

Analysis of CF \cdots FC interactions on cyclohexane and naphthalene frameworks

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Abstract

Intramolecular CF \cdots FC interactions in selected organofluorine compounds (all-*syn*-1,2,3,4- and all-*syn*-1,2,4,5-tetrafluorocyclohexane, 1,8-difluoronaphthalene, 4,5-difluorophenanthrene, 2,2',5,5'-tetrafluorobiphenyl) were studied at the MP2/aug-cc-pVDZ level using the recently developed noncovalent interaction (NCI) method. For the optimised minima, all CF \cdots FC interactions that are identified by this method are classified as attractive, also in those cases where suitable isodesmic reaction energies fail to provide evidence for an energetic stabilisation. Possible relations between these interactions and the observable J_{FF} spin-spin coupling constant values are discussed.

Keywords: CF \cdots CF interactions, organofluorine compounds, one-bond C-F spin-spin coupling constants, NCI method.

1. Introduction

The incorporation of fluorine into organic compounds is widely used for tuning the properties of high-performance molecules. This is due to the high electronegativity of fluorine, its low steric impact and the inherent stability of the C-F bond.^{1,2,3} As a consequence fluorine is found in many commercial products and particularly those associated with the pharmaceuticals, agrochemicals and the organic materials industries.⁴ With this background we are interested in evaluating the stereoelectronic properties of the C-F bond, or multiple C-F bonds in organic frameworks.⁵ As part of that programme Durie *et al.* reported the synthesis and structures of all-*syn*-1,2,4,5-tetrafluorocyclohexane (**1**) and the all-*syn*-1,2,3,4-isomer (**2**, see Figure 1).^{6,7} These cyclohexanes were unexpectedly crystalline and, according to X-ray structure analysis, possess a high degree of facial polarity due to the fluorine atoms occupying only one face of the cyclohexane ring (Figure 1). Such compounds with high polarity, but low viscosity, have potential as motifs in eg. liquid crystal materials.

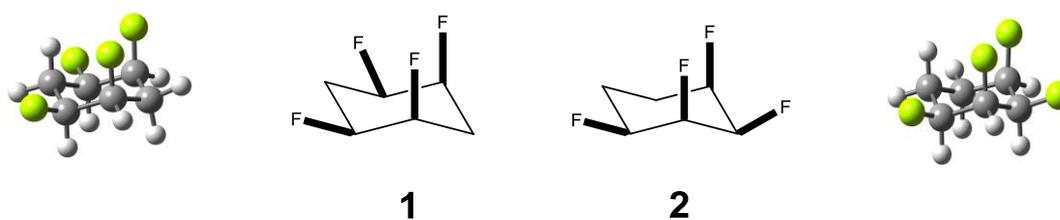


Figure 1: Structures of compounds **1** and **2**

For compound **2**, where the diaxial fluorines are chemically nonequivalent, an experimental ${}^4J_{\text{FF}}$ spin-spin coupling constant (SSCC) of 29 Hz was observed between the axial fluorine atoms. A significantly lower ${}^4J_{\text{FF}}$ value of 14 Hz was observed between the equatorial fluorines.⁶ The rather large ${}^4J_{\text{FF}}$ SSCC value for the axial fluorine atoms is intriguing suggesting through space coupling. There is theoretical and

experimental evidence to suggest that organic bound fluorine atoms may form either attractive or repulsive intra- and inter- molecular CF...FC interactions.^{8,9,10,11} However, like classical H-bonds involving fluorine,^{12,13,14} such CF...FC interactions are still poorly understood. CF...FC interactions have been classified as Type **I** and Type **II**, depending on the structural arrangements (Figure 2).⁸

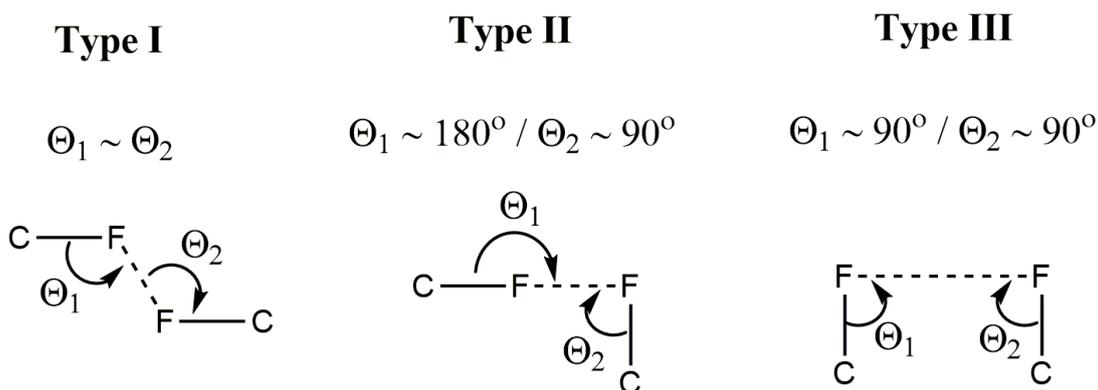


Figure 2: Graphical representation and classification of CF...FC interactions in accordance with the literature (Types **I** and **II**) and the Type **III** discussed here.

In the present work we analyze the ${}^4J_{\text{FF}}$ SSCCs of **2** in the light of the CF...FC interaction between the axial F atoms. Because the C-F bonds are in a *syn* orientation, this would correspond neither to Type **I** nor **II**, but rather to a Type **III** interaction (Figure 2). We extend this analysis to 1,8-difluoronaphthalene (**3**) and its regioisomers (Chart 1). We also studied the CH₃F, CH₂F₂, CHF₃ and CF₄ dimers in different arrangements. These molecules are discussed in the framework of the quantum theory of atoms in molecules (QTAIM),¹⁵ the recently developed non-covalent interactions (NCI) method,¹⁶ and natural bond orbitals (NBO) analysis,¹⁷ together with experimental and computed J_{FF} SSCCs.

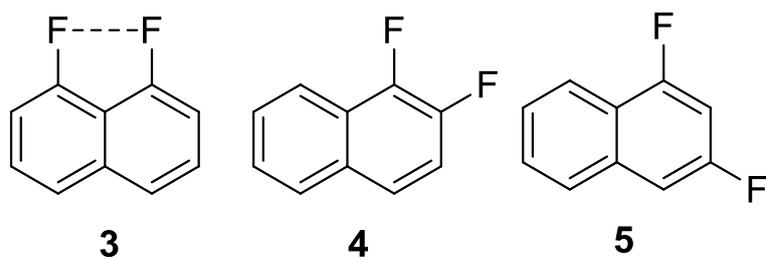


Chart 1: Structures of compounds **3-5** highlighting the proposed F...F interaction for the regioisomer **3**.

