	0.57	0.042
	5B′	3.29	0.57	0.042
	6B′	3.10	0.58	0.041
	6A	3.95	0.57	0.046
$\pi_{C(1)-C(2)} \rightarrow \sigma^*_{C(7)\text{-}C(7')}$	**6A′**	3.94	0.58	0.046
	6B	3.83	0.57	0.046
$n_{F(11)p(\pi)} \rightarrow \pi^*_{C(4')\text{-}C(5')}$	**4A**	18.42	0.43	0.088
	5A	18.92	0.42	0.088
	5B	18.86	0.42	0.088
	6A′	18.40	0.43	0.088
$n_{F(11)p\pi'} \rightarrow \pi^*_{C(5')\text{-}C(6')}$	**4A′**	18.58	0.43	0.089
	5A′	18.92	0.42	0.088
	5B′	18.95	0.42	0.088
	6A	18.45	0.43	0.087
	6B	18.80	0.42	0.088
	6B′	18.80	0.42	0.088

As in the case of [2.2]cyclophanes, the differences in the $\Delta E^{(2)}$ values of the F$_4$-[2.2]cyclophanes in the various interactions are mainly due to $F(i,j)$. According to Table 6, the interactions involving the π and π^* orbitals of the same aromatic ring have constant $\varepsilon(j) - \varepsilon(i)$ (0.28 hartree), and their $F(i,j)$ values range from 0.01 to 0.07 hartree, which indicates that the stabilization is proportional to the overlap between the orbitals. On the other hand, the through-space interactions have higher $\varepsilon(j) - \varepsilon(i)$ values (0.32 au) when $\varepsilon(j)$ belongs to the nonsubstituted ring and $\varepsilon(i)$ belongs to the fluorinated one. This large energy difference explains the smaller number of through-space interactions between the occupied orbitals belonging to the fluorinated rings and the unoccupied orbitals of the nonsubstituted rings. As for the other interactions shown in Table 6, the difference in the $\Delta E^{(2)}$ values are mainly due to the $F(i,j)$ term, which is proportional to the overlap integral, $S(i,j)$, according to the molecular orbital qualitative theories.[52]

3.6. Repulsive Interactions, NSA. The NSA analysis was applied to all the resonance structures **4A**−**6B′**. The main interactions are those taking place between the NLMOs of the same aromatic ring, $\pi_{C(1')\text{-}C(2')} \leftrightarrow \pi_{C(3')\text{-}C(4')}$ and $\pi_{C(2)-C(3)} \leftrightarrow \pi_{C(4)-C(5)}$, (Table 7), which occur in all the RS. Moreover, a large number of through-bond interactions involving the π orbitals of the rings and the σ orbitals of the bridges are also observed. The magnitude of these interactions varies from 1.0 to 10.0 kcal/mol, as for example, $\pi_{C(1)-C(2)} \leftrightarrow \sigma_{C(7)\text{-}C(7')}$, $\sigma_{C(8)\text{-}C(8')} \leftrightarrow$

TABLE 7: NSA Analysis for the Main RS of the F_4[2.2]cyclophane Isomers (kcal·mol^{-1})[a]

