C_{sp^3}–F bond activation by nucleophilic attack of the $\{Pt_2S_2\}$ core assisted by non-covalent interactions†

Ainara Nova,[a] Rubén Mas-Ballesté,[ab] Gregori Ujaque,[a] Pilar González-Duarte*[a]
and Agustí Lledós*[a]

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The high nucleophilicity of the sulfur atoms in $[Pt_2(dppp)_2(\mu\text{-}S)_2]$ triggers a C–F activation process in 1,3-difluoro-2-propanol that leads to the $[Pt_2(dppp)_2(\mu\text{-}S)(\mu\text{-}SCH_2CH(OH)CH_2F]F$ product through a S_N2 mechanism, where the O–H···F hydrogen bond established from the alcohol group of the organic substrate is essential for assisting the departure of the fluoride anion.

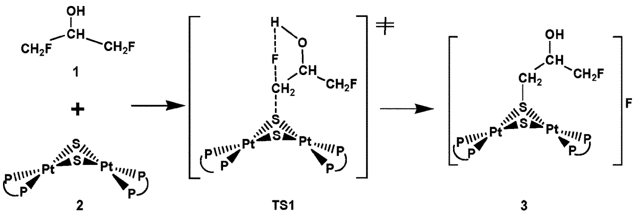
The carbon–fluorine bond is among the strongest single bonds formed by carbon. Its activation attracts interest for the many technological applications of fluorocarbon compounds as well as for their involvement in environmental issues.[1] While a variety of methods have been developed to activate the C–F bond in fluoroarenes and fluoroalkenes,[2] activation of the saturated counterparts has been less successful.[3] Current strategies focus mainly on the use of transition metal complexes as reducing agents.[4] In addition, cleavage of aliphatic C–F bonds has been achieved by means of the nucleophilic attack of sulfur-,[5] oxygen- or nitrogen-containing compounds.[6] Also, an unusual mechanism involving phosphine ligands has been recently proposed by Macgregor.[7] Here we present the activation of a C_{sp^3}–F bond as a result of a S_N2 process assisted by non-covalent interactions under rather moderate reaction conditions.

The role of non-covalent interactions as a factor that can determine the kinetics and output of diverse reactions in biological systems is well known. For instance hydrogen bonds are involved in regulating chemical processes observed in respiratory proteins[8] and metal-containing hydrolases.[9] Despite these phenomena having been observed in biological systems for decades, only during the last few years have these concepts been applied successfully to synthetic bioinspired model systems.[10] Along this line, this work presents evidence that hydrogen bonding assists the C_{sp^3}–F activation by a S_N2 process using as nucleophile a metal complex containing the $\{Pt_2S_2\}$ core.

Complexes of general formula $[Pt_2(\mu\text{-}S)_2L_4]$ have been found to possess an outstanding ability to behave as nucleophiles towards metal centres, protic acids and organic electrophiles.[11,12] Regarding the last species, a complete description of the reaction pathways by which complexes $[Pt_2(\mu\text{-}S)_2(P{\cap}P)_2]$ ($P{\cap}P$ = dppe; dppp) react with CH_2Cl_2[13] was reported in 2002. Hor and co-workers also reported the reactivity of the sulfide bridges in $[Pt_2(\mu\text{-}S)_2(PPh_3)_4]$ towards a series of organic dihalides.[14] These results provided evidence for the exceptional ability of the $\{Pt_2S_2\}$ core to cleave C–Cl bonds and prompted us to investigate the activation of the less reactive C–F bonds.

In order to attempt the cleavage of a C_{sp^3}–F bond we selected 1,3-difluoro-2-propanol (**1**), which is the major component of the pesticide Gliftor.[15] Moreover, the presence of an OH group in the selected compound should allow us to test the effect of hydrogen bonding in the C–F activation. Reagent **1** and $[Pt_2(\mu\text{-}S)_2(dppp)_2]$ (**2**) were made to react in refluxing toluene for one day[16] affording a new product, which according to the spectroscopic data (*vide infra*) can be described as a complex of formula $[Pt_2(dppp)_2(\mu\text{-}S)(\mu\text{-}SCH_2CH(OH)CH_2F]F$ (**3**) (see Scheme 1).