2. Computational details

The Gaussian09 program¹⁸ was used to optimise all molecules described in the paper at the MP2/aug-cc-pVDZ level including basis set superposition error (BSSE) corrections through the counterpoise method.^{19,20} Spin-spin coupling constants (SSCCs) were also computed with the same program at the BHandH/EPR-III level;^{21,22} this and related levels have performed very well in the computations of SSCCs.^{23,24} SSCCs were also computed at the second-order polarization propagator approximation (coupled cluster singles and doubles) SOPPA(CCSD)²⁵ method and the EPR-III basis set for ¹⁹F and the cc-pVDZ basis set for ¹H and ¹³C atoms by using the Dalton 2013 program.²⁶ NBO analysis²⁷ was carried out for the optimised conformers at the MP2/aug-cc-pVDZ level. The QTAIM method¹⁵ was applied on the obtained MP2/aug-cc-pVDZ electron densities for each compound with the AIMALL program.²⁸ NCI calculations were also performed on the obtained MP2/aug-cc-pVDZ electron densities by using the NCIPLOT 3.0 program.¹⁶ In addition, geometry optimisations, QTAIM and NCI calculations were performed at selected levels of density functional theory (DFT) with a variety of basis sets. These results are deposited in the electronic supplementary information (ESI).

3. Results and discussion

Based on QTAIM, Alkorta *et al.*²⁹ have shown that fluorine atoms may form intramolecular attractive closed-shell CF...FC interactions and found a good correlation between experimental ${}^4J_{\text{FF}}$ SSCCs and the electron density ρ at the CF...FC bond-critical point (BCP). We have found that the CF...FC distance in **1** and **2** are highly dependent on the theoretical level and basis set used (Tables S1 and S2 in the ESI). When the QTAIM is applied to geometries of **1** and **2** obtained with different methods/basis sets (see ESI for details and molecular graphs in Figures S1 and S2), a CF...FC bond path is obtained only for methods that find a CF...FC distance ≤ 2.79 Å, i.e. the X-ray-derived value in **2**.⁶ In contrast, the NCI method finds CF...FC interactions that are classified as attractive with all theoretical methods applied here (Figures S3 - S6). Our findings reinforce the conclusion of Lane *et al.*,³⁰ that the QTAIM BCP criterion is too restrictive to infer bonding formation for weak long-range interactions. In contrast, the NCI method has been proposed as suitable tool to study such interactions, being able to differentiate repulsive from attractive interactions.³¹

By applying the QTAIM and the NCI methods to **3** and **4** (see details in the ESI), a CF...FC interaction is predicted for **3**, but not for **4** (Figure 3), even though the CF...FC distance in the latter is only ca. 2.7 Å. The positive Laplacian value at the CF...FC BCP obtained by QTAIM for **1-3** (Table S3) indicate a closed-shell interaction. Indeed, Osuna *et al.*,⁹ have found, by using Symmetry-Adapted Perturbation Theory (SAPT), that CF...FC interactions operating in fluorinated hydrocarbons are closed-shell described by both dispersive and electrostatic interactions.

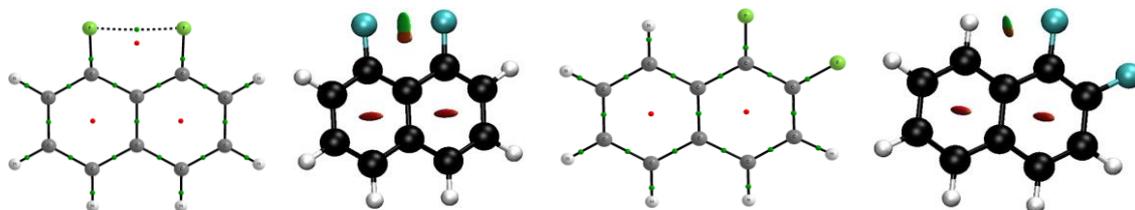


Figure 3: QTAIM and NCI molecular graphs for compounds **3** and **4** (MP2/aug-ccpVDZ). Both methodologies indicate formation of an F...F interaction for **3**, but not for **4**. QTAIM and NCI parameter details in the ESI.

In order to relate the intermolecular attractive interactions predicted by NCI to actual energetic stabilisation, we studied intermolecular CF...FC interactions in some prototypical model systems. Corroborating previous results by Osuna et al,⁹ BSSE corrected MP2/aug-cc-pVDZ potential energy surfaces (PESs) built for linear arrangements of CH₃F, CH₂F₂, CH₃F and CF₄ dimers (Figure 4) indicate that CF...FC interactions are repulsive for CH₃F and CH₂F₂ dimers in any relative orientation, and attractive for CHF₃ and CF₄ dimers, respectively (Figure S7 in the ESI). Such result may be rationalised by the orientation of the dipole moments between each monomer of the dimer pairs in some instances (Figure 4), but is not true for the CHF₃ in the “chelate III” dimer arrangement, which shows attractive CF...FC interactions (ca. 0.12 kcal mol⁻¹ for 3 CF...FC interactions).