	dE(kcal/mol)									
NLMO(*i*) ⇔ NLMO(*j*)	4A	4A′	5A	5A′	5B	5B′	6A	6A′	6B	6B′
$\pi_{C(1)C(2)} \Leftrightarrow \pi_{C(1')C(2')}$	-	-	-	-	-	-	**4.50**	-	**5.02**	-
$\pi_{C(1)C(2)} \Leftrightarrow \pi_{C(1')C(6')}$	-	-	-	-	-	-	-	**4.29**	-	-
$\pi_{C(1')C(2')} \Leftrightarrow \pi_{C(1)C(6)}$	-	-	-	**0.84**	-	-	-	-	-	-
$\pi_{C(1')C(2')} \Leftrightarrow \pi_{C(2)C(3)}$	-	-	-	**5.20**	-	-	-	-	-	-
$\pi_{C(1)C(2)} \Leftrightarrow \pi_{C(2')C(3')}$	-	-	-	-	-	-	-	**3.14**	-	-
$\pi_{C(1)C(2)} \Leftrightarrow \pi_{C(3')C(4')}$	-	-	-	-	-	-	**2.11**	-	-	-
$\pi_{C(1)C(2)} \Leftrightarrow \pi_{C(4')C(5')}$	-	-	-	-	-	-	-	**2.00**	-	-
$\pi_{C(1')C(2')} \Leftrightarrow \pi_{C(3')C(4')}$	-	10.46	-	8.47	-	8.51	7.63	-	8.08	8.05
$\pi_{C(1)C(2)} \Leftrightarrow \sigma_{C(7)C(7')}$	-	-	-	-	-	-	*7.28*	*7.36*	*9.70*	-
$\pi_{C(1')C(2')} \Leftrightarrow \sigma_{C(7)C(7')}$	-	*8.40*	-	*8.95*	-	*8.87*	*9.49*	-	*8.12*	*8.05*
$\pi_{C(1)C(6)} \Leftrightarrow \pi_{C(1')C(2')}$	-	**3.59**	-	-	-	**2.56**	-	-	-	**3.33**
$\pi_{C(1)C(6)} \Leftrightarrow \pi_{C(1')C(6')}$	**6.25**	-	-	-	**2.66**	-	-	-	-	-
$\pi_{C(1')C(6')} \Leftrightarrow \pi_{C(2)C(3)}$	-	-	**1.31**	-	**1.63**	-	-	-	-	-
$\pi_{C(1)C(6)} \Leftrightarrow \sigma_{C(7)C(7')}$	*8.41*	*8.38*	*7.31*	*7.20*	*5.35*	*5.27*	-	-	-	*9.90*
$\pi_{C(1')C(6')} \Leftrightarrow \pi_{C(2')C(3')}$	7.47	-	8.46	-	7.94	-	-	7.06	-	-
$\pi_{C(1')C(6')} \Leftrightarrow \sigma_{C(7)C(7')}$	*8.42*	-	*8.72*	-	*8.75*	-	-	*9.95*	-	-
$\pi_{C(1')C(6')} \Leftrightarrow n_{F(12)\ p\pi}$	12.30	-	11.98	-	12.06	-	-	12.27	-	-
$\pi_{C(2)C(3)} \Leftrightarrow \pi_{C(1')C(2')}$	-	**3.63**	-	-	-	**6.79**	-	-	-	**4.28**
$\pi_{C(2)C(3)} \Leftrightarrow \pi_{C(2')C(3')}$	**6.02**	-	-	-	**8.77**	-	-	-	-	-
$\pi_{C(2')C(3')} \Leftrightarrow \pi_{C(2)C(3)}$	-	-	**5.84**	-	-	-	-	-	-	-
$\pi_{C(2)C(3)} \Leftrightarrow \pi_{C(3')C(4')}$	-	**3.29**	-	**1.60**	-	**3.32**	-	-	-	**2.36**
$\pi_{C(2)C(3)} \Leftrightarrow \pi_{C(4)C(5)}$	10.57	10.58	9.21	9.18	9.09	9.08	-	-	-	9.81
$\pi_{C(2')C(3')} \Leftrightarrow n_{F(9)\ p\pi}$	12.71	-	11.27	-	11.69	-	-	12.91	-	-
$\pi_{C(3)C(4)} \Leftrightarrow \pi_{C(2')C(3')}$	-	-	-	-	-	-	-	**1.18**	-	-
$\pi_{C(3)C(4)} \Leftrightarrow \pi_{C(3')C(4')}$	-	-	-	-	-	-	**2.94**	-	**4.36**	-
$\pi_{C(3)C(4)} \Leftrightarrow \pi_{C(4')C(5')}$	-	-	-	-	-	-	-	**1.97**	-	-
$\pi_{C(4)C(5)} \Leftrightarrow \pi_{C(1)C(6)}$	7.68	7.58	8.39	8.36	8.34	8.30	-	-	-	8.20
$\pi_{C(4)C(5)} \Leftrightarrow \sigma_{C(8)C(8')}$	*7.79*	*7.76*	*1.41*	*1.41*	*1.43*	*1.44*	-	-	-	*9.96*
$\pi_{C(4)C(5)} \Leftrightarrow \pi_{C(3')C(4')}$	-	**3.11**	-	-	-	**0.53**	-	-	-	**2.33**
$\pi_{C(4)C(5)} \Leftrightarrow \pi_{C(4')C(5')}$	**6.31**	-	-	-	-	-	-	-	-	-
$\pi_{C(4)C(5)} \Leftrightarrow \pi_{C(5')C(6')}$	-	**3.48**	-	-	-	-	-	-	-	-
$\pi_{C(4')C(5')} \Leftrightarrow \pi_{C(1')C(6')}$	10.55	-	8.17	-	7.94	-	-	-	-	-
$\pi_{C(4')C(5')} \Leftrightarrow \sigma_{C(8)C(8')}$	*8.53*	-	*0.55*	-	-	-	-	*9.99*	-	-
$\pi_{C(3')C(4')} \Leftrightarrow n_{F(10)\ p\pi}$	-	12.30	-	11.94	-	12.09	12.85	-	12.16	12.23
$\pi_{C(4')C(5')} \Leftrightarrow n_{F(11)\ p\pi}$	12.27	-	14.70	-	14.55	-	-	12.29	-	-
$\pi_{C(5')C(6')} \Leftrightarrow n_{F(11)\ p\pi}$	-	13.10	-	14.71	-	14.57	12.86	-	14.53	14.54
$\sigma_{C(3')C(4')} \Leftrightarrow n_{F(10)\ p\pi'}$	7.65	7.66	7.73	7.74	7.65	7.65	7.72	7.67	7.73	7.73
$\sigma_{C(5')C(6')} \Leftrightarrow n_{F(11)\ p\pi'}$	8.97	8.91	8.30	8.30	8.30	8.30	8.91	8.91	8.29	8.29
$\sigma_{C(8)C(8')} \Leftrightarrow \pi_{C(2)C(3)}$	*1.56*	*1.58*	*8.00*	*7.80*	*8.03*	*7.98*	-	-	-	-
$\sigma_{C(8)C(8')} \Leftrightarrow \pi_{C(2')C(3')}$	*0.86*	-	*9.34*	-	*8.02*	-	-	*0.90*	-	-
$\sigma_{C(8)C(8')} \Leftrightarrow \pi_{C(3')C(4')}$	-	*8.25*	-	*8.39*	-	*6.90*	*9.49*	-	*7.59*	*7.34*

[a] Through-space and through-bond interactions are depicted in bold and in italics, respectively.

$\pi_{C(2)-C(3)}$, and $\sigma_{C(8)\text{-}C(8')} \Leftrightarrow \pi_{C(2')\text{-}C(3')}$ interactions. Besides these interactions, the NSA analysis gave evidence of an important group of destabilizing through-space interactions, $\pi_{C(2)-C(3)} \Leftrightarrow \pi_{C(3)'\text{-}C(4')}$, $\pi_{C(2)-C(3)} \Leftrightarrow \pi_{C(1')\text{-}C(2')}$, and $\pi_{C(1)-C(6)} \Leftrightarrow \pi_{C(1')\text{-}C(6')}$, among others. In general, the through-space interactions of the F_4-[2.2]cyclophanes are less destabilizing than those of the [2.2]cyclophanes, which are responsible for the lower deformation in the planes of the aromatic rings of the F_4[2.2]cyclophanes. Other destabilizing interactions occur between the π or σ orbitals of the rings and the lone pairs of the fluorine atoms, $\pi_{C(3')\text{-}C(4')} \Leftrightarrow n_{F(10)p(\pi)}$ and $\sigma_{C(5')\text{-}C(6')} \Leftrightarrow n_{F(20)p(\pi)}$, whose destabilizations vary between 8.0 and 15.0 kcal·mol^{-1}. Therefore, the NSA analysis demonstrated that the repulsive interactions take place through the two mechanisms: through-bond and through-space (Figure 4), and the lone pairs of the fluorine atoms also interact repulsively with the σ and π occupied orbitals of the aromatic rings.

3.7. Molecular Orbitals. To investigate the effect of fluorination on the transannular interactions, the molecular orbitals were analyzed, especially the occupied frontier orbitals. As in

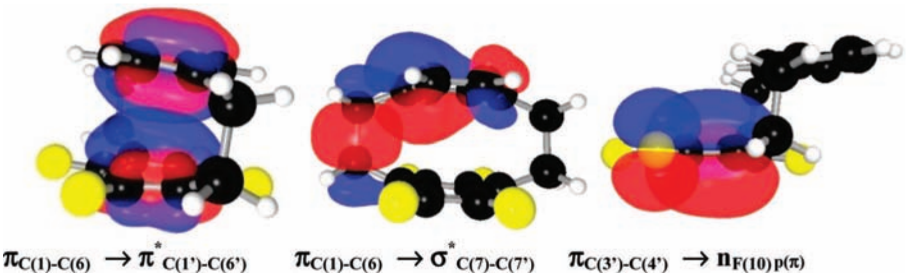


Figure 4. Through-space and through-bond repulsive interactions and interactions involving the lone pairs of the fluorine atoms in the case of the RS **4A** and **5A′**.

the case of the nonsubstituted isomers,[20] some orbitals suggest that transannular interactions may occur, indicating a bonding character in the inter-ring region.[53] However, only some fluorinated isomers have molecular orbitals with shapes that suggest the possible occurrence of through-space transannular interactions (Figure 5). The HOMO-3 suggests through-space interactions take place in **4**, although the NBO analysis showed that such transannular interactions happen for one of the RS of **4** only, whose contribution to the overall structure is low. Through-space interactions also occur in **5a**, which is in agreement with the AIM and NBO analyses. In the case of **6a** and **6b**, the molecular orbitals indicate that through-space interactions are possible, as already verified by the NBO analysis.

