**Understanding the influence of the trifluoromethyl group on the chemo-, regio-, and stereoselectivity of [3+2]-cycloadditions of thiocarbonyl   
*S*-methanides with α,β-unsaturated ketones. A molecular electron density theory study**

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**Abstract**

Experimentally (G. Mlostoń et al., J. Fluor. Chem. 190 (2016) 56–60), it has been found that the type of the obtained cycloadduct of the [3+2] cycloaddition (32CA) reaction of thiocarbonyl *S*-methanides with α,β-unsaturated ketones depends strongly on the location of the trifluoromethyl group. In the case of enones containing the CF3CH=CH moiety, the 32CA reaction occurs chemo- and regioselectively onto the C=C double bond giving trifluoromethylated tetrahydrothiophene derivatives. On the other hand, enones containing the CF3–C=O fragment react as carbonyl heteroethylenes leading to trifluoromethylated 1,3-oxathiolanes also in a chemo- and regioselective manner. Our aim in the present work is to perform a theoretical study of the all chemo-, regio-, and stereo-isomeric reaction paths of these 32CA reactions within the Molecular Electron Density Theory. Activation Gibbs free energies, calculated at the B3LYP/6-311G(d,p) level in tetrahydrofurane at -40°C, show that the *ortho*/*endo* reaction path giving the trifluoromethylated tetrahydrothiophene is more favoured, while the *meta/endo* reaction path leading to trifluoromethylated 1,3-oxathiolanes is more preferred in total agreement with experimental findings. The low activation barriers in combination of the Electron Localization Function topological analysis of the most relevant points along the Intrinsic Reaction Coordinate reveals the *pseudomonoradical* character of the studied 32CA reactions.

**KEYWORDS**:Thiocarbonyl *S*-methanide ; trifluoromethyl group ; [3+2] cycloaddition reactions ; selectivity ; molecular electron density theory.

**1. Introduction**

Due to the great variety and availability of three-atom-components (TACs) and ethylene derivatives, [3+2] cycloaddition (32CAs) reactions are widely used for the preparation of five-membered carbocyclic and heterocyclic compounds of chemical, pharmacological and biological interests.[1-4] A 32CA reaction occurs when a TAC reacts with an unsaturated bond to generate a five-membered cycloadduct. Conventionally, most of chemists name this kind of cycloaddition reactions as ‘*1,3-dipolar* ones’ to display involvement of the ‘*1,3-dipole’* species in the reaction toward unsaturated bonds to form a five-membered cycloadduct. Nevertheless, using ‘TAC’ and ‘[3+2]’ terms instead of ‘*1,3-dipole’* and ‘*1,3-dipolar’* expressions, respectively, are conceptually more adequate as many TACs dos not present a zwitterionic structure.[5,6]

Thiocarbonyl ylides (TCYs)[7] belong to the family of sulfur-centered TACs characterized by the presence of two *sp2* carbon atoms attached to the central sulfur atom. TCYs were established as key intermediates for the preparation of sulfur-containing heterocyclic compounds and the conventional methods for the preparation of TCYs and their chemical reactivity have been widely reviewed.[8-12] The most important contributions to the chemistry of TCYs were made by Huisgen and co-workers[13] and a rich bibliography of the 32CA reactions can be found in the literature. The participation of TCYs of benzo[c]thiophenes was firstly recognized by Pedersen[14] and a profound advance into the chemistry of TCYs was achieved by Kellogg and al..[15] Huisgen and al.[16] also studied the stereospecificity of 32CA reactions of TCYs with N-Sulfinylamines,[16a] thiobenzophenone,[16b] α,β unsaturated esters and nitriles,[16c] 1,2-bis(trifluoromethyl)- ethene-1,2-dicarbonitrile,[16d] thiones,[16e] and 2,3-Bis(trifluoromethyl) fumaronitrile.[16f] 32CA reactions of TCYs, generated from adamantanethione S-Methylide, were also studied by Huisgen and al.[17] and the first 32CA of fullerene C60 with a TCY has been realized by Ishida and al.[18]

Recently, the 32CA reactions of TCYs involving a large variety of dipolarophiles were extensively studied by Mlostoń and co-workers,[19] including sulfur dioxide,[19a] thiocarbonyl derivatives,[19b] 3,3,3-trifluorobyruvic acid derivatives,[19c] N,N’-(thiocarbony1) diimidazole.[19d] The dimerisation of TCYs was also reported by Mlostoń and al.[20,21] and El-Sayed and al..[22]

Despite the broad bibliography devoted to experimental works on the 32CA reactions of TCYs, only few theoretical and computational studies on this subject can be found in the literature. For instance, Domingo and al.[23] performed a theoretical study of the 32CA reaction between TCYs and tetracyanoethylene. Asr and al.[24] also performed a theoretical study of the 32CA reactions of hetaryl thioketones at the B3LYP/6-31G(d) computational level. Houk and al.[25] carried out a theoretical study of the 32CA reactions of TCYs with dimethyl 2,3-dicyanofumarate and 2,3-dicyanomaleate at the B3LYP/6-31+G(d) level of theory. It is important to note that, based on experimental observations and quantum chemistry calculations, 32CA reactions were mechanistically classified into three categories: (*i*) the “concerted” process, involving simultaneous formation of the two new sigma bonds; (*ii*) a stepwise diradical mechanism, involving a diradical intermediate; and (*iii*) a stepwise dipolar mechanism, involving a zwitterionic intermediate. However, it was established that most of 32CA reactions take place through a one-step mechanism in which the formation of the two sigma bonds is more or less asynchronous.[6,26]

It is well-known that the elucidation of reaction mechanism is a great importance in physical organic chemistry. In 2016 Domingo proposed the Molecular Electron Density Theory[27] (MEDT) for the study of the reactivity in Organic Chemistry, in which changes in the electron density, but not MO interactions, as the Frontier Molecular Orbital (FMO) theory proposed,[28] are responsible for the feasibility of an organic reaction. In MEDT, several quantum-chemical tools, such as the analysis of the Conceptual Density Functional Theory(CDFT) indices,[29,30] and the topological analysis of the Electron Localisation Function[31] (ELF) and the Quantum Theory of Atoms in Molecules[32] (QTAIM) are used to rigorously characterise the molecular mechanism of the studied reactions.[27]

Recent advances made in the theoretical understanding of 32CA reactions based on MEDT have allowed establishing a very good correlation between the electronic structure of TACs and their reactivity.[6] Accordingly, depending on the electronic structure of the simplest TACs, *pseudodiradical*, *pseudomonoradical*, carbenoid and zwitterionic, 32CA reactions have been classified into *pseudodiradical* type *(pdr-type)*, *pseudomonoradical* type *(pmr-type)*, carbenoid type (*cb-type)* and zwitterionic type *(zw-type)* reactions, respectively.[6]

Due to the growing interest of fluorinated heterocyclic compounds, various fluorinated compounds were involved as ethylene partners in the 32CA reactions of TCYs for the preparation of novel classes of five-membered heterocycles.[33,34] Recently, Mlostoń and al.[34] reported the 32CA reactions of thiocarbonyl *S*-methanides with two different fluorinated enones (see Scheme 1). Interestingly, the products of these 32CA reactions were found strongly depend on the position of the activating CF3 group on the ethylene derivative. Thus, in the case of enones containing the CF3CH=CH moiety, the 32CA reaction takes place chemo- and regioselectively onto the C=C double bond to give trifluoromethylated tetrahydrothiophenes, while in the case of enones containing the CF3–C=O unit, the carbonyl group act as heteroethylene leading to trifluoromethylated 1,3-oxathiolanes, also in a chemo- and regioselective manner (Scheme 1).

