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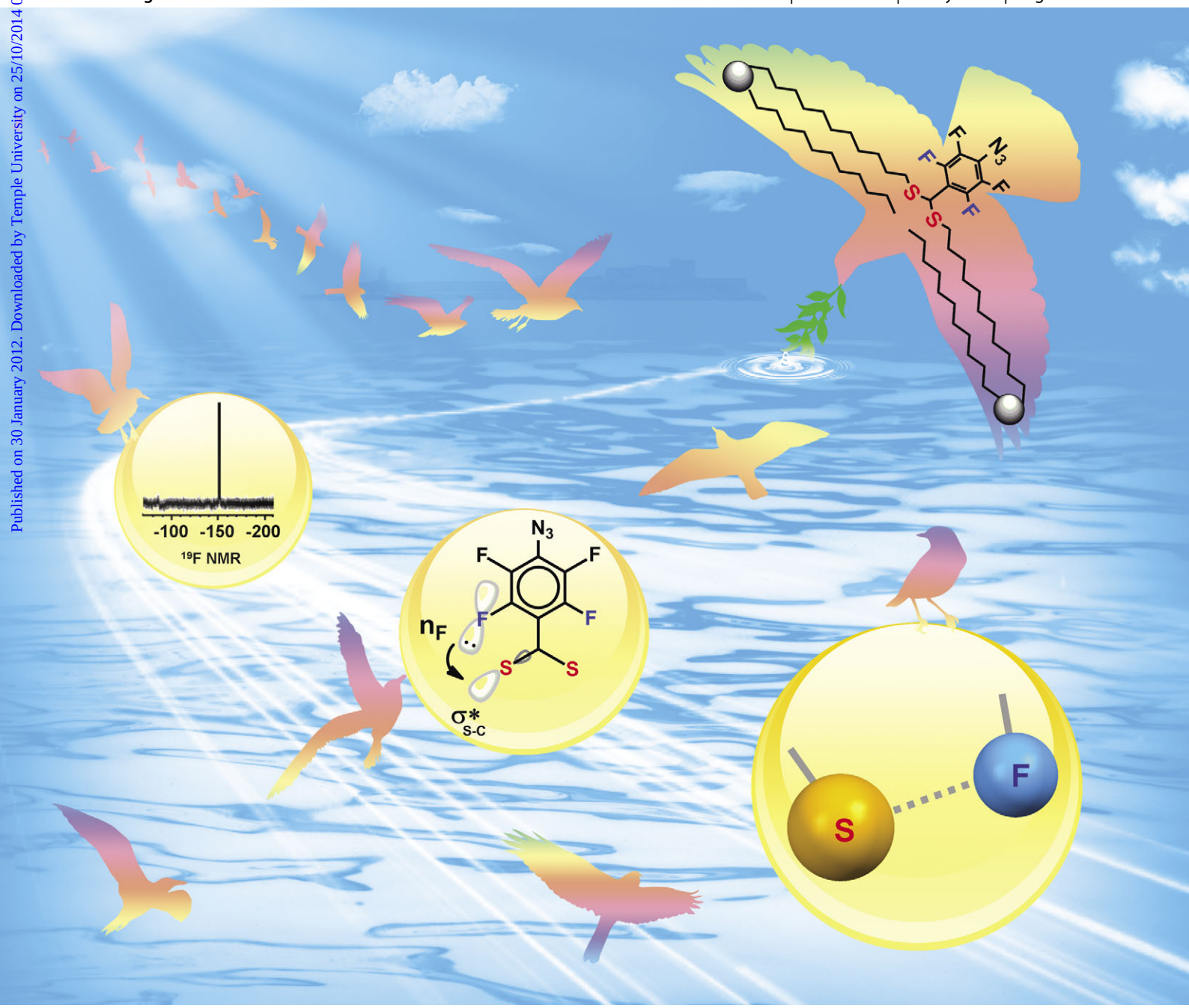

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COMMUNICATION

Rationalizing the F···S interaction discovered within a tetrafluorophenylazido-containing bola-phospholipid†

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A bola-lipid bearing tetrafluorophenylazido chromophore in the diacyl chain displayed puzzling ^{19}F NMR, leading to the evidence and rationalization of a F···S weak interaction that is important for altering molecular structures and imposing novel and special properties on fluorinated compounds.