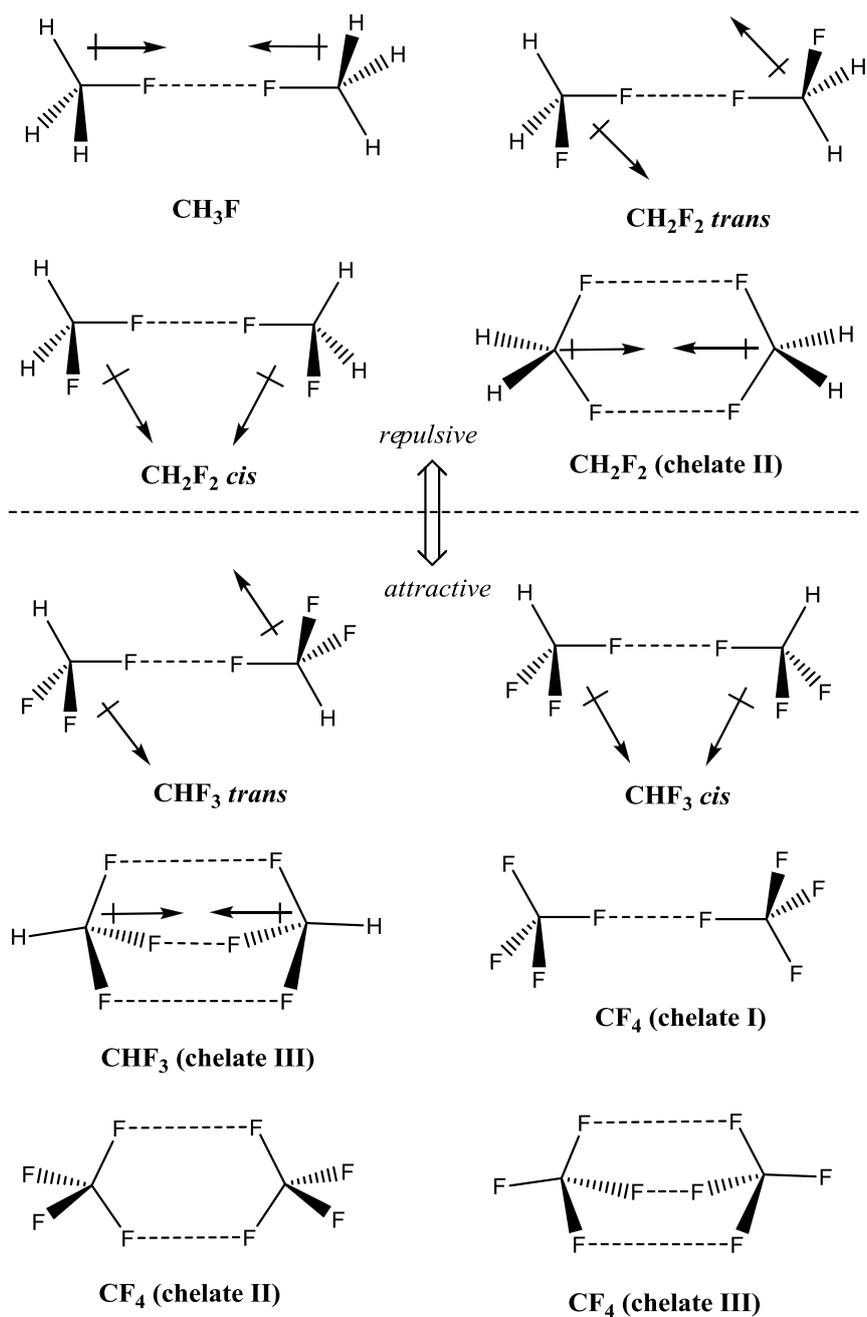


Figure 4: Representations of CH_3F , CH_2F_2 , CHF_3 and CF_4 dimers. Dipole orientations for each monomer are also represented.

The CH_3F dimer has its monomer dipoles oriented one against each other, being the most repulsive interaction in comparison with the other dimers. CH_2F_2 *trans*

arrangement dipoles have an antiparallel orientation and although its PES is repulsive throughout, the fluorine-fluorine repulsion in this dimer is less pronounced than in the CH₃F dimer. As expected, CH₂F₂ in a *cis* arrangement is more repulsive than CH₂F₂ in a *trans* arrangement, evidencing the role of dipole moment orientations in dimer energy stabilizations. The importance of the dipole orientations is also confirmed by the CHF₃ dimers *cis* and *trans* arrangements (Figure S7b). The CHF₃ dimer with a *trans* arrangement forms an attractive CF...FC interaction, which starts to be attractive from 2.75 Å and have approximately same stabilization energy as the CF₄ dimer with both *cis* and *trans* arrangements (ca. 0.2 kcal mol⁻¹ in the equilibrium geometry), which monomers have zero dipole moments. The *cis* arrangement of the CHF₃ dimer in the other hand has no antiparallel arrangements of its dipole moments and has a CF...FC interaction that is slightly repulsive (0.01 kcal mol⁻¹) at the MP2/aug-cc-pVDZ level. All those different arrangements indicate that relative dipole arrangements influence the energy of dimers.

NCI isosurfaces were computed for some of the dimers at selected CF...FC distances (Figure S8 in the ESI). At distances of 3 Å characteristics of attractive interactions were found for all dimers studied, including the CH₃F dimer with its purely repulsive PES (ca. +1 kcal mol⁻¹ at that distance, Figure S7).

In comparison to these intermolecular CF...FC interactions, it is not straightforward to assess if such interactions are attractive or repulsive when they occur intramolecularly, as in compounds **1-3**. Isomer **3** has a slightly larger dipole moment than **4** (3.45 D vs. 3.43 D, at MP2/aug-cc-pVDZ), but **3** is 0.76 kcal mol⁻¹ more stable than **4** at the MP2/aug-cc-pVDZ level (0.74 kcal mol⁻¹ according to CCSD(T)/aug-cc-pVTZ single points).³² Although it is not expected that CF...FC interactions should

stabilise **3** by as much as 0.8 kcal mol⁻¹ in comparison to **4** (cf. the maximum attractive of ca. 0.2 kcal mol⁻¹ in CHF₃ *trans* and CF₄ chelate I dimer arrangements), it may, together with the fact that repulsive C^{δ+}-F^{δ-} dipoles are closer in **4** than in **3**, contribute to some extent for this difference. This interpretation is consistent with both QTAIM and NCI methods, which indicate that this interaction is attractive in **3**. Indeed, Alkorta and Elguero²⁹, as well as Matta *et al.*³³ showed, through QTAIM analysis, that CF...FC interactions in **3** and many derivatives of this compound are attractive, but cannot stabilize this isomer in comparison to the more stable 1,5-difluoronaphtalene which has a zero dipole moment. However, recently Jabłonski,³⁴ indicated that intramolecular CF...FC and other ambiguous attractive/repulsive interactions should be determined on the basis of energy measurement methods, as e.g. the “open-closed” method and isodesmic reactions rather than QTAIM or related methods.

Before we discuss energetics in more detail (*vide infra*), we turn to the possible relation between such CF...FC interactions and J_{FF} SSCCs, important indicators of through-space interactions. The experimental $^4J_{\text{FF}}$ values are 59.0 Hz and of 6.5 Hz for **3** and 1,3-difluorobenzene,³⁵ respectively, the latter being the parent molecule of **5**. This large difference of more than 50 Hz is clearly related to the “through space” CF...FC interaction in **3**. The J_{FF} value in 1,2-difluorobenzene, the parent molecule of **4**, is even more disparate from that in **3** (ca. -21 Hz),³⁵ but this is a three-bond coupling, which may follow a different through-bond mechanism. Del Bene *et al.*³⁶ studied through-bonds $^nJ_{\text{FF}}$ SSCCs in different fluorinated benzenes, and showed that $^3J_{\text{FF}}$ are large and negative for the studied compounds, as for 1,2-difluorobenzene, the $^3J_{\text{FF}}$ value of which is dominated by both PSO and SD terms. By contrast, $^4J_{\text{FF}}$ “may be either positive or negative and large or small depending of the kind of atoms between the C-F bonds” as for 1,3-difluorobenzene, which has an experimental value of 6.5 Hz and is dominated by

the PSO term.³⁶ Although the $^3J_{\text{FF}}$ value in **4** is in agreement with that of its 1,2-difluorobenzene parent molecule, the $^4J_{\text{FF}}$ value in **3** is not in agreement with that in 1,3-difluorobenzene, hence corroborating that an “through space” SSCC transfer mechanism is operating in **3**, but not in **4**. The Ramsey contributions (FC, SD, PSO and DSO terms) are collected for **3-5** in Table 1, indicating that J_{FF} in **3** is dominated by the FC term, while in **4** and **5** it is dominated both by the SD and PSO terms. These findings are in line with the general understanding that “through-space” J_{FF} SSCCs are transferred through the FC term with a positive contribution to J_{FF} .³⁷ Indeed, the contributions to $^4J_{\text{FF}}$ of **3** were previously studied in the literature and it was indicated that its FC value consists of ca. 75 Hz due to “through-space” mechanism and ca. -19 Hz due to a through-bond mechanism.³⁸

Table 1: Theoretical contributions (BHandH/EPR-III level) for $^nJ_{\text{FF}}$ SSCCs in **1-4** [in Hz], and $^nJ_{\text{FF}}$ experimental values from the literature. Values obtained at the SOPPA(CCSD)/EPR-III level are shown in parenthesis.