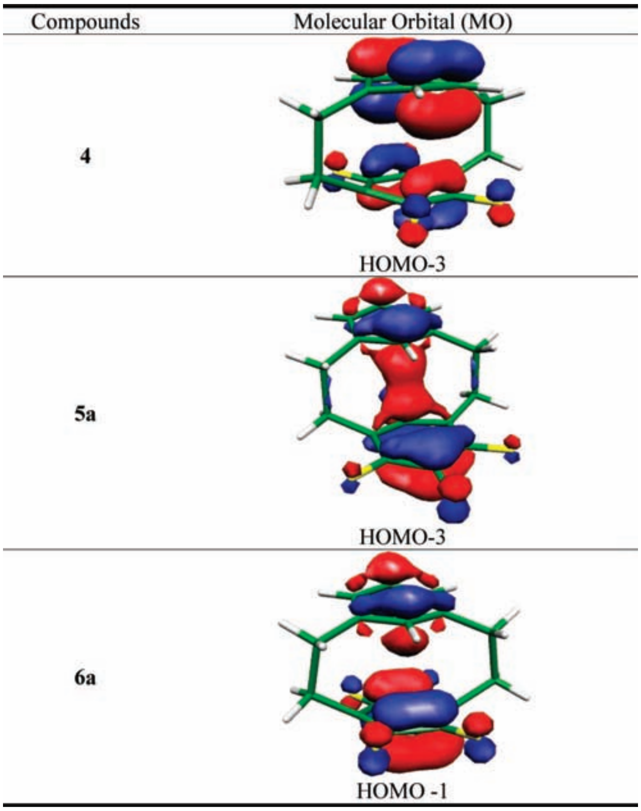


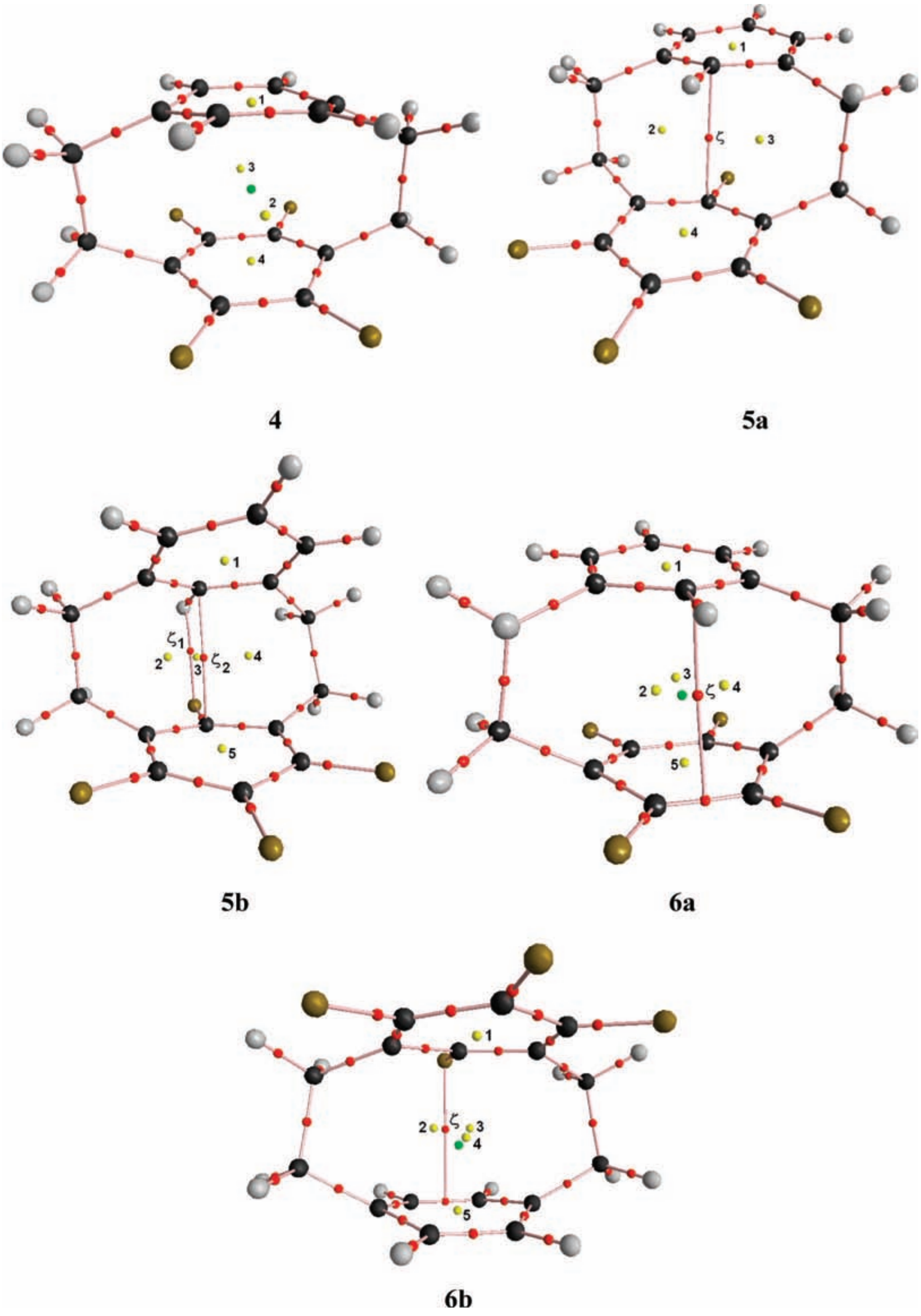
Figure 5. Frontier orbitals of the F_4-[2.2]cylophanes.