The aim of the present work is to perform a MEDT study of the 32CA reactions of thiocarbonyl *S*-methanides experimentally studied by Mlostoń[34] in order to understand the role of the trifluoromethyl group CF3 on the mechanism and on the chemo-, regio- and stereoselectivity of the 32CA reactions of diphenylthiocarbonyl *S*-methanide **TCY** with α,β-unsaturated ketones 3-trifluoromethylated 1-phenylprop-2-en-1-one **FCC** (*reaction #1*)and with 1-trifluoromethylated 3-phenylprop-2-en-1-one **FCO** (*reaction #2*) (Scheme 1). For this purpose, all competitive reaction paths involved in these 32CA reactions were investigated and analysed, namely, the two C=C/C=O chemoselective reaction paths, the two *ortho/meta* regioselective reaction paths and the *endo/exo* stereoisomeric approach modes. ELF topological analyses along the most favourable reactive channels were performed to put in evidence the reactivity type of **TCY** participating in these 32CA reactions.

**< Scheme 1 >**

**2. Computational methods**

DFT calculations were carried out with the B3LYP[35] exchange–correlation functional, together with the standard 6-311G(d,p) basis set,[36] implemented in the Gaussian 09 package.[37] This level of theory has been proven to be suitable for the analysis of both geometric and electronic properties of 32CA reactions. Optimisations were performed using the Berny analytical gradient optimisation method.[38] The stationary points were characterised by frequency computations in order to verify that TSs have one and only one imaginary frequency. The IRC paths[39] were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second order Gonzalez-Schlegel integration method.[40] Solvent effects of tetrahydrofuran (THF) were taken into account using the polarisable continuum model (PCM) developed by Tomasi’s group[41] in the framework of the self-consistent reaction field (SCRF).[42]

The global electron density transfer[43] (GEDT) was computed from natural population analysis[44] (NPA), of the atoms belonging to each framework (f) at the TSs; i.e. GEDT (f)= The sign indicates the direction of the electron density flux in such a manner that positive values mean a flux from the considered framework to the other one. CDFT indices[29,30] were calculated using the equations given in reference 30.

The ELF[45] study was performed with the Multifwn program[46] for some selected structures of the potential energy surface.

**3. Results and discussion**

**3.1 Analysis of the potential energy surface of the 32CA reactions of TCY with FCC and FCO**

First, the chemo-, regio-, and stereoselectivity of two 32CA reactions of **TCY** reactions are studied. The first reaction is between **TCY** and 3-trifluoromethylated 1-phenylprop-2-en-1-one **FCC**, *reaction #1*, and the second reaction is between **TCY** and 1-trifluoromethylated 3-phenylprop-2-en-1-one **FCO**, *reaction #2*, (see Scheme 1)**.**

Due to the presence of two unsaturated double bonds, C=C and C=O, on **FCC** and **FCO** moieties**,** and the asymmetry of the TAC, **TCY**, different competitive reaction paths are feasible. A total of eight reaction paths were investigated and analysed for each 32CA reaction. These reaction paths correspond to the two possible C=C/C=O chemoselective reaction paths, the two possible *ortho*/*meta* regioselective reaction paths and the two possible *endo/exo* stereoselective reaction paths. As solvent effects and temperature on 32CA reactions are well-known and they have received considerable attention,[47-49] our calculations were also performed in gas phase and in THF at -40°C to mimic experimental conditions.[34]

**3.1.1 32CA reaction of TCY with FCC (*reaction #1* )**

For the 32CA reaction of **TCY** with **FCC** (see Scheme 1), eight TSs were localized and characterized. They are denoted: **TS-FCC-CC-on**, **TS-FCC-CC-ox**, **TS-FCC-CC-mn**, **TS-FCC-CC-mx**, **TS-FCC-CO-on**, **TS-FCC-CO-ox**, **TS-FCC-CO-mn**, **TS-FCC-CO-mx** and the corresponding methanone and oxathiolane cycloadducts are denoted: **CA-FCC-CC-on**, **CA-FCC-CC-ox**, **CA-FCC-CC-mn**, **CA-FCC-CC-mx**, **CA-FCC-CO-on**, **CA-FCC-CO-ox**, **CA-FCC-CO-mn**, **CA-FCC-CO-mx**, respectively (see Scheme 2). The gas phase energies and the Gibbs free energies in THF at -40°C are summarized in Table 1.

**< Scheme 2 >**

The calculated activation and reaction energies, given in Table 1, clearly show that the C=C *ortho/endo* reaction path yielding to the formation of the methanone **CA-FCC-CC-on**, *via* **TS-FCC-CC-on**,is favoured both kinetically and thermodynamically.Indeed, **TS-FCC-CC-on** is located only 1.77 kcal/mol above reactants, in gas phase. The calculated activation Gibbs free energy in THF for **TS-FCC-CC-on** is the lowest one, 13.04 kcal/mol. Moreover, the calculated Maxwell-Botlzmann populations, in THF, reveal that **TS-FCC-CC**-**on** and **TS-FCC-CC-ox** are predominant by 66.47% and 33.53%, respectively, and the populations of the remaining TSs are negligible, indicating that the C=C *ortho/endo* reaction path is the most kinetically favoured one.On the other hand, the calculated Gibbs free energies in THF also show that C=C *ortho/endo* reaction path, yielding to the formation of the favoured **CA-FCC-CC**-**on** is the most exergonic reaction path by -53.23 kcal/mol. Therefore, **CA-FCC-CC-on** is predicted to be the most, thermodynamically, favoured cycloadduct with a population of 81.76% in THF (Table 1). These results clearly show that the C=C chemoselectivity is more favoured than the C=O one as expected experimentally for *reaction #1*, and the major cycloadduct, namely **CA-FCC-CC-on,** is formed via the *ortho/meta* reaction path. The Gibbs free energy profiles for the 32CA reaction of **TCY** with **FCC**, in THF at -40°C, are schematized in Figure 1. The geometries of the eight TSs corresponding to the possible pathways (*reaction #1*) prepared using CYLView,[50] are given in Figure 2. The XYZ cartesian coordinates of all optimized structures, in gas phase and in THF, are given in the Electronic Supplementary Information (ESI).