	1	2	3	4	5
J_{FF}	21.91 (18.88)	34.53 (28.78)	55.21 (53.48)	-6.56 (-11.29)	-4.97 (-1.20)
FC	24.17 (20.74)	35.95 (29.98)	57.51 (51.13)	1.85 (-0.53)	-3.40 (-0.94)
SD	3.74 (2.79)	4.15 (3.22)	-6.07 (-1.40)	22.71 (15.72)	-6.96 (-2.53)
PSO	-6.90 (-5.59)	-6.65 (-5.47)	2.82 (2.81)	-31.25 (-26.62)	6.31 (3.17)
DSO	0.90 (0.94)	1.08 (1.05)	0.94 (0.93)	0.13 (0.14)	-0.92 (-0.91)
$^nJ_{\text{FF}}$ exp.	---	29.0	59.0	-20.8 ^[a]	6.5 ^[a]

^[a] $^nJ_{\text{FF}}$ exp. for **4** and **5** correspond to 1,2-difluorobenzene and 1,3-difluorobenzene, respectively. (calculated $^3J_{\text{FF}} = -13.09$ Hz for 1,2-difluorobenzene).

The significantly different FC contributions to J_{FF} in **3** and **4** are interesting, given that both have rather similar calculated distances between the fluorine atoms (2.617 Å

and 2.726 Å for **3** and **4**, respectively, at the MP2/aug-cc-pVDZ level). However, **3** has parallel C-F bonds, while **4** has an angular relationship between these bonds, with calculated F-C-C angles of 119.5°. Thus, it is not only the distance between the two fluorine atoms that is important in determining the extent of “through-space” coupling in **Type III** intramolecular CF...FC interactions, but also the angular relationship between the C-F bonds.

Based on the well known angular and distance dependence of CF...FC interactions and J_{FF} SSCCs,³⁹ Mallory *et al.*,^{40,41} proposed a lone-pair overlap theory, according to which the “through-space” J_{FF} mechanism in many 1,8-difluoronaphthalene derivatives occur through overlap of the 2p lone-pair orbitals on the fluorine atoms. Confirmed by Contreras *et al.*⁴² and Tuttle *et al.*,³⁸ this model is being used to rationalise not only through-space J_{FF} values, but also “through-space” J_{FN} and J_{PP} couplings.^{43,44} Indeed, plots of the corresponding NBOs indicate that whereas **1-3** have considerable overlap between the fluorine 2p orbitals, whereas **4** does not (Figure 5). Indeed, Natural J-coupling analysis⁴⁵ of the Ramsey Fermi Contact (FC) term indicates that the fluorine 2p lone-pair orbitals give the main contributions to this term in **1** (+33.8 Hz for each F 2p lone pair), **2** (+38.6 Hz and +23.6 Hz for the the different F 2p lone pairs) and **3** (44.1 Hz for each F 2p lone pair, BHandH/EPR-III level). Such contribution is smaller for **4** (+8.8 Hz for each F 2p lone pair) and even negative for **5** (-16.5 Hz and -13.2 Hz for F in the 8 and 6 positions, respectively).

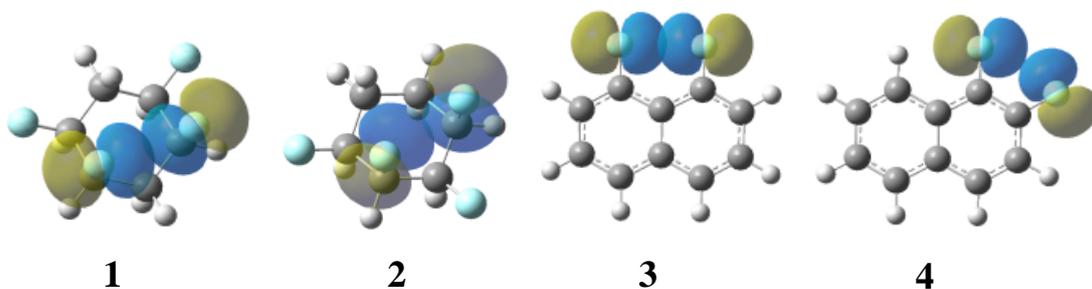


Figure 5: NBO orbital plots for fluorine 2p lone-pair orbitals in compounds **1-4**. Surfaces were obtained with for a isovalue of 0.04 au. Only **1-3** show overlap between the lone-pairs.

This model can explain “through-space” SSCCs, but does not assess fluorine-fluorine interactions as repulsive or attractive.⁴⁰ They can be either, as shown by the results for the $\text{CH}_{4-x}\text{F}_x$ dimers (Figure S7). According to our NCI results, which was here performed for noncovalent interactions, but could also be applied to the covalent framework,¹⁶ the $\text{CF}\cdots\text{FC}$ interaction is attractive in compounds **1-3**. We now turn to a critical analysis of this finding.

Among the two possible chair conformers of 1,3-difluorocyclohexane (compound **6**, Figure 6), the diequatorial conformer **6b** is predicted to be $1.16 \text{ kcal mol}^{-1}$ more stable than the diaxial form **6a** at the MP2/aug-cc-pVDZ level, even though the latter has an attractive $\text{CF}\cdots\text{FC}$ interaction according to the NCI method (Figure 7). The apparent stability of **6b** is presumably due to its smaller dipole moment (2.49 D) in comparison with **6a** (3.63 D). The calculated ${}^4J_{\text{FF}}$ for the latter is 14.25 Hz (consistent with its 3.0 \AA of separation between the fluorine atoms), while it is very small (0.03 Hz) for the diequatorial conformer **6b**, even though this has a “W” geometry of the F-C-C-C-F bonds.

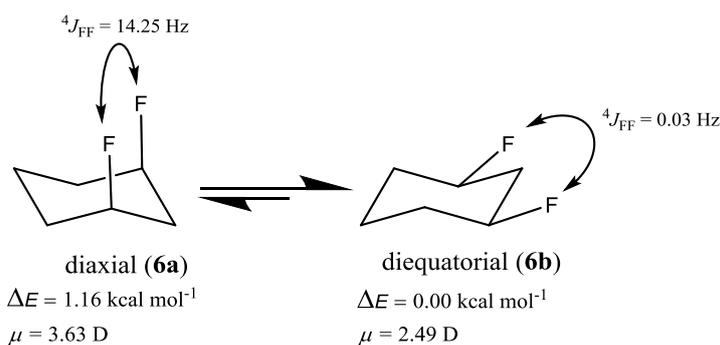


Figure 6: 1,3-difluorocyclohexane (**6**) conformers. ${}^4J_{\text{FF}}$ and relative energies are also indicated.