The reaction product was characterized in solution by means of multinuclear NMR (Fig. 1) and ESI and FAB mass spectrometry (see Fig. S1–S5 in supporting information†). NMR data of **3** confirm that **2** reacts selectively with only one of the two C–F bonds in **1**. Thus, while the $^{31}P\{^1H\}$ NMR spectrum of **2** shows four chemically equivalent phosphorus nuclei (δ −0.08 ppm, $^1J_{Pt,P}$ = 2615 Hz), that of **3** is indicative of an asymmetric structure (Fig. 1(A)). At high temperature (50 °C), two signals centred at 2.98 ppm ($^1J_{Pt,P1}$ = 2405 Hz) and 2.45 ppm ($^1J_{Pt,P2}$ = 3010 Hz) are observed, suggesting that the structure of **3** contains two inequivalent pairs of phosphorus atoms. In contrast, at low temperature (−40 °C) four inequivalent phosphorus nuclei are observed (δ_{P1} 3.69 ppm, $^1J_{Pt,P1}$ = 2417 Hz; $\delta_{P1'}$ 3.00 ppm, $^1J_{Pt,P1'}$ = 2370 Hz; δ_{P2} 3.21 ppm, $^1J_{Pt,P2}$ = 2960 Hz; $\delta_{P2'}$ 2.54 ppm; $^1J_{Pt,P2'}$ = 2985 Hz). These results are indicative of a dynamic process, which we attribute to the rotation of the alkyl group around the C–S bond. At low temperature, this rotation is stopped



Scheme 1 Reaction between 1,3-difluoro-2-propanol (**1**) and $[Pt_2(dppp)_2(\mu\text{-}S)_2]$ (**2**).

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[a] *Departament de Química, Universitat Autónoma de Barcelona, 08193 Bellaterra, Barcelona, Catalonia, Spain. E-mail: agusti@klingon.uab.es; Pilar.Gonzalez.Duarte@uab.es; Tel: +34-935811363*
[b] *Departamento de Química Inorgánica, Universidad Autónoma de Madrid, Madrid, 28049, Spain*

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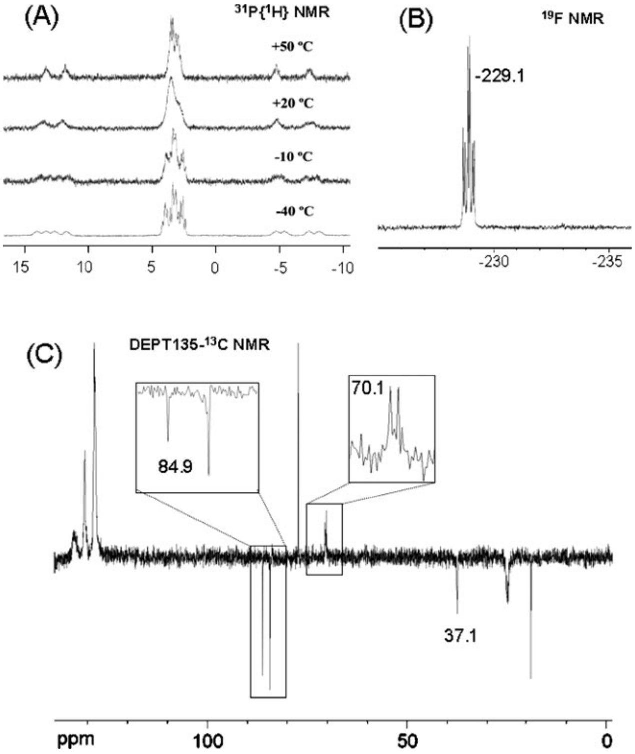