**< TABLE 1 >**

**< Figure 1 >**

**< Figure 2 >**

**3.1.2 32CA reaction of TCY with FCO (reaction #2 )**

For the 32CA of **TCY** with **FCO** (see Scheme 1), eight TSs were also localized, namely, **TS-FCO-CC-on**, **TS-FCO-CC-ox**, **TS-FCO-CC-mn**, **TS-FCO-CC-mx**, **TS-FCO-CO-on**, **TS-FCO-CO-ox**, **TS-FCO-CO-mn**, **TS-FCO-CO-mx,** and the corresponding methanones and oxathiolanes are: **CA-FCO-CC-on**, **CA-FCO-CC-ox**, **CA-FCO-CC-mn**, **CA-FCO-CC-mx**, **CA-FCO-CO-on**, **CA-FCO-CO-ox**, **CA-FCO-CO-mn**, **CA-FCO-CO-mx**,respectively (see Scheme 3). The gas phase energies and Gibbs free energies in THF at -40°C for *reaction #2* are summarized in Table 2. The calculated activation and reaction energies, given in Table 2, point out that the C=O *meta/endo* reaction path yielding to the formation of the oxathiolane **CA-FCO-CO-mn**,*via* **TS-FCO-CO-mn**,is kinetically favoured both in gas phase and in solution. The gas phase calculated activation energies for **TS-FCO-CO-mn**, **TS-FCO-CO-mx**, **TS-FCO-CC-mx** are 2.31, 2.06, and 2.32 kcal/mol, respectively. The calculated activation Gibbs free energies, including entropic and solvent effects, for **TS-FCO-CO-mn**, **TS-FCO-CO-mx, TS-FCO-CC-mx** are 14.61, 14.91, and 15.27 kcal/mol, respectively. The estimated populations of these TSs in THF are: 77.36% (**TS-FCO-CO-mn)**, 16.34% (**TS-FCO-CO-mx**), and 6.25% (**TS-FCO-CC-mx).** The populations of the remaining TSs are negligible. These results indicate that the C=O *meta/endo* reaction path, yielding to the formation of **CA-FCO-CO-mn** is the most kinetically favoured one.

The calculated Gibbs free energies in THF also show that all the studied reaction paths are exergonic. Nevertheless, **CA-FCO-CO-mx** is predicted to be the most, thermodynamically, favoured cycloadduct although the difference, in Gibbs free energy, between **CA-FCO-CO-mx**, **CA-FCO-CO-mn**, **CA-FCO-CC-mx** is very small. These results clearly show that the C=O chemoselectivity is more favoured the C=C one, as expected experimentally for *reaction #2* and the major cycloadduct, **CA-FCO-CO-mn,** is kinetically formed via the *meta/*endo reaction path (Table 2). The Gibbs free energy profiles for the 32CA reaction of **TCY** with **FCO**, in THF at -40°C, are schematized in Figure 3. The geometries of the eight TSs corresponding to the possible reaction paths (*reaction #2*) are given in Figure 4. The XYZ cartesian coordinates of all optimized structures in gas phase and in THF are given in the ESI.

**< Scheme 3 >**

**< TABLE 2 >**

**< Figure 3 >**

The geometries of the TSs involved in the 32CA reaction of **TCY** with **FCO** are given in Figure 4. All TS are associated to asynchronous bond formation processes in which the formation of the single bond involving the non-substituted carbon of **TCY** appears more advanced.

**< Figure 4 >**

From the energy calculations given in Tables 1-2, it can be concluded that the chemoselectivity (C=C *vs.* C=O) depends on the location of the trifluoromethyl group. In the case of enone containing the CF3CH=CH moiety, the 32CA reaction with **FCC** (*reaction* *#1*) occurs chemo- and regioselectively onto the C=C double bond to give trifluoromethylated tetrahydrothiophene derivatives. By contrast, in the case of enone containing the CF3–C=O moiety, the 32CA reaction with **FCO** (*reaction* *#2*) takes place chemo- and regioselectively onto the C=O double bond leading to trifluoromethylated 1,3-oxathiolane derivative. We note that the favoured regioselectivity corresponds to bond formation between the non-substituted carbon atom of **TCY** and the carbon atom which bearing the CF3 group in fluorinated enones **FCC** and **FCO**. By contrast, the *endo* stereoselectivity is preferred both for *reaction #1* and *reaction #2*.

* 1. **Analysis of the CDFT-based reactivity indexes**

Analysis of the reactivity indices defined within the CDFT is a powerful tool to understand the reactivity of organic molecules participating in polar reactions.[30] Consequently, an analysis of the CDFT-based reactivity indices of the isolated reactants was performed.The global properties (electronic chemical potential *μ*, chemical hardness *η*, electrophilicity *ω* index and nucleophilicity *N* index of **TCY**, **FCC** and **FCO** were calculated (Table 3).

**<TABLE 3 >**

It turns out that the electronic chemical potential *µ*[51] of **TCY**, **-**3.44eV**,** is higher than that of **FCC**, **-**5.15 eV, and **FCO** ,**-**4.93 eV, indicating that along a polar 32CA reaction the electron density will flux from **TCY** to **FCC/FCO**, thus being classified as the forward electron density flux (FEDF).[52]

The electrophilicity *ω* index[53] of **TCY**, 2.03 eV, is lower than that of **FCC**, 2.78 eV and **FCO** , 2.89 eV; the three compounds being classified as strong electrophiles.[30] By contrast, the nucleophilicity *N* index[54] of **TCY**, 4.47 eV, is higher than that of **FCC**, 1.84 eV, and **FCO**, 2.33 eV. Thus, while **TCY** is classified as a strong nucleophile, **FCC** is classified as a marginal nucleophile, and **FCO** is classified as a moderate nucleophile.[30] Consequently, it is expected that **TCY** participates as a strong nucleophile towards the electrophilic **FCC** and **FCO** in these 32CA reactions.

**3.3 ELF topological analysis at the ground state of TCY**

In order to elucidate the Lewis-like structure of **TCY**, ELF topological analysis was performed using the Multiwfn program.[46] The basin populations, using different basis sets, are recapitulated in Table 4.

**< TABLE 4 >**

Table 4 shows that the topology of the ELF[55] of the **TCY** structure depends strongly on the basis set size. Indeed, using 3-21G(d) and 6-31G(d) basis sets, in addition to the monosynaptic basin V(S) on the sulphur atom, the presence of two monosynaptic basins, V(C1) and V(C2), on the C1 and C2 carbons, are observed. However, using extended basis sets (6-311G(d,p), cc-pvDZ, cc-pvTZ, and aug-cc-pvTZ), the two monosynaptic basins on C1 and C2 atoms disappear. In addition, the population of the V(S,C1) and V(S,C2) disynaptic basins is increased to get 3.0 e on each C-S bond. This behaviour can be explained by the great delocalisation of electron density due to the presence of extended functions in large basis sets. Noting that, going from 3-21G(d) to 6-31G(d), an important decrease of the population of the monosynaptic basins on C1 and C2 is observed. However, all basis sets show the presence of a monosynaptic basin V(S) about 3.0 e on sulphur atom. The 6-311G(d,p) ELF structure of **TCY** is given in Figures 5.

**< FIGURE 5 >**

Thus, while the3-21G(d) and 6-31G(d) basis sets suggest a *pseudodiradical* structure for **TCY,** the use of larger basis sets suggest a zwitterionic one. However, it interesting to note that the conversion of the B3LYP/6-311G(d,p) zwitterionic structure of **TCY** in a*pseudomonoradical one* demands a low energy cost (EC) (see Sections 3.4 and 3.5).

**3.4 ELF Mechanistic study of the 32CA reaction of TCY with FCC (*reaction #1*)**

The IRC curve indicates that the 32CA reaction of **TCY** with **FCC** follows a one-step mechanism. In Table 5, the bond lengths, the GEDT and the ELF basin populations of some selected points on the IRC profile of the most favourable reaction path of *reaction #1* are given. The positions of the ELF attractors are represented in Figure 6. The XYZ cartesian coordinates of these relevant points are given in the ESI.

An important aspect of 32CA reactions is the analysis of the polarity of the process. The GEDT value at the TS, 0.23 e, shows an electron density fluxes from **TCY** to **FCC** (Table 5), the 32CA reaction being classified as the FEDF.[48] This GEDT value points out a polar 32CA reaction, which was anticipated by analysis of CDFT-based reactivity indices of the isolated reactants (Table 3).