3.8. Electronic Density Topological Properties−AIM. The AIM analysis was applied to the F_4-[2.2]cyclophanes, **4-6b**, employing the MP2/6−31+G(d,p) model for determination of the electronic density. The atom numbering is the same as the one adopted in Table 4. The obtained topologies agree with the Poincaré−Hopf rule. In comparing the molecular graphs of isomers **4**−**6b** (Figure 6), we find that only **5a** and **5b** display critical points, ζ. These critical points characterize through-space transannular interactions, as already reported for the nonsubstituted isomers **2a** and **2b**.[20] Not only does **5b** exhibit a critical point connecting carbons belonging to different rings, ζ_2, but it also has a BCP located between the fluorine atom and the hydrogen atom, ζ_1. The ζ_1 parameters lie within the limits established for the occurrence of a hydrogen bond, with ρ_b = 0.017 and $\nabla^2\rho_b = 0.072$. Moreover, this BCP has an extremely high ellipticity value, $\varepsilon_b = 0.493$, which indicates topological instability for this hydrogen bond.[54] On the other hand, the ε_b values in ζ_1 and the distance between ζ_1 and RCP 3 are within the stability limits for H−H interactions in polycyclic aromatic hydrocarbons,[55] which shows that, according to Matta et al.,[55] this hydrogen bond should have a stabilizing character, despite the topological instability. In contrast to this hydrogen bond, the other through-space interactions may be attractive or not, since we reckon that the presence of a BCP indicates there is an interaction between two atoms, but this does not imply that this interaction is necessarily attractive. As in the case of isomer **3**, **6a** and **6b** have a BCP located between two benzene rings. The BCP in **6a** is connected to two other BCPs, while the BCP of **6b** is linked to a nuclear attractor (NA), in this case a fluorine atom and another BCP. This means that conflict mechanisms take place, and the conflict structures are energetically and topologically unstable. So a conformational change, no matter how small, should modify the distance between the benzene rings and these BCPs should therefore disappear.[56]

The highest electron density values were obtained for the BCPs of the C−C bonds of the rings, with ρ_b around 0.31 au. This gives evidence of preferential electron density accumulation and consequent increase in bond order (Table 8). The electron density of the C−C bonds of the bridges and of the C−H and C−F bonds is lower, around 0.21, 0.28, and 0.25 au, respectively. Furthermore, the densities of the BCPs of the C−C bonds of the fluorinated rings are slightly higher than those of the nonsubstituted rings. This is in agreement with the results obtained using the NBO method, which suggests that there is a conjugation of the lone pair of the fluorine atoms with the orbitals of the C−C bonds of the fluorinated ring. The electron densities on the RCPs of the fluorinated and nonsubstituted rings remain unaffected, 0.02 au, which indicates that the fluorination has no effect on the electron density in the center of the ring. Moreover, the electron density decreases more sharply in the RCPs of the macrocycles and in the cage critical points, CCPs.

The values obtained for Laplacian of the electron density distribution agree with those predicted by the Bader method,[36] which indicates that the Laplacian distribution is negative in the CPs where the electron density is locally concentrated, and it is positive where there is electron density depletion. The most negative $\nabla^2\rho_b$ values are those of the ring C−C bonds. The C−F bonds have positive Laplacian values, which suggest that these bonds are considerably polarized, despite the above-mentioned conjugation. The positive Laplacian value indicates density depletion in the RCPs and CCPs. The C−C bonds of the fluorinated rings always have higher ellipticity, ε, than those of the C−C bonds of the nonsubstituted rings, which gives an indication of the increased π character of the C−C bonds in the fluorinated rings. This is in agreement with the geometric changes (section 3.1) and the NBO analysis (section 3.5), which showed that there are conjugations of the lone pair of the fluorine atoms with the fluorinated ring.

The results obtained for the BCPs of **2a** and **2b** characterize the transannular interactions of these compounds as being of the closed-shell type.[20] Similarly, the properties of the BCPs ζ of **5a** and **5b** show that the transannular interactions in the fluorinated derivatives are also of the closed-shell type (Table 9), with ρ_b close to zero in ζ, positive values close to zero for $\nabla^2\rho_b$, and a positive value for the total energy density, H_b, which is very close to zero. Nevertheless, the critical points of the covalent bonds of the fluorinated rings, $\text{BCP}_{\text{ring(F)}}$, have higher ρ_b values and negative values for $\nabla^2\rho_b$ and H_b, compared to the respective BCP_{ring} of **2a** and **2b.**[20] This confirms the conjugation of the lone pairs of the fluorinated rings, as observed by means of the NBO method. Comparing the kinetic, G_b, and potential, V_b, energy density values in ζ_1, ζ_2, and $\text{BCP}_{\text{ring(F)}}$, we find that both values are



4 **5a** **5b** **6a** **6b**

Figure 6. Molecular graphs for **4**−**6b**, where the critical points (CPs) are denoted by points and the atoms by spheres. The bond critical points (BCPs) are denoted by red points, the ring critical points (RCPs) are represented by yellow points, and the cage critical points (CCPs) can be seen as green points.

very much decreased in ζ_1 and ζ_2. The ellipticity, ε, in ζ_1 and ζ_2 is very low compared to those of the BCP$_{\mathrm{ring(F)}}$. Besides that, the G_b, V_b, and H_b values of the BCP$_{\mathrm{ring(F)}}$ are always more negative than those of the BCP$_{\mathrm{ring}}$.

A procedure analogous to the one used by Matta et al.[55] in the study of hydrogen−hydrogen interactions in polycyclic aromatic hydrocarbons and also employed by Freitas and Galembeck[57] in the study of the interaction of an inhibitor with the aminoacids of the allosteric site of the reverse transcriptase shows that the bond path (BP) is not curved, despite the low difference between BCP and RCP $\rho_b - \rho_r$, values, the large differences between bond path length and distance between the atoms, $r_b - r_r$, and the low ellipticity ε. This is an indication that stable interactions take place (Table 9). However, the ellipticity in ζ_1 of **5b** is an exception because it is an intramolecular hydrogen bond of low stability, as discussed previously. As in the cases of the nonsubstituted isomers **2a** and **2b**, applying the same criteria to the fluorinated **5a** and **5b** shows that the BCP does not collapse with the RCP upon small geometry changes.

TABLE 8: Properties of the BCPs, RCPs, and CCPs of the F$_4$-[2.2]Cyclophanes (au)