The introduction of fluorine atoms into organic molecules often imparts them with novel and special physicochemical and biological properties which are not only the direct consequence of the strong C–F bond, but also often originate from the weak intra- and intermolecular interactions engendered by the C–F bond. While the inductive effects of the C–F bond are relatively well understood, the need for a better understanding of the special properties of fluorinated compounds has led to an increased interest in the non-covalent weak dipolar interactions such as C–F···π, C–F···C=O, C–F···H–C, C–F···H–X (X = N, O...) *etc.* and their specific influence on molecular structure and properties.[1] For example, the above-mentioned weak F interactions are found in the Protein Data Bank (PDB) which favors selective protein–ligand interactions.[1a] Meanwhile, the generally weak non-covalent interactions brought about by selective aromatic fluorine substitution have been shown to increase the affinity of a molecule for a macromolecular recognition site.[1d] In this work, we report a F···S weak interaction discovered serendipitously during our investigation on the photoactivatable bola-lipid probe **1** (Fig. 1) in which the tetrafluorophenylazido chromophore is introduced through a thioacetal bridge into the middle of the diacyl acid chain. The weak F···S interaction disclosed here is of significance with respect to altering molecular structures and imposing novel and special properties on fluorinated compounds. We present our work below aiming at rationalizing this remarkable F···S interaction.

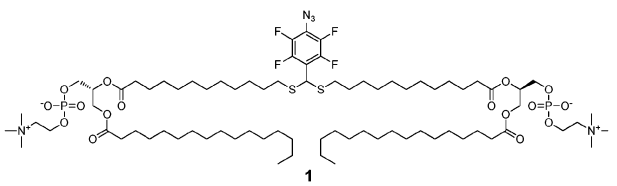

Fig. 1 The bola-phospholipidic probe **1**.

The bola-phospholipid **1** was synthesized using a reported procedure (Scheme S1, ESI†).[2] **1** gave all satisfactory spectral analysis except the ^{19}F NMR spectral data, which displayed surprisingly only one distinct resonance (at −152 ppm) (entry 1 in Table 1), in contrast to our previously synthesized probes[3] or any other reported compounds containing tetrafluorophenylazide for which two groups of ^{19}F resonances can be expected, each one corresponding to one pair of fluorine atoms (in the *ortho* and *meta* position with respect to the azido function, respectively).[4] To clarify this discrepancy, we recorded the ^{19}F NMR spectrum of **2** (entry 2 in Table 1), the precursor for synthesizing **1** (Scheme S1, ESI†). Similarly, only one sharp ^{19}F signal at −151 ppm was observed. Interestingly, by replacing the fatty acyl chain in **2** with two shorter and smaller propyl groups, the ^{19}F NMR spectrum of the resulting compound **3** displayed a broad signal at around −135 ppm in addition to the sharp signal at −151 ppm (entry 3 in Table 1). These results suggest that the bulky alkyl chains contribute to the unexpectedly abnormal ^{19}F NMR spectrum. We further substituted the thioacetal moiety in **3** with an acetal function to obtain the model compound **4** (entry 4 in Table 1). In this case, two sharp ^{19}F NMR signals were detected corresponding to the two pairs of fluorine atoms at the *ortho* and *meta* positions, as expected. Consequently, these data imply that the S atoms in the thioacetal group are also responsible for the unexpected disappearance of the second ^{19}F NMR signal expected for **1**.