The topological analysis of the ELF[51] along the reaction path was also used as a valuable tool to understand the bonding changes along the reaction. In order to explain the bond formation in the 32CA reaction, some relevant points of IRC curves of the most favourable *ortho/endo* reaction path were trained. The ELF analysis of valence basins and their corresponding N populations of the relevant points are given in Table 5 and represented in Figure 6. The XYZ cartesian coordinates of these relevant points are given in the ESI.

**< TABLE 5 >**

**< Figure 6 >**

For isolated reactants, no V(C) monosynaptic basins is observed at the C1 or C2 carbons of **TCY**. The first V(C2) monosynaptic basin appearances at **P1** with a population of 0.43 e, and with an EC of 1.31 kcal/mol higher (blue curve), which becomes populated to 0.60 e at the TS. Then, the formation of the second V(C3) monosynaptic basin is observed at **P2**, integrating 0.28 e. The first more relevant topological change takes place at **P3**, in which the two V(C2) and V(C3) monosynaptic basins have merged in a new V(C2,C3) disynaptic basin integrating 1.47 e. This topological changes are associated to the formation of the first C2-C3 single bond. **P4** is characterised by the presence of two V(C2) and V(C3) monosynaptic basins, integrating 0.28 and 0.35 e, respectively. The second more relevant topological change takes place at **P5**, in which the two V(C1) and V(C4) monosynaptic basins present at **P4** have merged in a new V(C1,C4) disynaptic basin integrating 1.47 e. This topological changes are associated to the formation of the second C1-C4 single bond.

Along the reaction path, the V(C1,S), V(S,C2) of TCY and V(C3,C4) disynaptic basins of **FCC** experience a decreasing of the electron density due to their participation in the formation of the two new bonds C2-C3 and C1-C4, and in the generation of the second V’(S) monosynaptic basin at the sulphur (Figure 7).

In spite of that **TCY** does not present any V(C) monosynaptic basis at the B3LYP/6-311G(d,p), the presence of the V(C2) monosynaptic basin at **P1** with a very low EC, 1.31 kcal/mol, suggest that **TCY** experiences the reactivity of a*pseudomonoradical* TAC.[56] Based on this ELF analysis, the proposed mechanism of the 32CA reaction of **TCY** with **FCO** is illustrated in Scheme 4.

**< FIGURE 7 >**

**< SCHEME 4 >**

**3.5 ELF Mechanistic study of the 32CA reaction of TCY with FCO (*reaction #2*)**

The IRC curve indicates that the 32CA reaction of **TCY** with **FCO** follows a one-step mechanism. In Table 6, the bond lengths, the GEDT and the ELF basin populations of some selected points on the IRC profile of the most favourable reaction path of *reaction #1* are given. The positions of the ELF attractors are represented in Scheme 5. The XYZ cartesian coordinates of these relevant points are given in the ESI.

The high GEDT value found at the TS, 0.36 e, which is higher than that in the TS of *reaction #1*, points out also a polar process. We note that the *reaction #2* is found more polar than *reaction #1* due the strong nucleophilicity of **FCO** in comparison with **FCC** (see table 3).

The ELF analysis of valence basins and their corresponding N populations of some characteristic points of the most favourable *meta/endo* reaction path are given in Table 6 and represented in Figure 8 and the XYZ cartesian coordinates of the relevant points are given in the ESI.

**< TABLE 6 >**

**< FIGURE 8 >**

In the case of *reaction #2*, a V(C2) monosynaptic basin, integrating 0.56 e, is already observed at the molecular complex **MC**, which is located 1.50 kcal/mol below reactants.

At TS, while the population of the V(C2) monosynaptic basin has been increased to 0.88 e, a new V(C5) monosynaptic basin, with a population of 023 e, is observed. The first more relevant topological change takes place at **P2**, in which the two V(C2) and V(C5) monosynaptic basins have merged in a new V(C2,C5) disynaptic basin integrating 1.35 e. This topological changes are associated to the formation of the first C2-C5 single bond. At **P4**, the formation of a new V(C1) monosynaptic basin, with a population of 0.20 e, is observed, with a EC of 16.16 kcal/mol (brown curve). The second more relevant topological change takes place at **P5**, in which while the V(C1) monosynaptic basin has disappeared, a new V(C1,0) disynaptic basin integrating 0.77 e. This topological changes are associated to the formation of the second C1-O single bond.

Similar to reaction #1, while the population of the V(C1,S), V(S,C2) of TCY and V(C5,O) disynaptic basins of FCO decrease along the reaction path, a new V’(S) monosynaptic basin

Like reaction #1, the presence of the V(C2) monosynaptic basin at **MC** suggests that **TCY** experiences the reactivity of a*pseudomonoradical* TAC,[56] which negates results shown by Hosseini.[57] The ELF attractor positions for the most relevant points of the IRC associated with the formation of the C2-C5 and C1-O single bonds along the *meta-endo* regioisomeric channel of the 32CA reaction between **TCY** and **FCO** are given in Figure 9 and based on this ELF analysis, the proposed mechanism of the 32CA reaction of **TCY** with **FCO** is illustrated in Scheme 5.

**< FIGURE 9 >**

**< SCHEME 5 >**

**4. Conclusion**

The chemo-, regio-, and stereoselectivity of the 32CA reactions of thiocarbonyl *S*-methanide (TCY) with two α,β-unsaturated ketones, **FCC** and **FCO**, have been studied within MEDT. The present study puts in evidence the crucial role played by trifluoromethyl group CF3 in orienting these selectivities. Indeed, in the case of the 32CA reaction of **TCY** with **FCC**, the calculations show that the C=C *ortho/endo* reaction path yielding to the formation of the methanone **CA-FCC-CC-on**, *via* **TS-FCC-CC-on,** is found the most favoured. By contrast, in the case of the 32CA reaction between **TCY** and **FCO**, the calculations point out that the C=O *meta/endo* reaction path yielding to the formation of the oxathiolane **CA-FCO-CO-mn,** via **TS-FCO-CO-mn,** is found the most favoured, in total agreement with experimental outcomes. The low calculated activation barriers in combination of the ELF analysis along the along the IRC reveal a *pseudomonoradical* character of the studied 32CA reactions.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**Figures and Schemes**