critical points	properties	compounds				
		4	**5a**	**5b**	**6a**	**6b**
		BCPs				
C(1)−C(2)	ρ_b	0.307	0.307	0.309	0.307	0.308
	$\nabla^2\rho_b$	−0.827	−0.823	−0.834	−0.821	−0.828
	ε	0.203	0.207	0.202	0.208	0.200
C(1′)-C(2′)	ρ_b	0.314	0.312	0.313	0.314	0.311
	$\nabla^2\rho_b$	−0.867	−0.856	−0.859	−0.869	−0.848
	ε	0.281	0.277	0.282	0.280	0.284
C(1)−C(6)	ρ_b	0.308	0.308	0.308	0.308	0.309
	$\nabla^2\rho_b$	−0.828	−0.831	−0.831	−0.830	−0.832
	ε	0.201	0.208	0.210	0.206	0.204
C(1′)-C(6′)	ρ_b	0.313	0.313	0.313	0.313	0.314
	$\nabla^2\rho_b$	−0.862	−0.863	−0.868	−0.862	−0.869
	ε	0.283	0.288	0.284	0.276	0.284
C(1)−C(7)	ρ_b	0.252	0.254	0.251	0.250	0.253
	$\nabla^2\rho_b$	−0.596	−0.604	−0.592	−0.587	−0.599
	ε	0.029	0.035	0.029	0.028	0.033
C(1′)-C(7′)	ρ_b	0.248	0.249	0.248	0.248	0.246
	$\nabla^2\rho_b$	−0.575	−0.582	−0.576	−0.575	−0.568
	ε	0.024	0.032	0.026	0.029	0.025
C(7)-C(7′)	ρ_b	0.211	0.223	0.217	0.221	0.221
	$\nabla^2\rho_b$	−0.420	−0.464	−0.441	−0.459	−0.460
	ε	0.020	0.012	0.019	0.016	0.016
C(2′)-F(9)	ρ_b	0.253	0.252	0.245	0.252	0.249
	$\nabla^2\rho_b$	0.215	0.193	0.187	0.207	0.187
	ε	0.019	0.042	0.038	0.020	0.036
C(6′)-F(12)	ρ_b	0.253	0.255	0.254	0.254	0.254
	$\nabla^2\rho_b$	0.215	0.206	0.210	0.207	0.208
	ε	0.019	0.011	0.011	0.013	0.015
		RCPs				
1	ρ_b	0.022	0.021	0.022	0.021	0.020
	$\nabla^2\rho_b$	0.164	0.160	0.160	0.160	0.152
2	ρ_b	0.009	0.013	0.014	0.012	0.009
	$\nabla^2\rho_b$	0.028	0.056	0.056	0.040	0.032
3	ρ_b	0.009	0.013	0.015	0.009	0.009
	$\nabla^2\rho_b$	0.028	0.056	0.072	0.028	0.032
4	ρ_b	0.021	0.020	0.014	0.012	0.008
	$\nabla^2\rho_b$	0.156	0.152	0.056	0.040	0.028
5	ρ_b	-	-	0.020	0.020	0.022
	$\nabla^2\rho_b$	-	-	0.152	0.152	0.164
		CCP				
	ρ_b	0.005	-	-	0.009	0.008
	$\nabla^2\rho_b$	0.020	-	-	0.032	0.028

TABLE 9: Data for the Critical Points (ζ and BCP$_{\text{ring}}$) in (au), $\rho_b - \rho_r$, $r_b - r_r$, BL, and BPL (au) for the Conformers 5a and 5b

compd	CPs	ρ_b	$\nabla^2\rho_b$	ε	G_b	V_b	H_b	$\rho_b - \rho_r$	$r_b - r_r$	BL	BPL
5a	ζ_1	0.020	0.060	0.169	0.014	−0.014	0.001	0.008	1.832	5.044	5.076
	BCP$_{\text{ring(F)}}$	0.313	−0.863	0.288	0.114	−0.444	−0.330	0.293	2.324	2.634	2.634
5b	ζ_1	0.017	0.072	0.493	0.017	−0.015	0.001	0.002	0.967	4.181	4.315
	ζ_2	0.018	0.056	0.146	0.013	−0.012	0.001	0.004	1.228	5.122	5.174
	BCP$_{\text{ring(F)}}$	0.313	−0.863	0.289	0.114	−0.444	−0.330	0.293	2.324	2.634	2.634

Besides the local topological properties of the CPs, a series of atomic properties such as the atomic charge, $q(\Omega)$, the first momentum of atomic charge distribution, $M(\Omega)$, the atomic volume, $v(\Omega)$, and the negative of the total atomic energy, $E(\Omega)$, were determined via integration over the atomic basins of the atoms not related by symmetry. The NPA charges, obtained from the NBO analysis, were compared with the AIM charges. Figure 7 shows the average properties of atom groups, such as carbons belonging to the nonsubstituted ring (C ring-I), carbons on the fluorinated ring (C ring-II), hydrogens on ring I (H ring-I), and carbons and hydrogens of the ethano bridges (C br-I, C br-II, H br-I, and H br-II), according to the ring to which they are bonded.

A comparison of Figure 7 panels a and b evidence some fundamental differences. The charges, $q(\Omega)$, of C ring-II are always more positive than the NPA charges. Furthermore, while the NPA charges of C ring-I are negative, the respective $q(\Omega)$ are null. Curiously, the NPA charges do not indicate that the fluorine atoms or the carbon atoms on the ethano bridges have negative charges, whereas $q(\Omega)$ demonstrated that only the fluorine atoms bear negative charges. Therefore, the $q(\Omega)$ charges give evidence that the electron-withdrawing fluorine atoms reduce the charge density of both the fluorinated ring and the ethano bridges. On the other hand, the NPA charges show that there might be a charge transfer from the nonsubstituted ring to the fluorinated one through the bridges; that is,