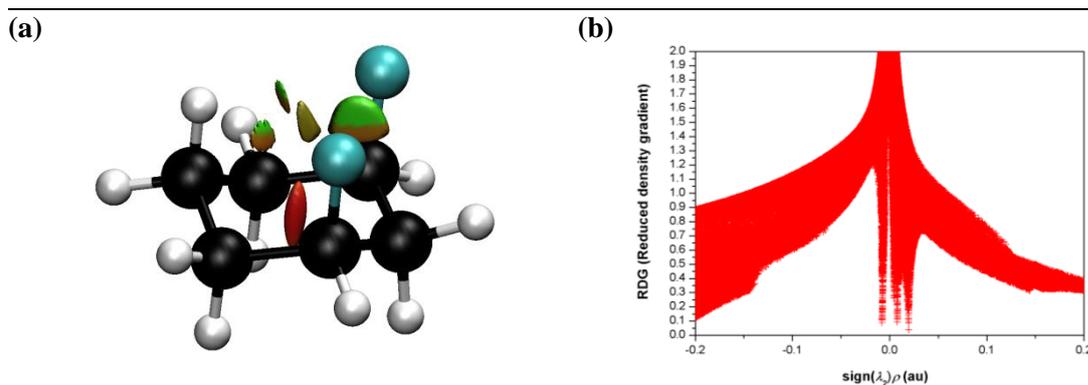
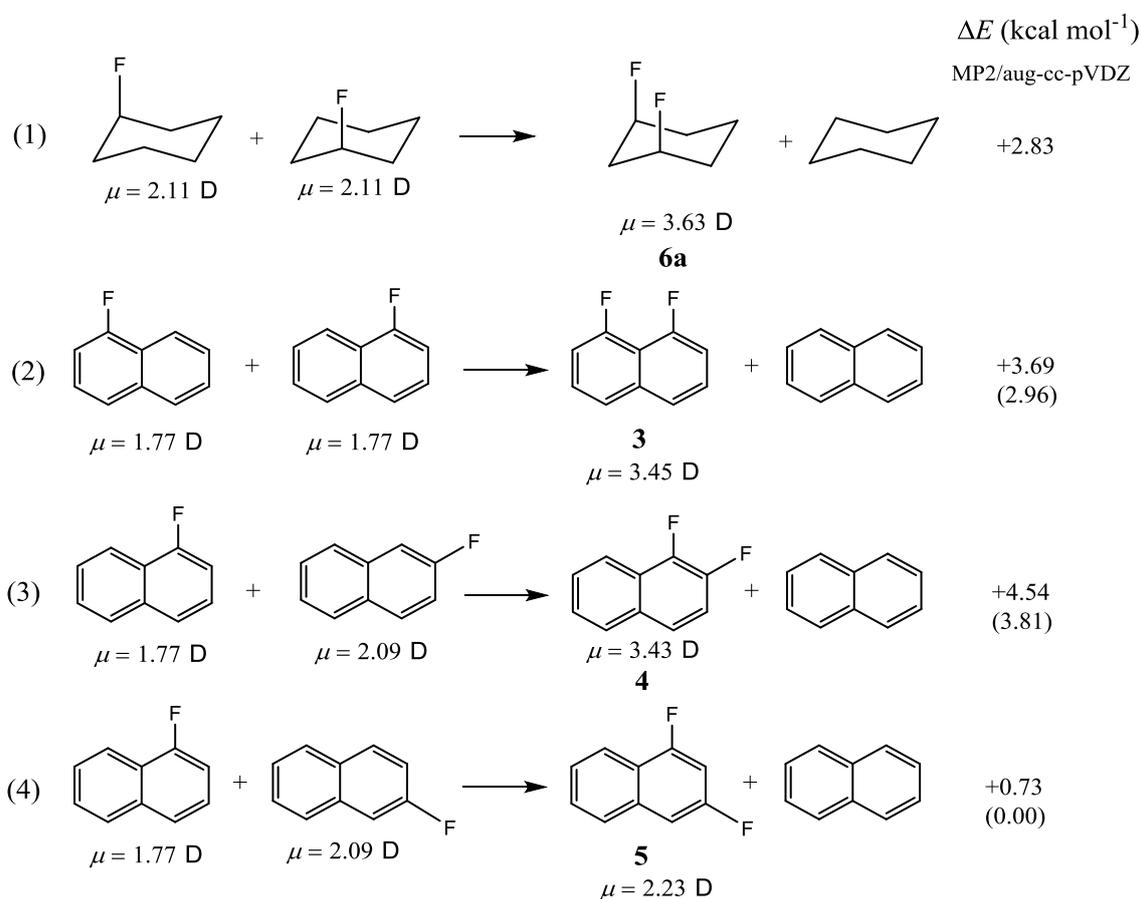


Figure 7: (a) *Diaxial* 1,3-difluorocyclohexane NCI isosurfaces obtained with density gradient (RDG) = 0.5 and blue-green-red color scale ranging from $-0.02 < \text{sign}(\lambda_2)\rho(r) < +0.02$ au at the MP2/aug-cc-pVDZ level. (b) Reduced RDG versus $\text{sign}(\lambda_2)\rho$ for 1,3-difluorocyclohexane.

Isodesmic reactions may indicate intramolecular non-covalent stabilization/destabilization energies and are commonly used in the literature for such purpose.⁴⁶ Isodesmic reaction (1) for formation of **6a** from two monofluorocyclohexanes (Scheme 1) would seem suitable to quantify the interaction between the two axial fluorines. This reaction is rather strongly endothermic, by $2.83 \text{ kcal mol}^{-1}$ at the MP2/aug-cc-pVDZ level, indicating that the $\text{CF}\cdots\text{FC}$ interaction in **6a** would be repulsive, in apparent contradiction with the NCI results. The same is found for the formation of **3** through isodesmic reaction (2), which is predicted to be endothermic by $3.69 \text{ kcal mol}^{-1}$. While part of this apparent destabilisation may again stem from the higher dipole moments of the difluoro products compared to the monofluoro reactants, this should not be the overriding cause in this case, because the

overall dipole moments along the reactions (i.e. the sums on both sides) change only little (see Scheme 1). It rather seems to be the expected dipolar repulsion between the two parallel C-F bonds (type III in Figure 2) that is reflected in the endothermicities of these isodesmic reactions. The same is found for isomer **4** (equation (3) in Scheme 1), although the isodesmic reactions reproduce the relative energies between isomers **3** and **4** quite well (compare the difference between the $\Delta\Delta E$ values given in parentheses in Scheme 1, 0.85 kcal mol⁻¹, with the actual energy difference, 0.76 kcal mol⁻¹). The higher destabilisation of **4** compared to **3** may be related to the closer proximity of the F-bonded (i.e. two positively charged) carbon atoms on the former.