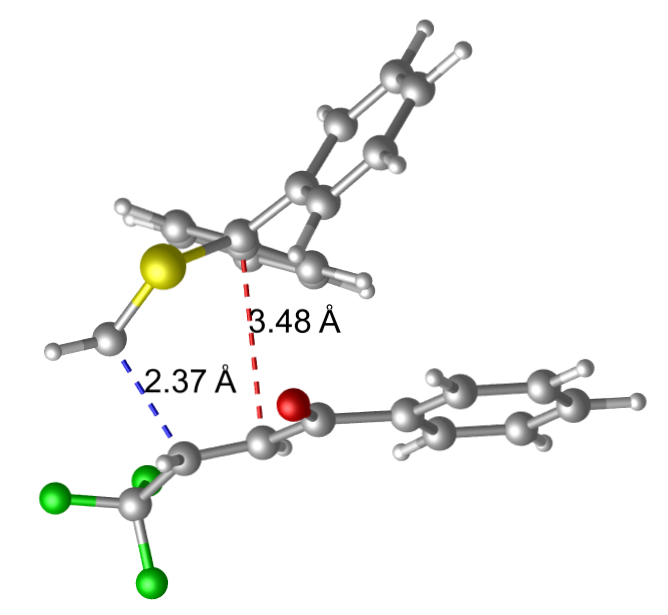
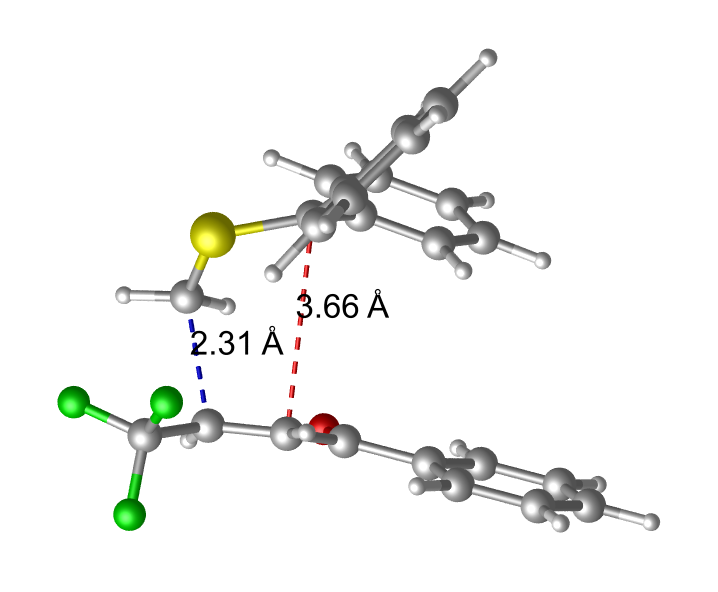
**Scheme 1** 32CA reactions of **TCY** with **FCC** (*reaction #1*),and with **FCO** (*reaction #2*), carried out at - 40°C in tetrahydrofuran (THF).



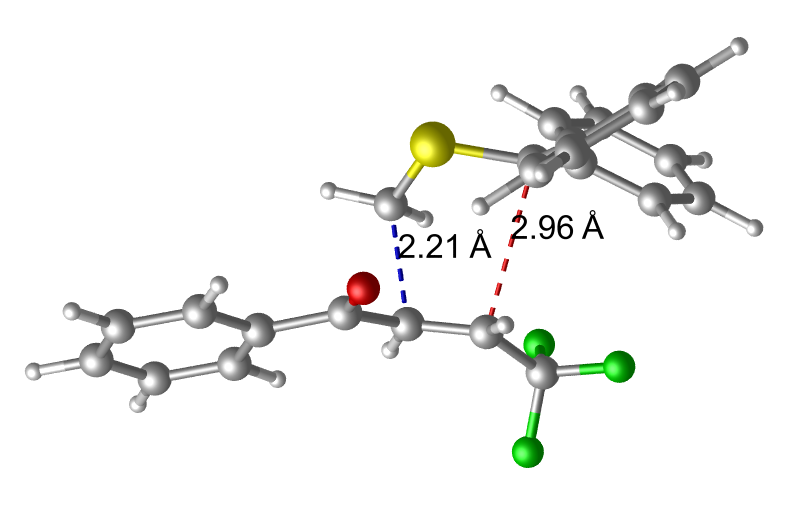
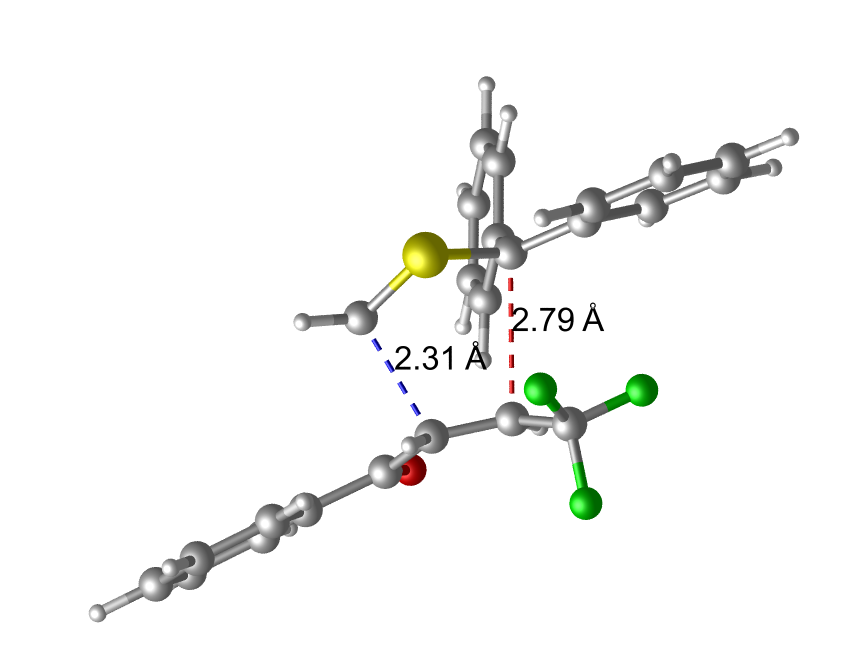
**Scheme 2** Reactive channels ofthe 32CA of diphenylthiocarbonyl *S*-methanide **TCY** with 3-trifluoromethylated 1-phenylprop-2-en-1-one **FCC** (*reaction #1*).



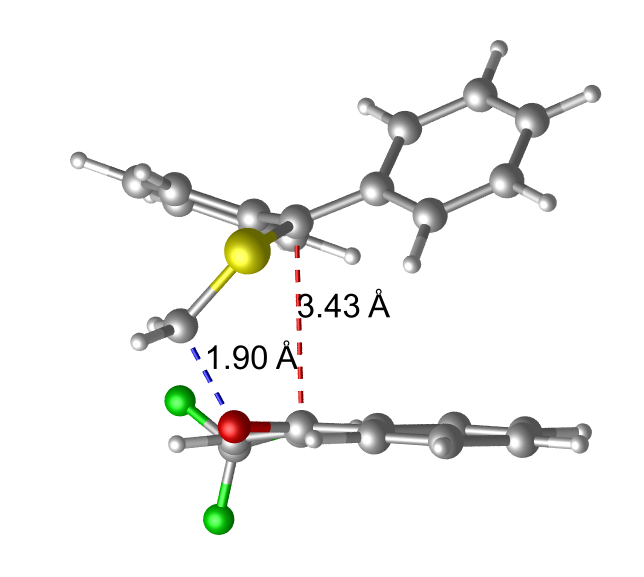
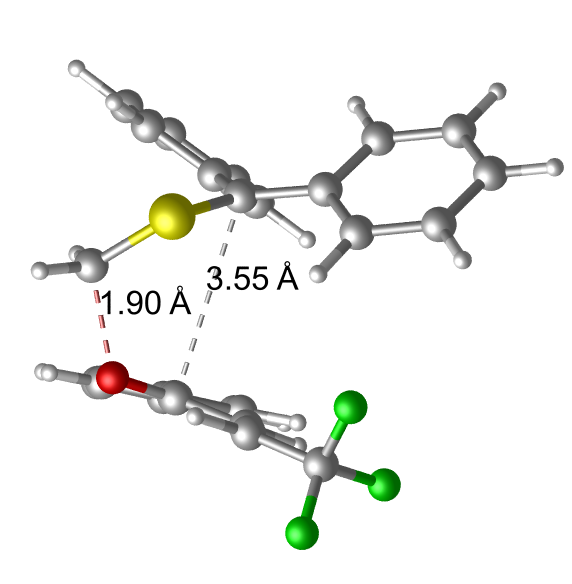
**Figure 1** Gibbs free energy profiles, in kcal/mol, for the eight competitive reaction paths of the 32CA reaction of **TCY** with **FCC** computed in THF at -40°C.

