Through-space ^{13}C–^{19}F coupling can reveal conformations of modified BODIPY dyes†

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The fact that only compounds 1a, 1b and 2a in the series 1–3 show long-range ^{13}C–^{19}F coupling can be used to draw conclusions regarding the structures of these molecules.

Through-space coupling between carbon and fluorine atoms that are forced together through geometric constraints is a well-known phenomenon,[1–3] but it is not often used as a tool to gauge molecular conformations.[4–6] Here we describe such an application as applied to 3,5-diaryl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY®) dyes 1–3.[7]

1a X = OMe, Y = CH$_2$CH$_2$
  b X = H, Y = CH$_2$CH$_2$
2a X = H, Y = S
  b X = H, Y = O

3a X = H
  b X = OMe
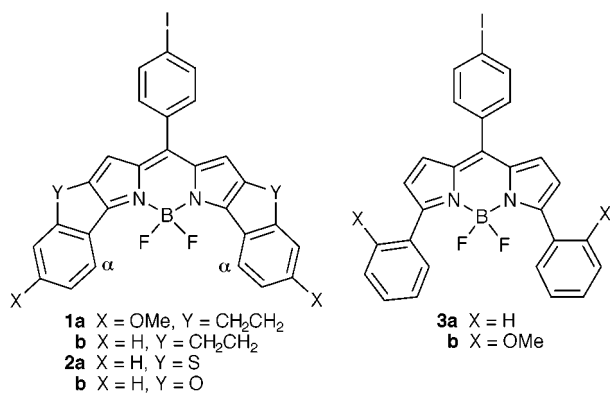
Briefly, the circumstances that led to this study were as follows. Our group is attempting to prepare new fluorescent dyes for biotechnological applications.[8,9] An important part of these studies is to refine the fluorescence properties of the target dyes by relating them to molecular structure. As part of our investigations to determine molecular structure we observed that a through-space ^{13}C–^{19}F coupling[10] is observed only for compounds **1a**, **1b** and **2a** in this series, and this parameter can be correlated with their molecular conformation. These compounds show a triplet in their ^{13}C{^{1}H} spectra (**1a** δ 130.1, t, J = 11.0 Hz; **1b** δ 128.4, t, J = 11.2; **2a** δ = 126.7, t, J = 5.2 Hz). APT and HETCOR experiments[11] established that the carbons responsible for these triplets were the ones marked **α** (henceforth referred to as C$^\alpha$). A combination of two decoupling experiments was performed on **1a** to prove that this splitting was due to coupling with the two fluorine atoms. First, a ^{13}C NMR spectrum was recorded without any decoupling, and the C$^\alpha$ appeared as a doublet of triplets (J = 164 and 11 Hz). A proton-coupled, fluorine-decoupled ^{13}C NMR spectrum of the same sample was then recorded, and the carbon of interest appeared as a doublet (J = 164 Hz). These experiments indicate that the triplet arises from coupling of the C$^\alpha$ to the two fluorine atoms.

A comparison of spectral data for compounds **1** and **2** is shown in Table 1. The ^{19}F and ^{11}B NMR chemical shifts for these dyes decrease in the order **1** > **2a** > **2b**, and the same trend was also observed in the ^{1}H NMR spectra of these

Table 1 Selected spectroscopic data for **1–2**

Compound	Chemical shift (δ/ppm)[a]		
	^{1}H[b]	^{19}F[c]	^{11}B[d]
1a	8.78	−137.5	9.29
1b	8.82	−137.3	3.98
2a[e]	8.75	−147.0	—
2b	8.24	−150.6	0.41

[a] In CDCl$_3$. [b] For C$^\alpha$–H or the corresponding C–H, at 300 MHz relative to a deuterium lock. [c] At 282 MHz relative to CFCl$_3$ as external reference. [d] At 64 MHz relative to BF$_3$·OEt$_2$ as external reference. [e] ^{11}B NMR data could not be obtained for this compound since it is relatively insoluble in the common organic solvents used for NMR studies.

materials. The observed C–F coupling constants in this series decrease in the same order. These observations imply that the factors that govern the ^{19}F chemical shifts also impact C–F coupling constants in this series.

It is unlikely that C$^\alpha$ is coupled to the fluorine atoms *via* covalent bonds in the aromatic system, for several reasons. First, if it were to occur, the observed value of 11 Hz would be an exceptionally large *J*-parameter for a five-bond coupling. Second, other carbons in compounds **1** and **2a** would most probably be affected in the same way if that coupling mechanism was operative, especially those that are less than five bonds away. Finally, similar five-bond coupling might then also be observed for compound **2b** and **3**, but they were not.

A single crystal, X-ray diffraction analysis was performed on compound **1a** to gain more insight into the nature of the C$^\alpha$–F interactions.‡ Molecule **1a** crystallizes in a bow-shaped conformation making the two fluorine atoms inequivalent (even though they are equivalent in the ambient solution phase ^{19}F NMR spectrum of this compound, Fig. 1). Moreover, there are four C$^\alpha$–F distances since the BF$_2$ entity does not reside at a
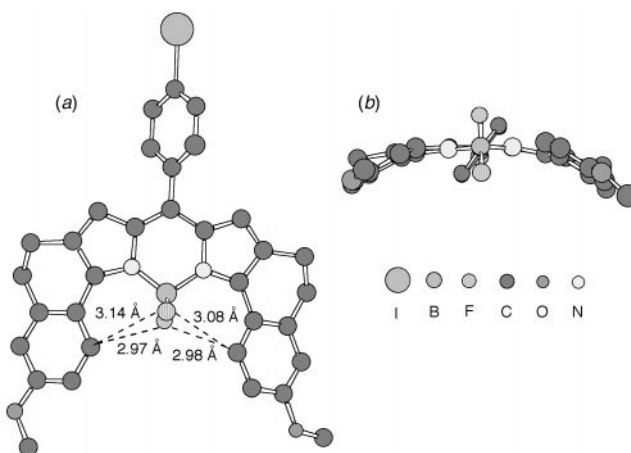