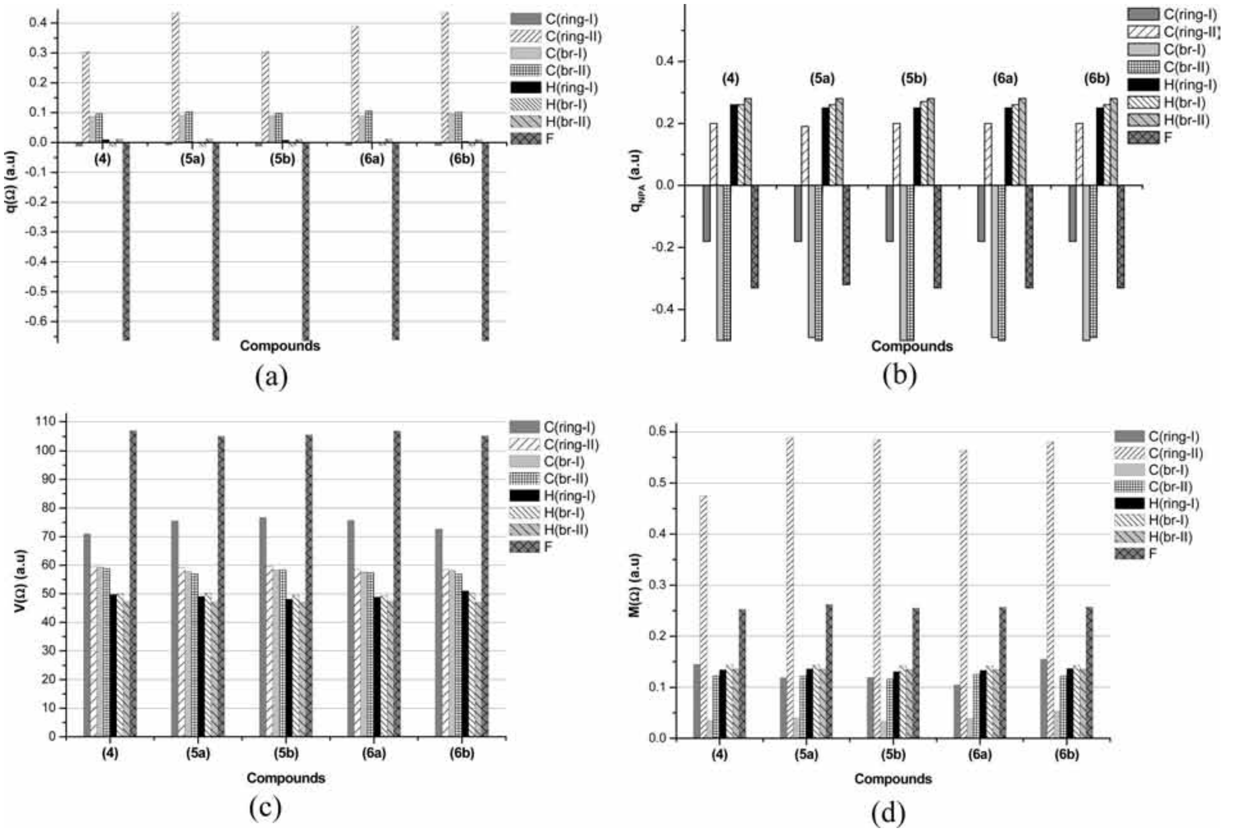


Figure 7. Average properties obtained by integration over the atomic basins (a) $q(\Omega)$, (b) q(NPA), (c) $\upsilon(\Omega)$ and natural atomic charges, and (d) $M(\Omega)$.

through-bond interactions take place, as seen by the negative charges on the bridge carbons. This is in agreement with the NBO analysis results.

The $M(\Omega)$ and $\upsilon(\Omega)$ values of the carbons (C ring-II) are the ones that vary the most; that is, they have higher and lower $M(\Omega)$ and $\upsilon(\Omega)$ compared to C ring-I. This gives evidence of the strong electron-withdrawing effect of the fluorine atoms on the electron density of the carbons on the fluorinated ring (Figure 7 panels c and d). This same effect is also observed in the case of the carbons belonging to the ethano bridges (Figure 7d). Moreover, the $M(\Omega)$ and $\upsilon(\Omega)$ values for the ethano bridges are little affected by the fluorination. As for the atomic charges, they are very similar in all the compounds. For instance, $-E(\Omega)$ values for the hydrogens are always around 0.6 au, and they are around 38.0 au for the carbons. Therefore, the $q(\Omega)$, $M(\Omega)$, and $\upsilon(\Omega)$ properties are affected not only by the fluorination but also by the position of the ethano bridges, while $-E(\Omega)$ remains unaffected.

3.9. Local Aromaticity.

Changes in the local aromaticity of the rings as a function of fluorination were analyzed by three criteria: one magnetic, NICS,[29b] a geometric HOMA,[27b] and an electronic, PDI.[58]

3.9.1. NICS.

Table 10 contains the NICS and NICS$_{zz}$ values for the perfluorinated and nonfluorinated rings of the [2.2]cyclophanes. The nonsubstituted and the fluorinated rings were designated rings I and II, respectively (Figures 1 and 8).

To aid understanding, the NICS values calculated for the inner cavity were designated NICS(in), while those obtained for the outer portion of the cavity were named NICS(out). Therefore, the notation NICS(in,I) indicates that the value was calculated inside the cavity, 1 Å away from the center of ring I. The NICS(0) value; that is, the NICS value calculated in the center of the aromatic rings, is significantly affected by substitution and becomes more negative compared to those of the nonsubstituted isomers (Table 10).[19] Probably this change in NICS(0) can be attributed to changes in the stagnation graph when the magnetic field is applied perpendicular to aromatic rings, that will change the diatropism in this direction. It is known that the more negative the NICS value, the more aromatic the system. So NICS(0) is not reliable for the estimation of aromaticity because this value is very much affected by both the σ electrons of the aromatic rings and the substituents.[59]

The NICS(in,II) values are always more negative than the respective NICS(in,I), except for **5a**, which indicates that the fluorine atoms affect the electron current density. This leads to an increase in the magnetic field within the inner cavity, in the surroundings of the fluorinated ring II, and suggests that there is an increase in the aromaticity.[60] There are also slight variations in the NICS values of the outer cavity, and the NICS(out,II) values are always slightly more negative than NICS(out,I), except for 6b. Although the changes are small, the results show that the fluorination influences the aromaticity of [2,2]cyclophanes. These results agree with those obtained by means of the NBO method, and they indicate that there is an intense interaction between the lone electron pair of the fluorine atoms and the antibonding orbitals of the substituted ring. This promotes an increase in the electron current density of the fluorinated ring, as was discussed in section 3.5.

Figure 9 compares the NICS(in) and NICS(out) values, as well as the values of their components in the *z* direction, NICS$_{zz}$, for each of the [2.2]cyclophane isomers. In the case of the compounds studied here, NICS(in) undergoes the largest variations compared to NICS(out). The NICS(in) values obtained for the fluorinated isomers **4**−**6b** are more negative than those of the nonsubstituted **1**−**2b**. This difference is not observed in the case of NICS(out), though. Similarly, NICS$_{zz}$ undergoes

TABLE 10: NICS and NICS Strain Component (NICS_{zz}) (ppm) of the Fluorinated Isomers of [2.2]Cyclophanes (4−6b)

compounds	position	NICS	NICS_{zz}
4 (ring I)	0	−8.98	−27.42
	in	−13.57	−43.10
	out	−9.65	−29.25
4 (ring II)	0	−15.05	−21.26
	in	−14.55	−41.22
	out	−10.24	−24.49
5a (ring I)	0	−9.06	−15.15
	in	−11.33	−31.37
	out	−10.04	−28.92
5a (ring II)	0	−14.30	−14.39
	in	−10.92	−23.54
	out	−10.06	−22.40
5b (ring I)	0	−8.82	−15.09
	in	−12.97	−27.67
	out	−9.34	−19.47
5b (ring II)	0	−14.99	−17.25
	in	−13.80	−32.40
	out	−10.22	−22.81
6a (ring I)	0	−9.39	−16.47
	in	−12.29	−32.40
	out	−10.20	−26.72
6a (ring II)	0	−14.77	−19.18
	in	−13.89	−35.38
	out	−9.94	−21.92
6b (ring I)	0	−9.13	−18.07
	in	−13.25	−38.22
	out	−8.98	−25.92
6b (ring II)	0	−15.90	−19.24
	in	−13.84	−31.74
	out	−11.33	−24.16

more significant variations in the inner part of the cavity than in the outer region. The NICS_{zz}(in) values are generally more negative than the NICS_{zz}(out) ones, which gives evidence that the sum of the magnetic fields, generated by the electron current density, is affected by the fluorination, and the main variation in this sum occurs for the inner part of the cavity of the fluorinated cyclophanes. It must be borne in mind that the NICS_{zz}(in) values are not always more negative in the vicinity of the fluorinated ring II, which indicates that the magnetic field is influenced not only by the substitution effects but also by the aromatic ring stacking (Figure 9a).[60] The NICS_{zz} values in the outer part of the aromatic rings undergo larger variations in the case of ring I than in the case of ring II. Therefore, the NICS analysis shows that the substitution with fluorine affects the aromaticity of the [2.2]cyclophanes in some complex way.