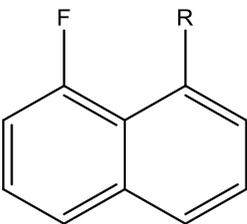
Scheme 1: Isodesmic reactions for compounds **3-6**. Energies (in kcal mol⁻¹) and dipole moments obtained at the MP2/aug-cc-pVDZ level are also indicated. The $\Delta\Delta E$ values relative to **5** are indicated in parenthesis.

That **4** is less stable than **3** due to electrostatics and that the CF \cdots FC interaction in **3** is indeed repulsive as indicated by isodesmic reactions is supported by NBO analysis. It is worth to mention that recently, contrary to QTAIM results, Weinhold *et al.*⁴⁷ showed by using the NBO method that CH \cdots HC interactions in *cis*-2-butene and related compounds are repulsive rather than attractive. By performing a Natural Steric Analysis (NSA)⁴⁸, we find that the overlap between the fluorine 2p lone-pair orbitals ($n_F \rightarrow n_F$ interactions) is repulsive by 0.93 kcal mol⁻¹ in **3** at the B3LYP/aug-cc-pVDZ level and that it is inexistent or smaller than 0.1 kcal mol⁻¹ in compounds **1**, **2** and **4**. On the other hand, the Natural Coulomb Electrostatic (NCE) Analysis,²⁷ which provides the potential Coulomb electrostatic energy by using natural charges with the classical Coulomb equation: ($E_{NCE} = \sum_{A,B} Q_A Q_B / R_{AB}$), indicates that **4** has the less negative electrostatic energy ($E_{NCE} = -160.0$ kcal mol⁻¹) in comparison with **3** ($E_{NCE} = -231.1$ kcal mol⁻¹) and **5** ($E_{NCE} = -244.9$ kcal mol⁻¹) and, hence, suffers the strongest electrostatic repulsions, in accordance with its closer proximity between $\delta^+C-\delta^-F$ bonds. By the same token, the Natural Resonance Theory (NRT)⁴⁹ indicates that the CF \cdots FC bond order in all compounds **1-5** is zero. Thus, the NBO method indicates that **3** should be more stable than **4** due to electrostatic interactions rather than an attractive CF \cdots FC interaction formation.

It is also well known that ¹⁹F atom chemical shifts (δ) are shielded in case the probed fluorine atom participates in attractive interactions and are rather deshielded in case it participates in repulsive interactions when in ipso positions in naphthalene rings.⁵⁰ Table 2 compares the experimental and theoretical δ values of **3** with 1-fluoronaphthalene and 1-fluoro-8-methylnaphthalene. Theoretical (BHandH/6-311+G**) and experimental values are in reasonable accordance, showing the same trends in the δ values, and indicate that the F atom in **3** is more deshielded than in 1-

fluoronaphthalene with its smaller H atom, but more shielded in 1-fluoro-8-methylnaphthalene, in accordance with the bigger size of the CH₃ group in the latter. Thus, both experimental and theoretical calculations are in agreement indicating that **3** fluorine atoms are more deshielded than the fluorine in 1-fluoro-8-methylnaphthalene and, hence,⁵⁰ that fluorine atoms in **3** interact one with each other repulsively.

Table 2: Experimental ¹⁹F chemical shift (δ_F in ppm) obtained in CDCl₃ and theoretical δ_F obtained at the BHandH/6-311+G** level on MP2/aug-cc-pVDZ optimised geometries .

Compound	¹⁹ F chemical shifts			
	δ_F (Exp)	$\Delta\delta_F$ (Exp)	δ_F (Theo) ^[c]	$\Delta\delta_F$ (Theo) ^[c]
 R = H ^[a]	-123.9	0.0	-138.8	0.0
R = CH ₃ ^[a]	-112.8	+11.1	-122.3	+16.6
R = F ^[b]	-115.8	+8.1	-125.9	+12.9

^[a] obtained from reference ⁵⁰

^[b] obtained from reference ⁵¹

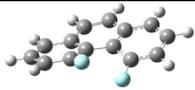
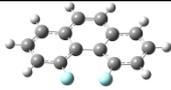
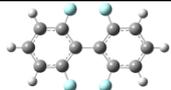
^[c] obtained from the calculated CFCl₃ ¹⁹F isotropic shielding tensor (σ_{CFCl_3}) minus the naphthalene derivative theoretically obtained ¹⁹F σ .

Classification of CF...FC interactions as attractive according to NCI may thus not always be unambiguous. As emphasized by Otero-de-la-Roza *et al.*⁵² “care is recommended when interpreting the sign of λ_2 in very weak interactions, because in these cases the sign might depend on the method of calculation”. NCI can identify non-bonded attractions as repulsive, e.g. for the CX₄ dimers at short CF...FC distances (see the NCI plot at 2 Å in Figure S8 in the ESI; the repulsive nature is apparent through the red ring around an otherwise green/blue isosurface). To probe whether the NCI method would also label intramolecular interactions as repulsive, we included 4,5-difluorophenanthrene (**7**) and 2,2',6,6'-tetrafluorobiphenyl (**8**) in our study. The corresponding H-H interactions in the parent biphenyl have led to intense debates in the

literature in order to characterize them either as repulsive or attractive.^{53,54} There are also debates in the literature about the nature of phenanthrene H-H interactions.⁵⁵ By changing the hydrogen atoms for fluorine atoms, one may expect increasingly repulsive interactions. Indeed, the global minimum of **7** has a twisted geometry, with a C(F)-C-C-C(F) dihedral angle value of 23.6 degrees as the equilibrium geometry (see sketch in Table 2), which is 2.61 kcal mol⁻¹ more stable than the planar geometry that has a negative frequency and, hence, is a transition state. By the same token the planar geometry of **8** has 2 negative frequencies and is a second-order saddle point that is 30.7 kcal mol⁻¹ less stable than the twisted equilibrium geometry (Table 2).

The CF...FC distances in those planar transition state geometries are very short at the MP2/aug-cc-pVDZ level (2.34 Å and 2.22 Å for **7** and **8**, respectively, Table 3). For these planar geometries, NCI indeed affords isosurfaces with attractive contributions (blue colour) surrounded by repulsive contributions (rings of red colour, Figure 8). These interactions would overall be classified as repulsive, as had been indicated for water dimers for very short OH...O interactions in the literature,³¹ or for the abovementioned CX₄ dimers (Figure S8 in the ESI). For these strongly repulsive systems, the assessment based on NCI is thus consistent with the energetics. However, quantification of the NCI data appears to be difficult: despite vastly different barriers for planarisation, 2.6 kcal mol⁻¹ and 30.7 kcal mol⁻¹ for **7** and **8**, respectively (i.e. 15.4 kcal mol⁻¹ per CF...FC interaction in the latter), both show very similar NCI plots, in terms of the isosurfaces (Figure 8a,c) as well as the raw RDG plots (Figure 8b,d).

Table 3: Relative energies (kcal mol⁻¹), C(F)-C-C-C(F) dihedral angles (degrees) and CF...FC distances (angstroms) values for the twisted and planar geometries of the fluorinated derivatives of phenanthrene and biphenyl.