Fig. 1 Spectroscopic characterization of product **3** by multinuclear NMR recorded in $CDCl_3$: (A) VT-$^{31}P\{^1H\}$ NMR, (B) ^{19}F NMR, (C) DEPT135-^{13}C NMR

and the alkyl group is oriented towards one of the phosphine ligands making the four phosphorus atoms inequivalent. In addition, the ^{19}F NMR spectrum of **3** showed two signals, one at δ −229.1 ppm ($^2J_{F,H}$ = 47.3 Hz, $^3J_{F,H}$ = 19.3 Hz, see Fig. 1(B)) that corresponds to the fluorine atom still bound to the aliphatic chain (^{19}F NMR signal corresponding to unreacted **1** appears at δ −232.2 ppm), and a second signal at δ −161.8 ppm, which is within the expected chemical shift range for fluoride ions forming hydrogen bonds in species such as $[F_2H]^-$ or $[(FH)_nF]^-$.[17]

Consistently with the proposed structure, the DEPT135-^{13}C NMR spectrum of **3** exhibits three different chemical shifts for the carbon atoms of the thiolate chain (CH_2: δ 37.1 ppm, 84.9 ppm ($^1J_{C,F}$ = 171 Hz); CH: δ 70.1 ppm ($^2J_{C,F}$ = 19 Hz)). As shown in Fig. 1(C), the fact that these signals are only coupled to one fluorine atom indicates that one C–F bond has been broken. The ^1H NMR spectrum recorded at room temperature allows to locate every proton in the $[SCH_2CH(OH)CH_2F]^-$ chain including a broad signal at δ 4.13 ppm attributable to the OH group (see supporting information†). The ESI and FAB mass spectra of **3** show one major peak whose position and isotope distribution are consistent with the molecular mass of the $[Pt_2(dppp)_2(\mu\text{-}S)(\mu\text{-}SCH_2CH(OH)CH_2F)]^+$ cation (m/z = 1355) (see Fig. S4 and S5 in supporting information†). Overall, spectroscopic data offer no doubt about the activation of one C–F bond in **1**.

In addition to achieving the C_{sp^3}–F bond activation, the reported synthetic procedure offers the advantage of a one step reaction, which is based on a nucleophile-containing species that is highly stable under open atmosphere and soluble in many organic solvents. In contrast, aromatic or aliphatic thiols often used in C–F bond activations oxidize easily in the presence of oxygen.[4,5]

The effect of the OH group in the organic substrate in order to facilitate the C–F activation was evaluated by comparing the reactivity of **2** towards an analogue of **1** devoid of the alcohol group, 1,3-difluoropropane (**4**). As we observed that **4** does not react with **2**, we conclude that the OH group assists somehow the C–F bond cleavage. Insights into the mechanism of this reaction and about the role of the OH group were obtained from DFT calculations.

Theoretical calculations confirm that the reaction mechanism leading to **3** is of the S_N2 type,[18] where the entering nucleophile is the bridging sulfide ligand in **2** that replaces the leaving fluoride in **1**. Given the generally observed inability of the F^- ion to act as leaving group in S_N2 reactions, the proposed pathway is very unusual for activating C–F bonds and exemplifies the outstanding nucleophilicity of the $\{Pt_2S_2\}$ core. According to the S_N2 mechanism, the transition state **TS1** presents an S–C–F angle of 171.9° and S···C bond forming and C···F bond breaking distances of 2.341 and 2.036 Å, respectively (Fig. 2). In **TS1** as well as in the final complex the thiolate group lies in an *exo* position. On the basis of the calculated geometry for both species, the leaving fluoride ion is involved in a strong hydrogen bond interaction with the alcohol function [(O)H···F 1.696 Å]. The role of the OH group in the fluoride elimination can also be evaluated by taking into account theoretical results we have recently reported on the reaction between **4** and **2**.[19] For the calculated transition state **TS2** we reported that S···C bond forming and C···F bond breaking distances values are 2.372 and 2.035 Å, respectively. In this case, in the absence of an alcohol group, the leaving fluoride can be suitably located to be slightly stabilized by weak C–H···F interactions with the alkyl chain of the chelating diphosphane ligand. These interactions