In light of the above findings, we went on to verify which pair of fluorine atoms in the tetrafluorophenylazido group in **1** corresponded to the missing ^{19}F NMR signal. We thus examined the ^{19}F NMR spectra of the model compounds **5** and **6** (entries 5 and 6 in Table 1). While **5** displayed a single ^{19}F peak as expected, **6** surprisingly exhibited two abnormally broad, chemically non-equivalent signals. This information indicated that the unusual ^{19}F NMR signal was due to the two fluorine atoms in the *ortho* position with respect to the thioacetal group. By coupling this finding with those obtained from **4** (entry 4 in Table 1), we proposed that the two S atoms interact with the adjacent F atoms, and thereby impede the

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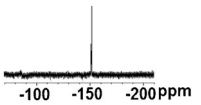
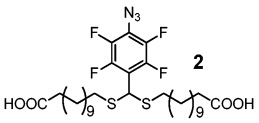
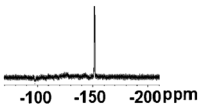
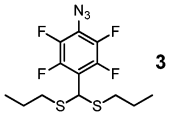
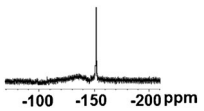
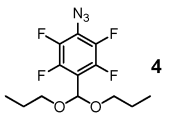
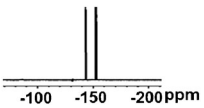
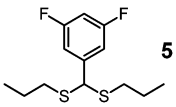
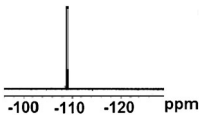
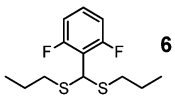
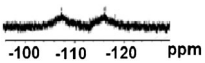
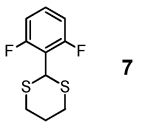
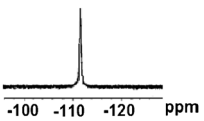
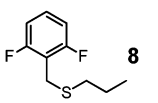
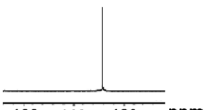
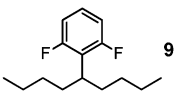
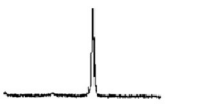
† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/c2cc18147a

Table 1 ^{19}F NMR room temperature spectra of various compounds[a]

Entry	Compound	^{19}F NMR
1	Probe **1**	
2	 **2**	
3	 **3**	
4	 **4**	
5	 **5**	
6	 **6**	
7	 **7**	
8	 **8**	
9	 **9**	

[a] All the spectra were run under identical conditions and were recorded at 564.6 MHz on Varian Inova-600 spectrometers. The chemical shifts are reported in parts per million (ppm) with respect to CF_3COOH used as an external reference.

free rotation of the fluorinated phenyl ring around the C1–C2 bond of the thioacetal compounds (Fig. 2). This phenomenon, in turn, gives rise to the chemical non-equivalence of the F atoms and results in the observed unusual ^{19}F NMR signals.

The F···S interaction could be ascribed to steric hindrance resulting either from the large size of the S atom or from an orbital interaction between the highly polarizable S atom and the extremely electronegative F atom, or a combination of both. To disentangle these contributions, we investigated three other model compounds (**7–9**) designed to modify the steric impediment.

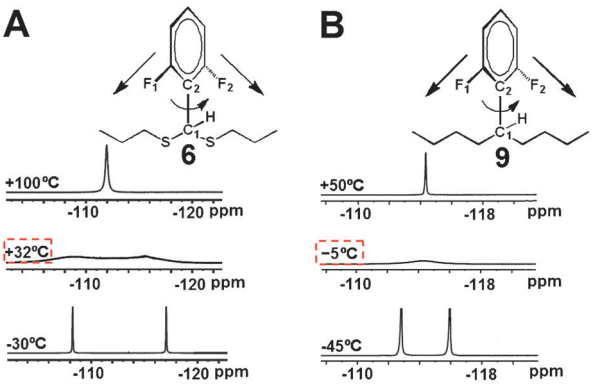


Fig. 2 Temperature-dependent ^{19}F NMR spectra of **6** (A) and **9** (B). The spectra marked with the red dashed frames are those recorded near the corresponding coalescence temperatures.