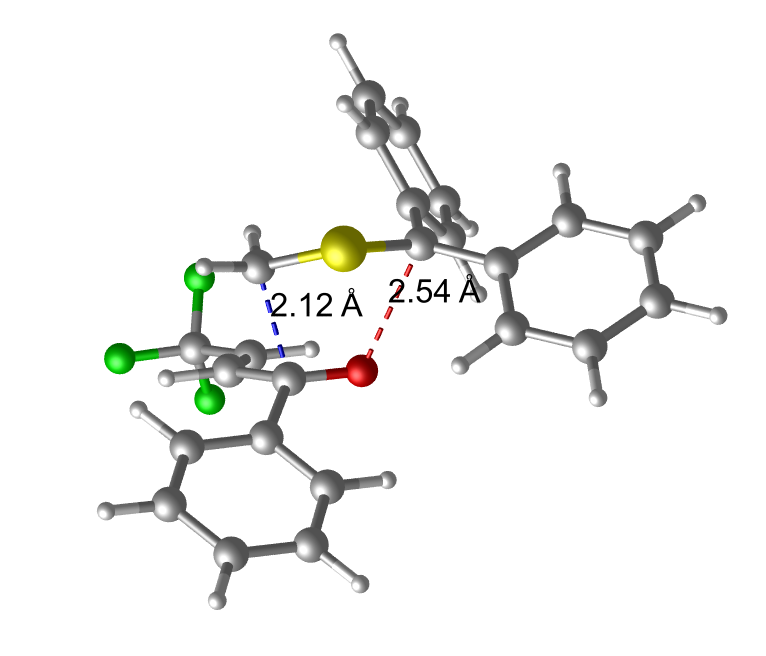
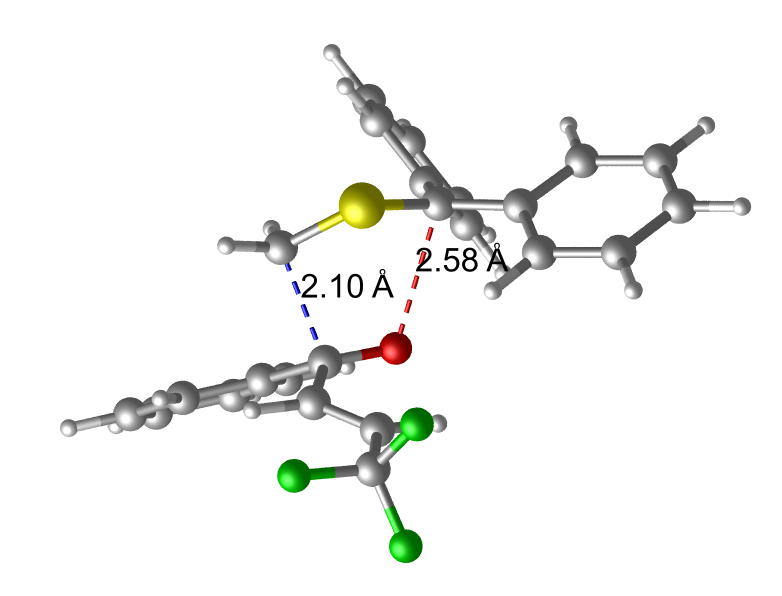
**TS-FCC-CC-on TS-FCC-CC-ox**

**TS-FCC-CC-mn TS-FCC-CC-mx**

**TS-FCC-CO-on TS-FCC-CO-ox**

**TS-FCC-CO-mn** **TS-FCC-CO-mx**

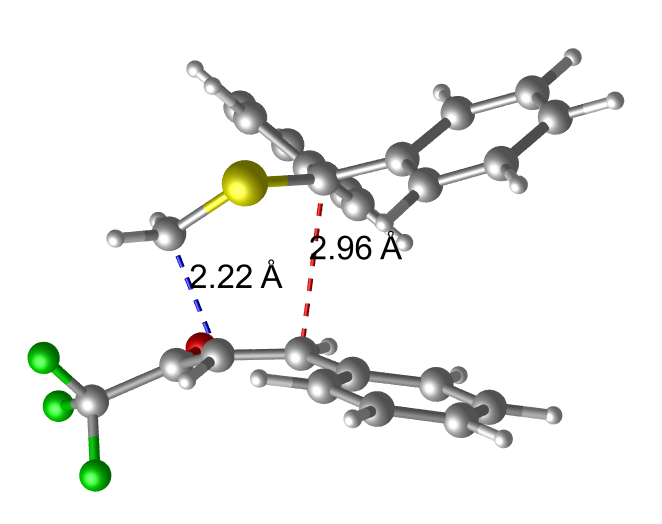
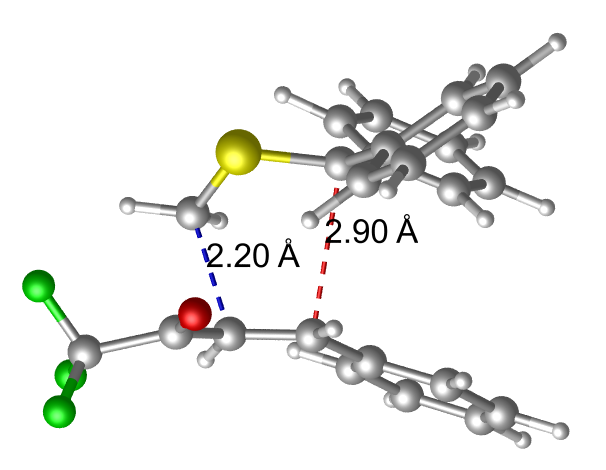
**Figure 2**  B3LYP/6-311G(d,p) geometries of the transition structures involved in the 32 CA reaction of **TCY** with **FCC** (*reaction #1*). Lengths are given in Angstroms.