	7 (twisted)	7 (planar)	8 (twisted)	8 (planar)
				
ΔE	0.00	2.61	0.00	30.7
φ [C(F)-C-C-C(F)]	23.6	0.00	59.6	0.00
CF \cdots FC	2.433	2.337	2.878	2.223

The twisted geometries of **7** and **8** show NCI isosurfaces corresponding to weakly attractive CF \cdots FC interactions (Figure 9). In accordance with the very small distance between the fluorine atoms in twisted phenanthrene **7** (2.43 Å), the experimental J_{FF} is very large: 170Hz.⁵⁶ In this way, if attractive, as indicated by the NCI method, the CF \cdots FC is an excellent pathway for transmission of the J_{FF} SSCC. The experimental J_{FF} for 2,2'-difluorobiphenyl (the parent molecule of **8**) is 16.5 Hz,⁵⁶ also in accordance with the calculated larger F \cdots F distance of 2.88 Å in twisted **8**.

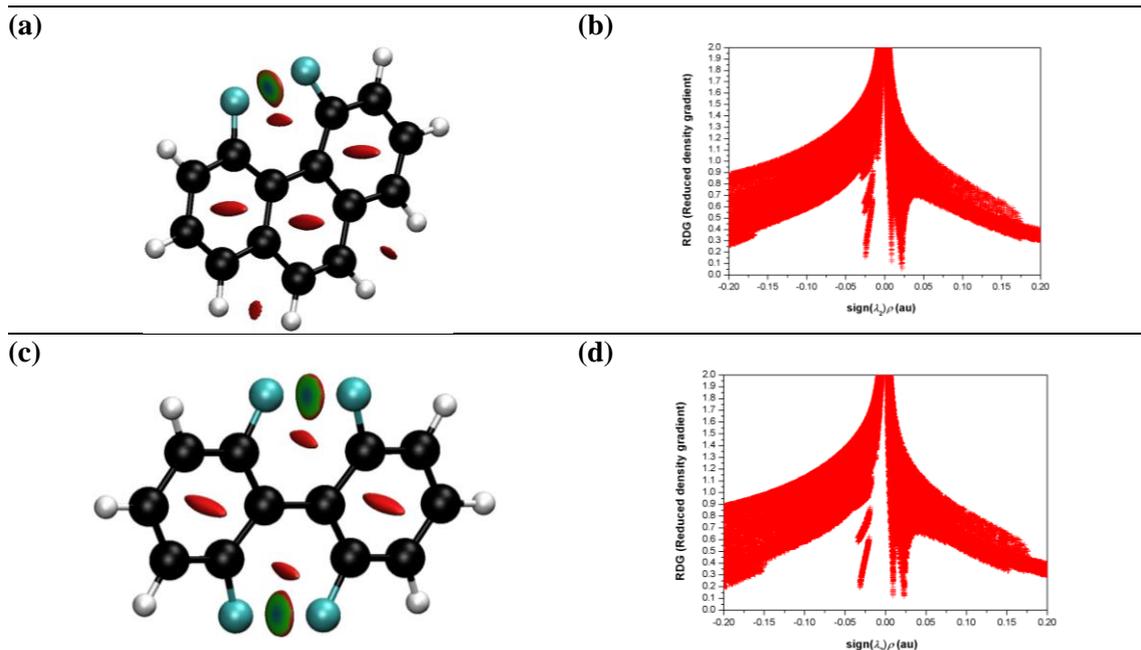


Figure 8: (a) NCI isosurfaces for planar **7** obtained with $\text{RDG} = 0.5$ and blue-green-red color scale ranging from $-0.02 < \text{sign}(\lambda_2)\rho(r) < +0.02$ au at the MP2/aug-cc-pVDZ level. (b) Reduced density gradient (RDG) versus $\text{sign}(\lambda_2)\rho$ for planar **7**. (c) NCI isosurfaces for planar **8** obtained with $\text{RDG} = 0.5$ and blue-green-red color scale ranging from $-0.02 < \text{sign}(\lambda_2)\rho(r) < +0.02$ au at the MP2/aug-cc-pVDZ level. (d) Reduced density gradient (RDG) versus $\text{sign}(\lambda_2)\rho$ for planar **8**.

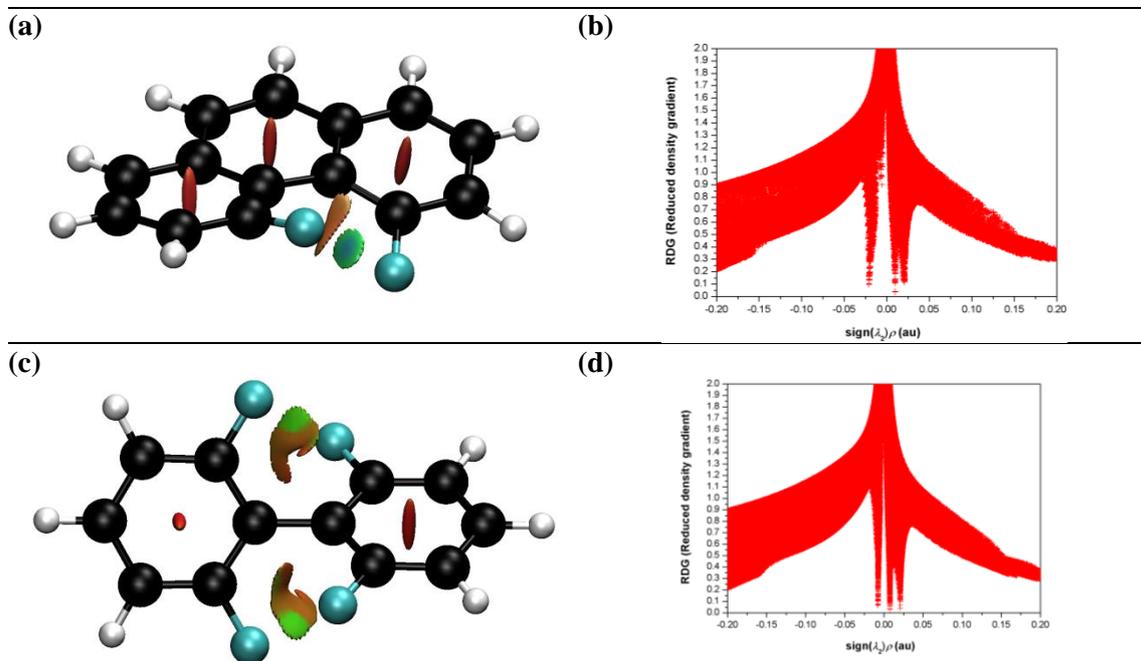
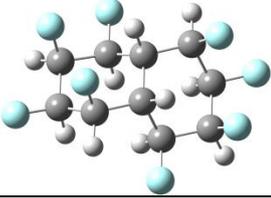
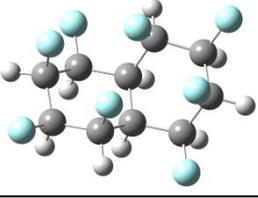


Figure 9: (a) NCI isosurfaces for twisted **7** obtained with $\text{RDG} = 0.5$ and blue-green-red color scale ranging from $-0.02 < \text{sign}(\lambda_2)\rho(r) < +0.02$ au at the MP2/aug-cc-pVDZ level. (b) Reduced density gradient (RDG) versus $\text{sign}(\lambda_2)\rho$ for twisted **7**. (c) NCI isosurfaces for twisted **8** obtained with $\text{RDG} = 0.5$ and blue-green-red color scale ranging from $-0.02 < \text{sign}(\lambda_2)\rho(r) < +0.02$ au at the MP2/aug-cc-pVDZ level. (d) Reduced density gradient (RDG) versus $\text{sign}(\lambda_2)\rho$ for twisted **8**.