Steric hindrance was reduced in **7** by decreasing the distance between F and S (*via* the cyclic thioacetal structure), and totally suppressed in **8** by removing one of the two S-containing alkyl chains. The ^{19}F NMR spectra of **7** and **8** displayed only one relatively sharp signal (entries 7 and 8 in Table 1), suggesting that the steric constraint between S and F did contribute to the reduction in rotational freedom observed for **1**, **2**, **3** and **6**. However, the steric hurdle was not the only contributing factor. Indeed, the ^{19}F NMR spectrum of **9**, in which each divalent S atom was replaced by a CH_2 moiety of similar size (24.04 Å^3 and 24.91 Å^3, respectively), also showed a single relatively sharp signal, as opposed to the two extremely broad ones observed for **6**. In other words, although the steric congestion in **6** and **9** is essentially comparable, the ^{19}F NMR spectra of each of the compounds are strikingly different. These results clearly suggest the eventual presence of an additional contributing factor impeding the rotation in the form of an orbital interaction between F and S.

To estimate the contribution of the interaction between F and S, we performed a series of temperature-dependent ^{19}F NMR experiments to investigate the conformational dynamic processes within the molecule.[5] We primarily focused on compound **6** rather than probe **1** because of the much higher thermal stability of **6**. The spectra obtained within the temperature range from −50 °C to 100 °C are reported in Fig. 2A and Fig. S3A (ESI†). As can be seen, fluorine atoms in **6** showed chemical non-equivalence at low temperatures, resulting in the observation of two distinct resonances, whereas only one resonance was observed at high temperatures, with a coalescence temperature (T_C) near 32 °C. This value allowed a free energy of activation for rotation to be estimated (12.8 ± 0.2 kcal mol^{-1}). This result agreed well with theoretical calculation, which predicted an activation energy of 12.9 kcal mol^{-1} (see ESI†). We further analyzed model compound **9**, with a coalescence temperature T_C of −5 °C being observed (Fig. 2B and Fig. S3B (ESI†)), leading to the evaluation of the free energy of activation ΔG of 11.4 ± 0.2 kcal mol^{-1}. Notably, this value is again in agreement with the calculated value (11.6 kcal mol^{-1}) (see ESI†). Because –S– and –CH_2– moieties have similar sizes, steric hindrance was expected to be the only effective contributing factor in the case of **9**. The difference in the ΔG values obtained for model compounds **6** and **9** could then be used to estimate the strength of the F···S interaction, *i.e.*, 1.4 kcal mol^{-1}. This value is considerably stronger than conventional van der Waals

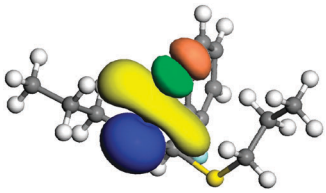


Fig. 3 Schematic representation of the electron delocalization from the fluorine lone pair (n_F) (green–orange) to the anti-bonding orbital of a S–C bond (σ^*_{S-C}) (yellow–blue) in **6**. Atom color code: C, gray; H, white; F, cyan; S, yellow.

forces (0.2–0.6 kcal mol^{-1}) and yet in the range of weak H-bonds. Therefore, the F···S interaction could be considered as a weak interaction.