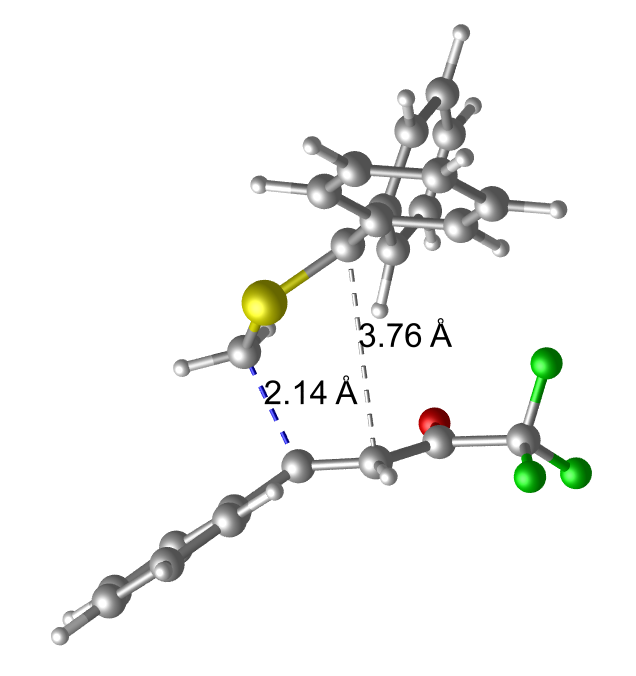
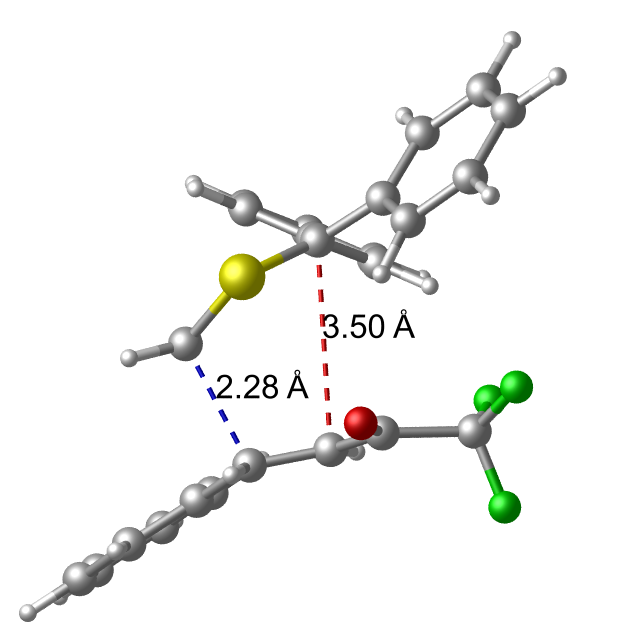
**Scheme 3** Possible reaction channels of the 32CA of diphenylthiocarbonyl S-methanide **TCY** with 1-trifluoromethylated 3-phenylprop-2-en-1-one **FCO** (*reaction* ***#2***).



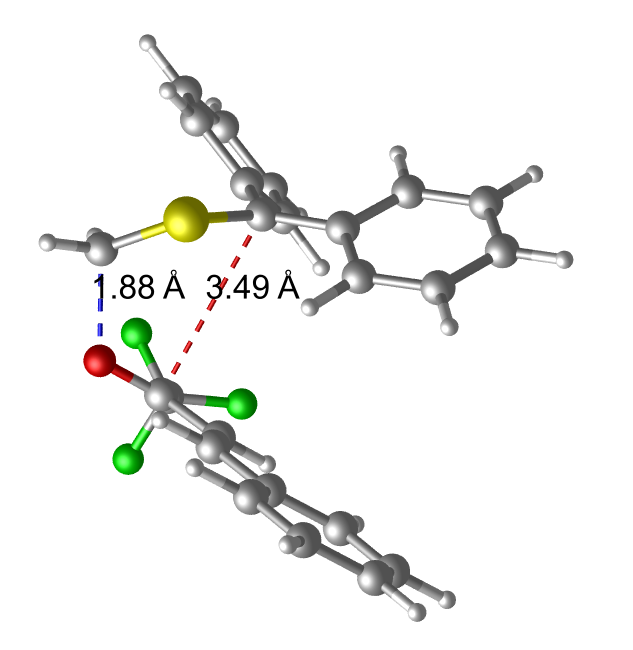
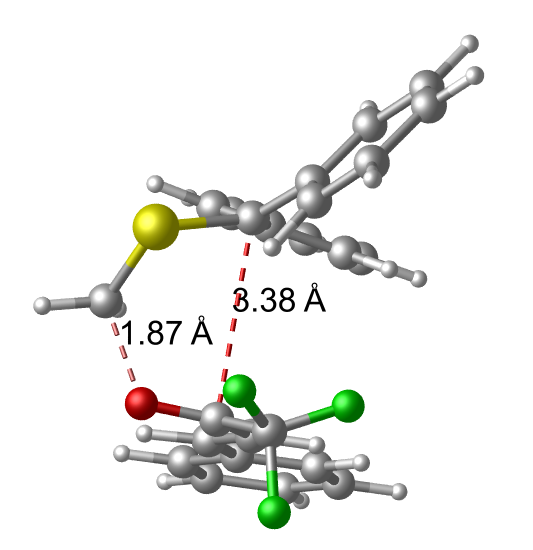
**Figure 3** Gibbs free energy profiles, in kcal/mol, for the eight competitive reaction paths of the 32CA reaction of **TCY** with **FCO** in THF at -40°C.

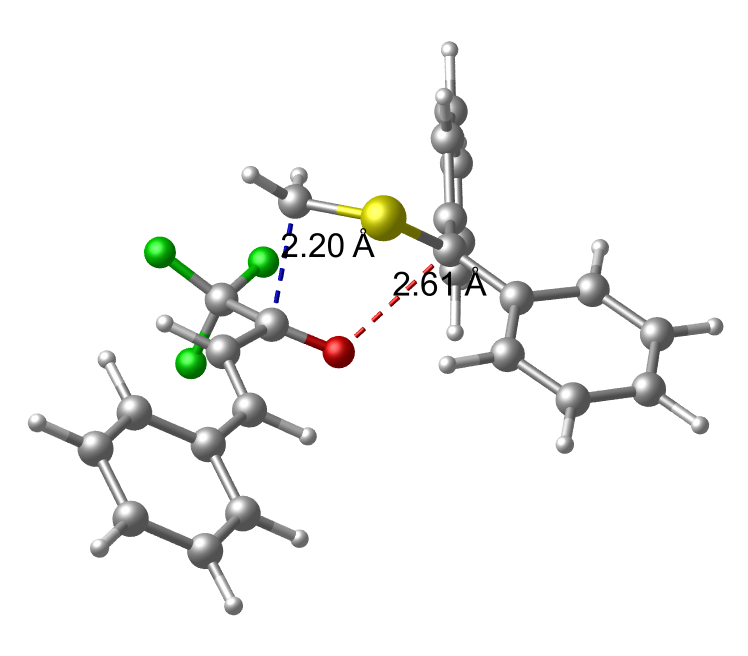
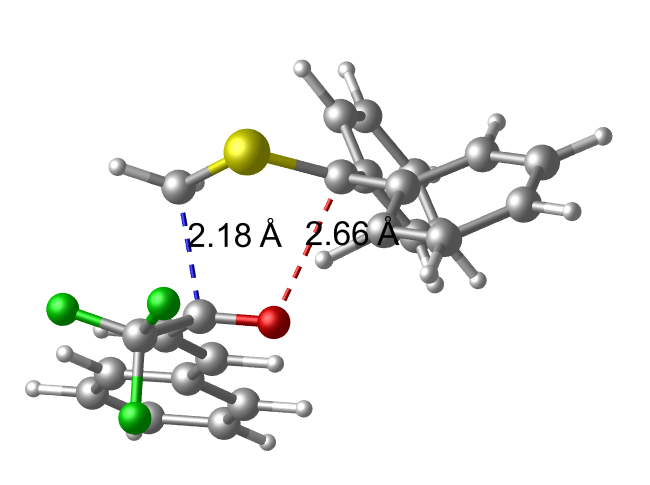
**TS-FCO-CC-on** **TS-FCO-CC-ox**

**TS-FCO-CC-mn** **TS-FCO-CC-mx**

**TS-FCO-CO-on** **TS-FCO-CO-ox**

**TS-FCO-CO-mn** **TS-FCO-CO-mx**

**Figure 4**  B3LYP/6-311G(d,p) geometries of the transition structures involved in the 32CA reaction of **TCY** with **FCO** (*reaction #2*). Lengths are given in Angstroms

|  |  |  |
| --- | --- | --- |
|  |  |  |
| **(a)** | **(b)** | **(c)** |

**FIGURE 5** B3LYP/6-311G(d,p) (a) ELF valence attractor positions, (b) ELF valence basins, (c) proposed Lewis-like structure of **TCY**.