Fig. 1 Chem3D representations of **1a** from X-ray crystallographic data: (*a*) top view showing C$^\alpha$–F distances; (*b*) side view illustrating curvature of the molecule.

position that is exactly equidistant to both aromatic rings in the crystal structure. The four C^{α}–F distances are similar; they vary between 2.97(1) and 3.14(1) Å, and average to 3.04(8) Å. More variance was observed for the C^{α}–H···F distances. Electron density maps were used to locate the protons in this molecule, and their positions were refined (though of course, not to the same degree of accuracy as the heavier atoms). Nevertheless, the shorter C^{α}–H···F distance is no less than 2.29(1) Å, the longer one is no more than 2.75(1) Å, and the average value was measured as 2.5(2) Å. Comparison of the average C–F distance {3.04(8) Å} with the sum of the van der Waals radii for carbon and fluorine (3.19 Å)[12] implies that an interaction between these atoms is likely. Similarly, the average C^{α}–H···F distance {2.5(2) Å} is less than the sum of the van der Waals radii for hydrogen and fluorine (2.62 Å).

It appeared from the solid state structural analyses, outlined above, that the C^{α}–F interaction observed in the ^{13}C NMR spectra of compounds **1** is due to a close interaction of these atoms, through space. Crystallographic data was not obtained for compounds **2**, but a series of calculations was performed to establish why the interaction was observed for **2a** but not **2b**. Briefly, these were performed in the Cerius2 collection of programs (Molecular Simulations, Inc.). Preliminary optimizations were performed *via* molecular mechanics using the Universal Force Field (designed to accommodate all the atoms in the periodic table).[13–15] Final geometry optimizations were obtained at the semi-empirical level using the AM1 method within MOPAC.[16,17] Throughout these calculations, the iodine atoms in the real molecules were substituted by chlorine atoms in the virtual compounds.

Calculations on the Cl-for-I analog of compound **1a** gave a minimized structure obtained having the same curved conformation observed from the X-ray diffraction study (Fig. 1). Moreover, all the bond parameters were similar (data not shown). This result indicated that the AM1 calculations were reliable for this molecular type.

Simulated structures of the Cl-for-I analogs of compounds **2** are shown in Fig. 2. Comparison of Fig. 1 and 2 shows that the latter are essentially planar: they do not have the bow-shaped structure that compound **1a** has. Distances between the F- and C^{α}-atoms increase in the order **1a** < **2a** < **2b**. They are no longer within the sum of the van der Waals radii for carbon and fluorine for compound **2b**.

These structural studies clarify why the trend on the F-to-C^{α} coupling constants should be as observed. The ethylene bridges of compound **1a** force the benzene rings inwards towards the fluorine atoms, giving an exceptionally close interaction between the C^{α} and F atoms. Conversely, the S and O atoms in compounds **2** pull the benzene rings outward, giving a relatively
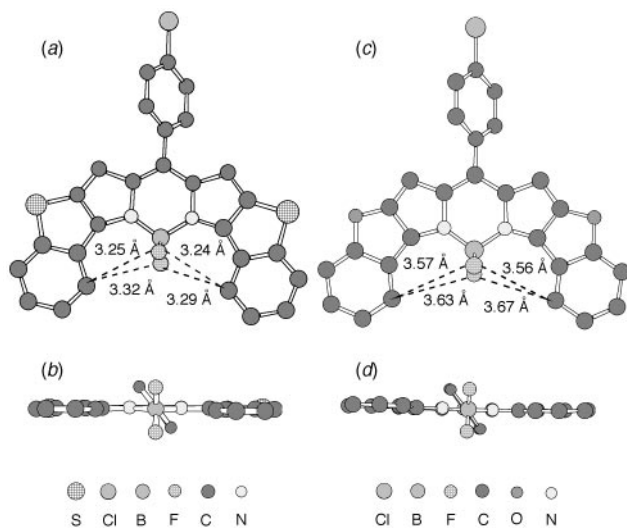
open structure. However, this effect is less important for **2a** than for **2b** for two related reasons that expand the five-membered rings containing the sulfur atoms. First, the atomic size of sulfur is greater than that of oxygen. Second, C–S bond lengths are longer than for C–O bonds (typically 1.75 Å for sp^2 C–S bond *vs*. 1.34 Å for sp^2 C–O bond).

It is surprising that couplings between the C^{α}–H···F atoms were not observed for compounds **1** and **2a**. It appears that the C^{α}–H···F coupling is too small to be observed conveniently in the proton NMR spectra of these compounds. However, the C^{α}–H resonance for compound **1a** was broader than other aromatic protons in this molecule (2.7 Hz at half-peak-height) and sharpened in a ^{1}H{^{19}F} experiment (2.1 Hz at half-peak-height).

There are two possible rationales for the coupling observed between the C^{α}–F atoms in compounds **1** and **2a**. One is a thermodynamically favorable H-bonding interaction between the aromatic hydrogen and the fluorine atoms. Similar interactions have been proposed before.[18–20] However, we believe that the coupling is really a consequence of crowding within the bay area that contains the BF$_2$ entity in these molecules. Whatever the origin of these effects, it's clear from the data presented here that they can be used as a tool to access molecular structure.

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Fig. 2 Chem3D representations of the Cl-for-I analogs from AM1 calculations: (*a*) top view of **2a** showing C^{α}–F distances; (*b*) side view of **2a**; (*c*) top view of **2b** showing C^{α}–F distances; (*d*) side view of **2b**.