To further test the hypothesis that the F···S interaction might arise from an orbital interaction, we performed *ab initio* molecular orbital (MO) calculations and natural bond orbital (NBO) analysis[6] on compounds **6** and **9**. The fully optimized geometries of **6** and **9** were obtained (Fig. S1, ESI†). Interestingly, the global energy minimum conformation for **6** (Fig. S1A, ESI†) had one F···S with inter-atomic distance (3.19 Å) shorter than the van der Waals contact, the alternative F···S distance being much larger (3.55 Å). In the case of **9**, this asymmetry was not detected (Fig. S1B, ESI†). The estimated value for the NBO delocalization energy ΔE_{del} was around 3.5 kcal mol^{-1} (Table S1, ESI†) for **6**, suggesting that a non-negligible F···S nonbonded interaction could arise from the orbital interaction between the divalent S moiety (the S–C bond) and the fluorine atom (Fig. 3). Notably, in a recent work, Gabbaï and Zhao obtained quite similar results by performing NBO analysis on a zwitterionic sulfonium fluoroborate; in this case, the same orbital interaction between S and F was invoked to explain both the stability and the reactivity of the considered fluoroborate molecule.[7] Also, Allegra *et al.* estimated, *via ab initio* calculations, that the presence of F···S interactions in substituted bithiophenes affected the conformations of these compounds and that the intensity of such interactions is in the range of H-bonds.[8] It is worth noting that the significantly large changes in the occupancies are only observed for the σ* orbital of the S–C bond (σ^*_{S-C}) and the n_F natural orbital of fluorine (Table S1, ESI†) with marginal changes for the bonding orbital of the S–C bond (σ_{S-C}) and the Rydberg orbital on S. These results clearly demonstrate that the orbital interaction between S and F may be the predominant F···S nonbonded interaction, its main origin being the electron delocalization from the fluorine lone pair to the low-lying σ* orbital of a C–S bond. Interestingly, another theoretical study carried out on *ortho* substituted arylselenides proposed that the n (from electron-pair donor) and σ* (from electron-pair acceptor) orbital overlap is indeed a contributing factor toward the intramolecular nonbonding interaction.[9]

Considering the few reports on the F···S weak interaction,[7–10] we next undertook a survey at the Cambridge Crystallographic Data Center (CCDC) which allowed us to find a considerable number of high resolution crystal structures exhibiting inter- and intramolecular F···S distances shorter than the sum of van der Waals radii of F and S (3.27 Å) (Fig. S2, ESI†). Fig. 4A represents an example of such a structure in which the F atom is situated close to the S atom (3.06 Å).[11] This is likely due to an attractive F···S interaction as opposed to the repulsive steric interaction. By further searching PDB, we also found that the F···S interactions existed in

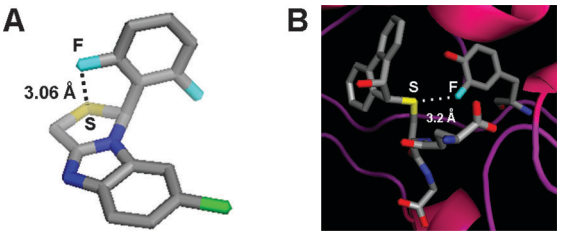


Fig. 4 Examples with the F···S distance shorter than 3.27 Å, the sum of van der Waals radii of F and S. (A) is a small molecular example; (B) is a protein/ligand complex with the 3-fluorotyrosine in the mutant glutathione (GSH) transferase. Atom color code: C, gray; F, cyan; S, yellow; Cl, green; N, blue; O, red.

protein complexes. Fig. 4B shows that the F atom of 3-fluorotyrosine in the mutant glutathione transferase lies very close to the S atom in the ligand (3.20 Å).[12] Collectively, all these data provide multiple evidence for the F···S interaction, which might exist ubiquitously and bring about considerable changes in structure and properties such as those described above.

It is worth mentioning that various weak interactions involving fluorine have recently attracted increasing interest following the flourishing development of fluorinated compounds in materials science and medicinal chemistry. Among them, the seemingly weak interactions often contribute critically to the special and unique properties manifested by some fluorinated compounds.[1a,c] The weak F···S interaction disclosed here has been largely ignored until now and has not received thorough investigation yet. Future studies on this and other fluorine interactions will undoubtedly enhance our understanding of the special properties demonstrated by fluorinated compounds, for which certain peculiar phenomena are often left unexplained.

We thank Dr Michel Giorgi for his help during the CCDC crystal structure survey.

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