Intrinsic Reaction Coordinate

TCY+FCC

CA

P3

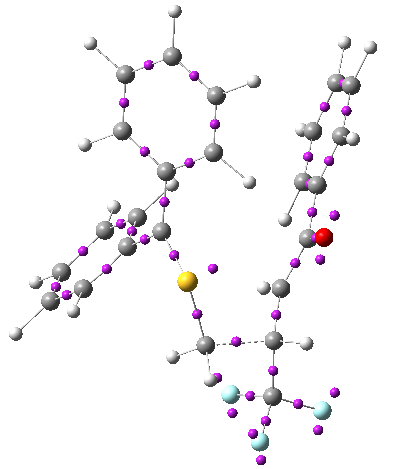
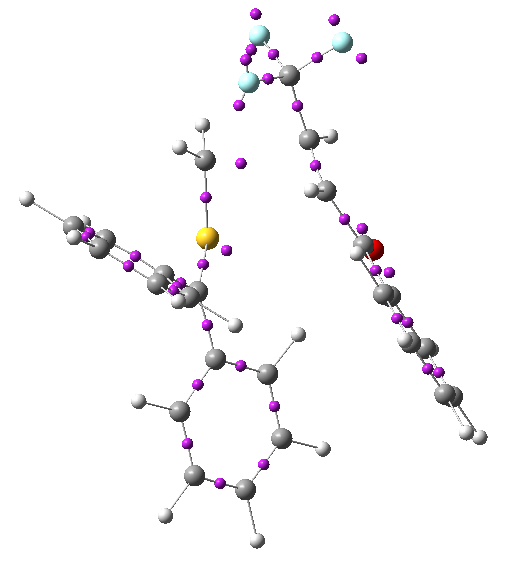
TS

P1

P5

MC

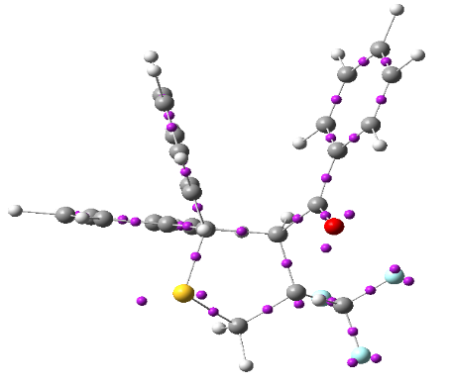
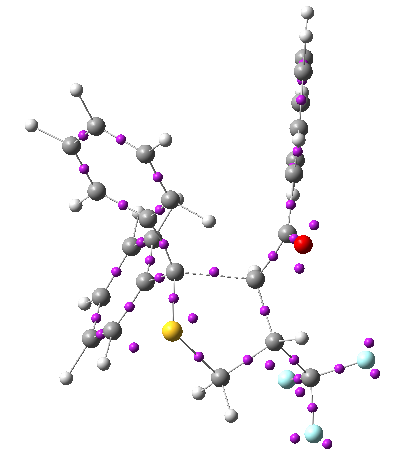
**Figure 6** Evolution of ELF valence basin populations along the IRC curve of the favoured pathway in *reaction #1*.



**V(C2,C3)**

**V(C2)**

**TS P3**



**V(C2,C3)**

**V(C2,C3)**

**V(C1,C4)**

**V(C1,C4)**

**P5 CA**

**FIGURE 7** ELF attractor positions for the most relevant points of the IRC associated with the formation of the C2-C3 and C1-C4 single bonds along the *ortho-endo* regioisomeric channel of the 32CA reaction between **TCY** and **FCC**.



**SCHEME 4** Proposed mechanism of the formation of the C2-C3 and C1-C4 single bonds along the *ortho/endo* regioisomeric channel of the 32CA reaction between **TCY** and **FCC**.

TCY+FCC

Intrinsic Reaction Coordinate

CA

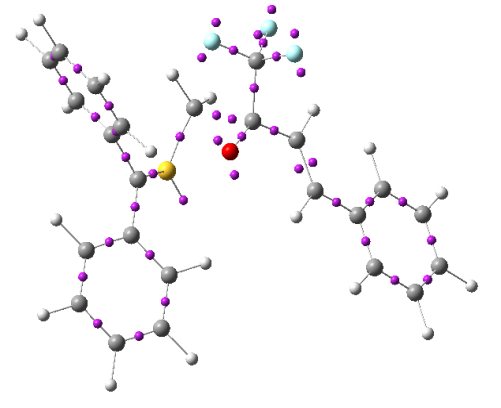
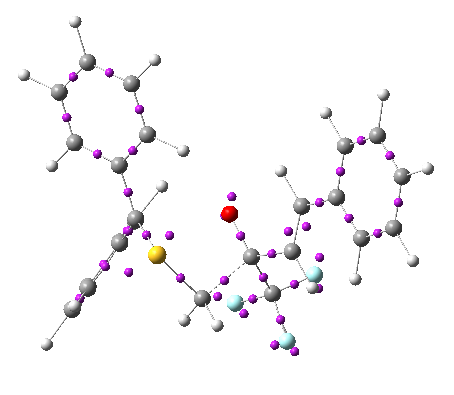
P3

TS

P5

MC

**FIGURE 8** Evolution of ELF valence basin populations along the IRC curve of the favoured pathway in reaction #2.

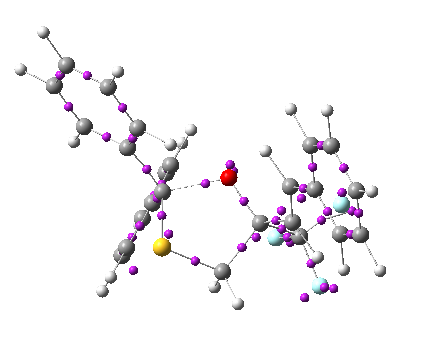
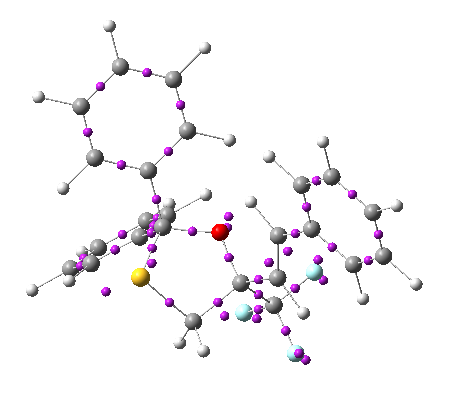
 

**V(C2,C5)**

**V(C5)**

**V(C2)**

**TS P3**

**V(C1,O)**

**V(C2,C5)**

**V(C1,O)**

**V(C2,C5)**

**P5 CA**

**FIGURE 9** ELF attractor positions for the most relevant points of the IRC associated with the formation of the C2-C5 and C1-O single bonds along the *meta-endo* regioisomeric channel of the 32CA reaction between **TCY** and **FCO**.



**SCHEME 5** Proposed mechanism of the formation of the C2-C5 and C1-O single bonds along the *meta-endo* regioisomeric channel of the 32CA reaction between **TCY** and **FCO**.