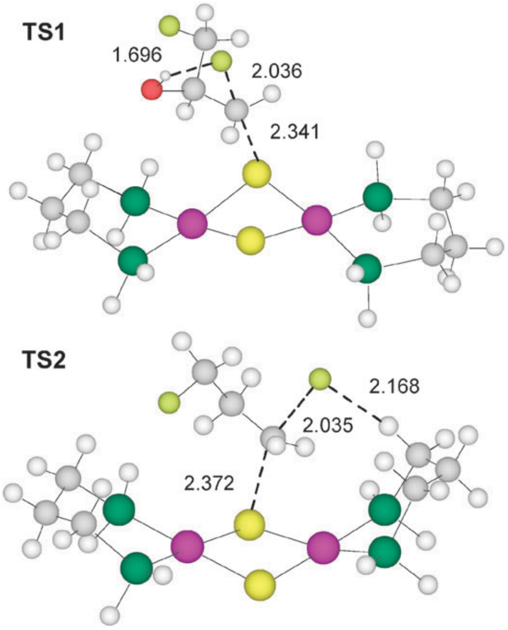

Fig. 2 Geometries of the transition states for the reaction of **2** with **1** (**TS1**) or **4** (**TS2**). Distances in Å. TS2 geometry obtained from ref. 19.

account for the greater deviation of the S–C–F angle in **TS2** (156.5°) from the ideal value of 180° than in **TS1** (171.9°).

The calculated values for the reaction barriers assess the role of the OH group adjacent to the C–F bond in assisting the release of the fluoride leaving group. The gas-phase energy barrier calculated for the reaction between **1** and **2** is 44.7 kcal mol^{-1}, and that for **2** and **4** is 51.9 kcal mol^{-1}. When the solvent toluene is included in the calculation by the PCM method, the difference in the energy barriers for these two reactions is even larger, with values of 36.6 and 46.4 kcal mol^{-1}, respectively. These theoretical results agree well with the experimental observation that **2** does react with **1** but it does not with **4**. In addition, the large value of the activation energy barrier agrees well with the experimental conditions required for the reaction of **1** with **2** (refluxing toluene). Overall, we have shown that the presence of the OH group stabilizes the transition state by means of the F···H–O supramolecular interaction that provides an electrophilic assistance to the C–F cleavage.

Hydrogen bond interactions have been proved in this work as an efficient way to assist the C–F activation. The assistance here reported has been provided by an OH group enclosed in the structure of the substrate. However, it can be envisaged that a new generation of $[Pt_2(\mu\text{-}S)_2L_4]$ complexes with terminal L ligands adequately functionalized may allow activation of various C–F bonds. Consistently with this notion, Nocera and co-workers designed the so called hangman ligands, which enclose an OH group with the correct orientation to assist the metal-mediated activation of O–O bonds in peroxy species.[20]

In summary, cleavage of the C_{sp^3}–F bond in 1,3-difluoro-2-propanol has been accomplished by a one-step reaction with $[Pt_2(dppp)_2(\mu\text{-}S)_2]$ under rather mild conditions. Theoretical investigations support an S_N2 process with one of the bridging sulfide ligands acting as nucleophile and the essential role of the OH group in assisting the departure of the fluoride anion. Overall, the well-known reactivity of the $\{Pt_2S_2\}$ core towards carbon–chlorine bonds can be extended to the activation of more inert bonds such as C–F. Further studies in this area for activating aliphatic and aromatic C–F bonds by means of the $\{Pt_2S_2\}$ core are in progress.

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