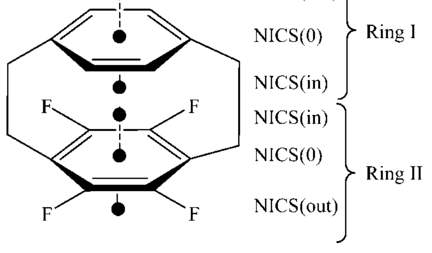


Figure 8. Points used for the determination of NICS values.

TABLE 11: HOMA, EN, and GEO for the Fluorinated and Nonfluorinated Cyclophanes

	ring I			ring II		
compounds	HOMA	EN	GEO	HOMA	EN	GEO
4	0.962	0.035	0.003	0.992	0.006	0.001
5a	0.970	0.029	0.001	0.987	0.011	0.002
5b	0.972	0.028	0.000	0.992	0.007	0.001
6a	0.965	0.033	0.002	0.992	0.007	0.001
6b	0.967	0.030	0.003	0.987	0.010	0.003
1	0.945	0.053	0.003	0.945	0.053	0.003
2a	0.972	0.028	0.001	0.972	0.028	0.001
2b	0.966	0.033	0.001	0.966	0.033	0.001
3	0.966	0.032	0.001	0.969	0.031	0.001

3.9.2. HOMA. The geometric criteria HOMA, EN, and GEO show that the HOMA values of ring II increase slightly upon fluorination, which indicates that aromaticity increases with substitution (Table 11). Moreover, this increase is justified by the sharp reduction in the EN term, which describes the decrease in aromaticity due to the lengthening or shortening of the bond lengths. In other words, fluorination drastically decreases the variation in the bond lengths compared to the standard values (Figure 10). On the other hand, the term describing the decrease in the aromaticity through the alternation of bond lengths, GEO, is kept constant. In brief, the fluorination leads to a decrease in the lengthening and shortening of the C−C bond lengths of the ring, thereby increasing the aromaticity of the fluorinated ring. Comparing the HOMA, EN, and GEO values of the nonsubstituted isomers, the values of their EN terms are higher than those of the fluorinated isomers, in the case of both rings I and II. Concerning **4**, substitution reduces not only the EN values of the ring where the substitution takes place, but also the EN values of the nonsubstituted ring (Figure 10).

3.9.3. PDI. Some years ago, Poater, Fredera, Duran, and Solà introduced a new aromaticity index, the para delocalization index (PDI).[58] This electronic criterion is defined by the mean of the AIM electron delocalization index of para related carbons. It was observed that for some polycyclic aromatic hydrocarbons, there is a good correlation between PDI and HOMA, but the correlation between PDI and NICS is not so remarkable. In general, all three criteria present similar results.[58a] For some carbazole derivatives these three indexes present very different behavior, which is attributed to the small range of these indexes for this series of compounds.[58c] PDI was used also for a variety of different systems, as in the reaction paths of cycloaddition reactions[58d] or in malonaldehyde derivatives.[58e]

Table 12 presents the PDI for the [2.2]cyclophanes (**1**, **2a**, **2b**, and **3**) and F_4-[2.2]cyclophanes (**4**, **5a**, **5b**, **6a**, and **6b**). It is possible to note that fluorination causes a small increase on the ring I, and a sharp decrease of aromaticity in the fluorinated ring, ring II. This is exactly the opposite that was observed for HOMA and EN, and it is also in contrast with the geometric changes and to the increase of δ_b and ε in C−C BCP of fluorinated rings. It can be only explained by an increase in the $\pi^*_{\text{C-C}}$ occupation due to donation form n_π orbital, as revealed by NBO analysis. The decrease of PDI in ring II is a consequence of the decrease of individual para delocalization indexes (DI) and can suggest that the Dewar resonance structures are less important for the fluorinated rings, due probably to the small contribution of resonance structures with C=F double bond.

In conclusion, both the NICS and HOMA criteria suggest that the fluorination leads to an increase in the aromaticity of [2.2]cyclophanes, especially in the case of the fluorinated rings. This is directly related to the reduced SE(IR) and ΔE values, as previously observed by means of the isodesmic reactions. In

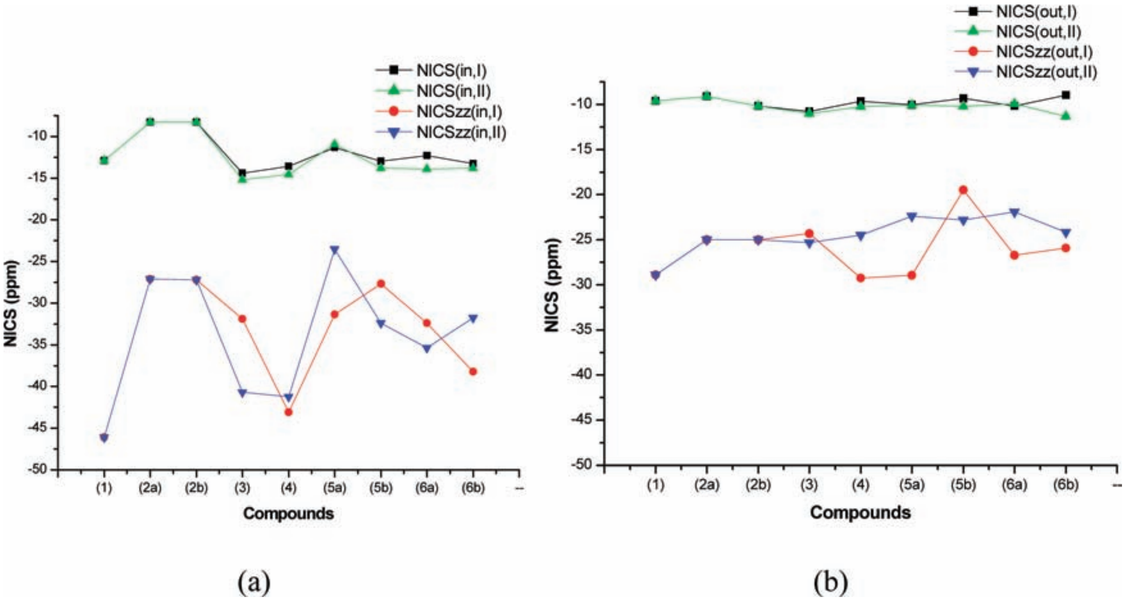


Figure 9. Behavior of the NICS(in) (a), NICS(out) (b), and NICS$_{zz}$ (ppm) values (a and b) of the nonsubstituted and fluorinated [2.2]cyclophanes (**1**−**6b**).