As a final example of close F...F contacts enforced through steric constraints we looked at an octafluorodecaline with all CF bonds in syn orientation (i.e. two units of **2** fused together at the CH-CH bridge) with a *cis* orientation of the two H atoms at the fused C-C bond.⁵⁷ The molecule can exist in two conformers that can be interconverted through concerted inversion of both chairs. In one of the conformers the pairs of axial F atoms in each ring are pointing away from each other, in the other they are pointing toward each other (**9-dist** and **9-prox**, respectively, Table 4). The "proximal" conformer has the F atoms from one ring approaching the F atoms in the other, thus forming many CF...FC interactions (a total of 5 attractive ones, according to the NCI isosurfaces in Figure 10a), whereas the "distal" conformer has only 2 (one within each cyclohexane ring, as in the parent **2**). Despite these many allegedly attractive CF...FC interactions, **9-prox** is 11.25 kcal mol⁻¹ less stable than **9-dist**. Again, the higher dipole moment in the former (Table 4) may contribute to its destabilisation, but it is clear that a large number of CF...FC interactions that are classified as attractive through the NCI method does not translate into noticeable energetic stabilisation.

Table 4: 9 *trans* and *cis* geometry representations and relative energies (kcal mol⁻¹) and dipole moments (D) obtained at the MP2/aug-cc-pVDZ level.

	9-dist	9-prox
		
ΔE	0.00	11.25
μ	5.12	8.17

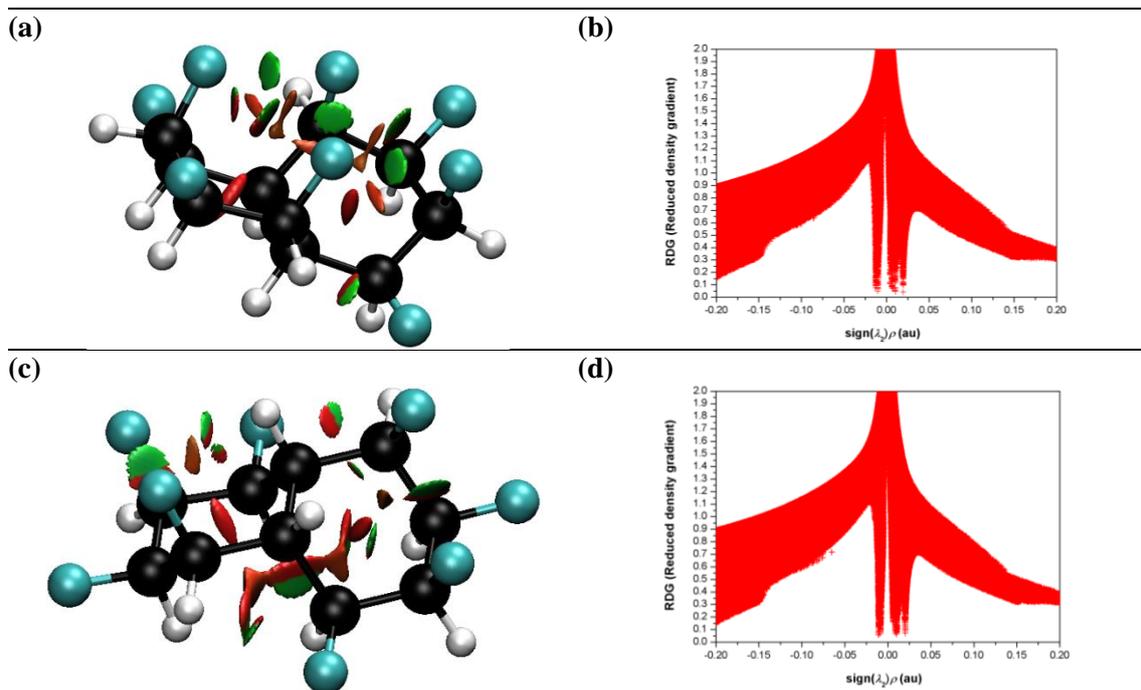


Figure 10: (a) NCI isosurfaces for **9-prox** obtained with RDG = 0.5 and blue-green-red color scale ranging from $-0.02 < \text{sign}(\lambda_2)\rho(r) < +0.02$ au at the MP2/aug-cc-pVDZ level. (b) Reduced density gradient (RDG) versus $\text{sign}(\lambda_2)\rho$ for **9-prox**. (c) NCI isosurfaces for **9-dist** obtained with RDG = 0.5 and blue-green-red color scale ranging from $-0.02 < \text{sign}(\lambda_2)\rho(r) < +0.02$ au at the MP2/aug-cc-pVDZ level. (d) Reduced density gradient (RDG) versus $\text{sign}(\lambda_2)\rho$ for **9-dist**.

4. Conclusions

We have applied a recently proposed electron-density based method for the analysis of noncovalent interactions, NCI, to a variety of organofluorine molecules. In essentially all ground-state minima, close CF...FC contacts that are encountered are classified as attractive by this method. This includes examples with *syn*-periplanar orientation of the CF bond dipoles such as diaxial CF bonds in cyclohexanes or peri CF bonds in naphthalene, where electrostatic repulsion would be expected. When the interactions between these *syn*-periplanar CF bonds are assessed through suitable isodesmic equations, no energetic stabilisation is found, in fact all turn out to be repulsive according to this criterion. Repulsive interactions are only recognised as such by NCI when the repulsion is very strong, as for example in planar o,o' fluorinated biphenyl. Thus, if attractive CF...FC interactions are identified by the NCI method, it should be kept in mind that these can be weak and may not govern actual isomer stabilities or conformational preferences. NCI should best be used in conjunction with other criteria, for instance based on energetic or spectroscopic properties. For the organofluorine compounds of this study, NBO analysis and experimental/theoretical ¹⁹F chemical shifts support the results from the isodesmic reactions and indicate that the CF...FC interactions are rather repulsive. This ambiguity notwithstanding, CF...FC interactions are important factors in organofluorine chemistry, as they influence through-space J_{FF} coupling constants and may contribute to the observed biological and physico-chemical properties of particular molecular systems.

Supporting Information Available: Additional graphical and tabular material, as well as optimised coordinates of all species discussed in this paper. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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