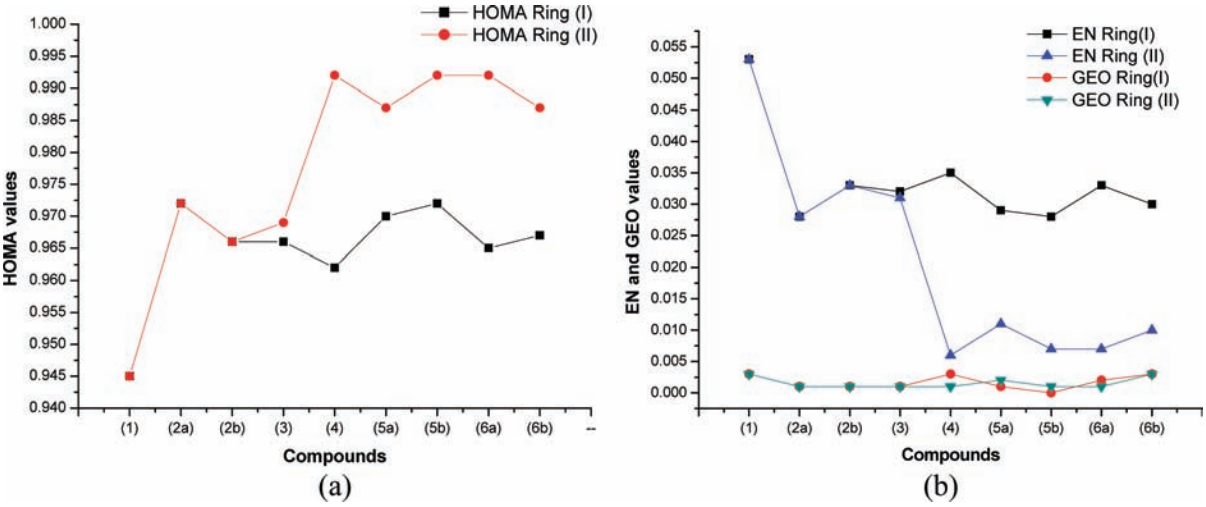


Figure 10. Variations of HOMA (a), EN, and GEO (b) values for the nonsubstituted and fluorinated [2.2]cyclophanes.

TABLE 12: PDI for the Fluorinated and Nonfluorinated Cyclophanes, ($\times 10^{-2}$)

compounds	ring I	ring II
4	5.32	4.53
5a	5.32	4.47
5b	5.38	4.51
6a	5.35	4.49
6b	5.33	4.45
1	5.31	5.31
2a	5.27	5.30
2b	5.30	5.29
3	5.19	5.21

TABLE 13: Magnetic Susceptibilities for 1−6 (cgs ppm)

compounds	$-\chi_M$
4	149.9
5a	153.2
5b	152.6
6a	150.7
6b	151.2
1	122.4
2a	131.7
2b	129.1
3	131.5

contrast, PDI presents the opposite figure, a significant decrease for the fluorinated rings. The discrepancy between these three indexes can be attributed to the small range presented by them, as observed in the cited study of carbazoles.[58c]

3.10. Global Aromaticity. The increased diamagnetic susceptibility, χ_M, was widely used to analyze the global aromatic character.[29b,61] Aromatic compounds present significantly exalted χ_M and high anisotropy. The first is normally obtained by a comparison between the bulk magnetic susceptibility and χ_M obtained by bond and atom increments, or it needs a suitable reference. This criterion is the only one that is uniquely associated with aromaticity, as stated by Schleyer and Jiao.[62] To overcome the choice of appropriate reference systems, and considering that **1**−**3** are isomers as well **4**−**6**, a direct comparison of χ_M was made for each of these two sets of compounds. A similar approach was used in the study of large [*N*]phenylenes[63] and for methano[10]annulenes.[64] Table 13 indicates that the para isomers, **1** and **4**, are the least aromatic, and the most aromatic are the anti-meta isomers, **2a** and **5a**. Only for the parent cyclophanes does the order of global aromaticity follow the order of HOMA (Table 11). The substitution by fluorine increases the global aromaticity, as also observed by NICS and HOMA criteria for local aromaticity. This can be related to the decrease of the tension energies, SE(IR), with substitution (Table 2). It is also curious to notice that the fluorination reduces the range of χ_M.

4.0. Conclusions

Geometric changes take place in the [2.2]cyclophanes containing one completely fluorinated ring, especially in the case of the rings and the bridge dihedral angles. The bond lengths and the inter-ring distances undergo slight variations. The isodesmic reactions showed that the para isomer, **4**, is the most strained among the fluorinated isomers, as observed in the case of the corresponding nonsubstituted isomer **1**. Furthermore, the partitioned treatment of the isodesmic reactions led to the conclusion that the fluorinated rings generally absorb more tension than the rings of the nonsubstituted isomers. The NBO and NSA analyses showed that there is conjugation of the fluorine lone pairs with the π system, which increases the electron density of the fluorinated ring. On the other hand, these analyses also gave evidence that the fluorination causes an increase in both the number and intensity of through-space interactions, but these interactions are restricted to the fluorinated isomers analogous to **2a** and **2b**; that is, **5a** and **5b**. Only some isomers display through-space interactions, which promote little significant stabilizations. Both the NICS, HOMA criteria, and the increased diamagnetic susceptibility, χ_M, suggest that fluorination results in an increase in the aromaticity of the [2.2]cyclophanes. This increase might be related to the reduction in the SE(IR) and ΔE values.

The AIM analysis furnished data that confirm the conjugation of the lone pair of the fluorine atoms. It also evidenced that the substitution does not increase the number of through-space and through-bond interactions. Only some frontier orbitals of **4**, **5a**, and **5b** suggested the occurrence of through-space interactions.

In contrast with the NBO, NSA, and AIM analyses, the atomic charges showed that the presence of the fluorine atoms results in a charge deficiency in the fluorinated ring, despite the π retro-donations of the fluorine atoms. This indicates that the σ-withdrawing effect is predominant in these compounds. The chemical-shift analysis demonstrated that the substitution affects the diamagnetic anisotropy of the whole molecule.

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Supporting Information Available: Geometric parameters, electronic energies, and chemical shifts. This material is available free of charge via the Internet at http://pubs.acs.org.

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