

# ChemComm

Chemical Communications

rsc.li/chemcomm



ISSN 1359-7345



ROYAL SOCIETY  
OF CHEMISTRY

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COMMUNICATION

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long-range H–F interactions in  $\alpha$ -fluoro amides



Cite this: *Chem. Commun.*, 2019, 55, 2253

Received 17th December 2018,  
Accepted 16th January 2019

DOI: 10.1039/c8cc09987a

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# Combined experimental and theoretical study of long-range H–F interactions in $\alpha$ -fluoro amides†

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A combined experimental and computational approach provided insight into the nature and conformational dependence of long-range  $^4J_{\text{HF}}$  couplings in  $\alpha$ -fluoro amides. The dependence of  $^4J_{\text{HF}}$  on substituents and the solvent was investigated. H–F coupling constants determined by NMR spectroscopy are in agreement with DFT calculations. NBO analysis revealed that a favourable  $n_{\text{F}} \rightarrow \sigma_{\text{NH}}^*$  interaction correlates with the magnitude of  $^4J_{\text{HF}}$ .

The introduction of fluorine into organic compounds is a valuable strategy to modify their physico-chemical properties and improve, *e.g.*, the pharmacokinetic profile of drugs.<sup>1–5</sup> One example are  $\alpha$ -fluorinated amides that have been used to tune ligand–protein interactions<sup>6–9</sup> and modulate the activity of small molecules with, for example, anticonvulsant,<sup>10</sup> antibacterial,<sup>11</sup> and cholesterol-lowering properties.<sup>12</sup>  $\alpha$ -Fluorination has also enabled control over the backbone conformation of  $\beta$ -amino acids and  $\beta$ -peptides.<sup>13–19</sup> Previous studies showed that  $\alpha$ -fluoro propionamides adopt mainly an antiperiplanar (ap) conformation, and to a lesser degree a *gauche* conformation (Fig. 1).<sup>20–22</sup> The driving force for the preferred ap conformation is the opposing dipoles of the vicinal C–F and C=O bonds.<sup>‡22–24</sup> Jaun and Seebach observed in  $\alpha$ -fluoro  $\beta$ -peptides a conformation dependent NH–F ( $^4J_{\text{HF}}$ ) coupling between fluorine and the adjacent amide proton.<sup>17–19</sup> This long-range coupling is reminiscent of hydrogen bond-mediated fluorine couplings,<sup>§25,26</sup> as *e.g.* in *ortho* fluorinated anilides or benzamides.<sup>27,28</sup> Its presence suggests that the ap conformation is not only driven by electrostatic dipole–dipole interactions but might be supported by an additional weak interaction between fluorine and the amide group.<sup>¶29–31</sup>

Herein, we probed the nature of the long-range  $^4J_{\text{HF}}$  coupling constant by studying a series of  $\alpha$ -fluoro amides bearing different

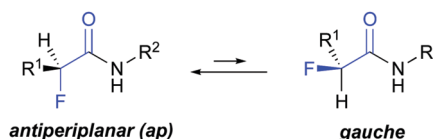


Fig. 1 Equilibrium between antiperiplanar (ap) and *gauche* conformers of  $\alpha$ -fluoro amides.

substituents with computational and experimental tools. We investigated the  $\alpha$ -fluoro amides in different solvents by NMR spectroscopy and in the solid state by X-ray crystal structure analysis. We show that the value of  $^4J_{\text{HF}}$  can be accurately predicted by DFT calculations and that a weak through-space stereoelectronic  $n \rightarrow \sigma^*$  interaction between the F and N–H moieties correlates with the magnitude of the  $^4J_{\text{HF}}$  coupling constant.

We started by synthesising  $\alpha$ -fluoro amides 1–5 as model compounds for our experimental studies (Scheme 1). These propionamide and malonamide derivatives were readily accessed from the appropriate  $\alpha$ -fluoro thioester by reaction with methyl amine, benzyl amine, and aniline. Notably, the thioester allowed even for effective amidation with the poor nucleophile aniline.<sup>32</sup>



Scheme 1 Synthesis of  $\alpha$  fluoro amides 1–5.

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† Electronic supplementary information (ESI) available: Details on the NMR spectroscopic analyses, DFT calculations, X-ray crystallography, and analytical data of 1–5. CCDC 1884973–1884976. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc09987a



$\alpha$ -Fluoro amide **1** with methyl substituents at C( $\alpha$ ) and at NH served as reference for our studies. Methyl ester derivative **4** was designed to probe the effect of an electron withdrawing group (EWG) at C( $\alpha$ ). We envisioned that an EWG would lower the electron density at the fluorine atom and thereby weaken the putative NH–F interaction. Such a weakened interaction would be reflected in a smaller long-range  $^4J_{\text{HF}}$  coupling. Conversely, the phenyl moieties of anilides **3** and **5** were expected to increase the acidity of the N–H group<sup>33</sup> and thus strengthen the F··H–N interaction. Amide **2** with a benzyl group at the NH was used to explore the effect of an aromatic moiety that is not directly attached to the amide moiety.

Before starting the spectroscopic analysis, we performed DFT calculations with representative  $\alpha$ -fluoro amides at the B3LYP/AUG-cc-pVTZ level of theory using the program Gaussian. For  $\alpha$ -fluoro amide **1** restrained geometry optimizations (in steps of 15°) *in vacuo* were performed for a series of F–C–C=O dihedral angles ( $\theta$ ). The ap conformer was found to be energetically favoured by 5 kcal mol<sup>-1</sup> over the *gauche* ( $\theta = -60^\circ$ ) conformer (Fig. 2, black curve). This is  $\sim 1$  kcal mol<sup>-1</sup> less than reported previously by Banks *et al.* and Tormena *et al.* who used the same functional but smaller basis sets.<sup>21,22</sup> In agreement with these reports, we also found that *in vacuo* the *gauche* conformer is not a local minimum on the potential energy surface. In contrast, the *gauche* conformer becomes a local minimum when the calculations were carried out with implicit solvation.<sup>21</sup> Unrestrained geometry optimization converged to a local minimum of  $\theta = -55.3^\circ$  with the polarizable continuum model (PCM) parametrized for CHCl<sub>3</sub> and  $\theta = -46.3^\circ$  with PCM parametrized for DMSO. Frequency calculations in implicit solvent for both ap and *gauche* conformations of **1** led to thermally corrected free energy differences ( $\Delta G_{\text{ap-g}}$ ) of 2.8 kcal mol<sup>-1</sup> in CHCl<sub>3</sub> and 1.8 kcal mol<sup>-1</sup> in DMSO. This computational finding suggests that the ap conformer is favoured over the *gauche* conformer regardless of the solvent.

Next, we computed the dependence of the  $^4J_{\text{HF}}$  coupling constant on the dihedral angle  $\theta$  for  $\alpha$ -fluoro amide **1** (Fig. 2, blue curve).<sup>34</sup> The calculated  $^4J_{\text{HF}}$  coupling curve shows a sharp

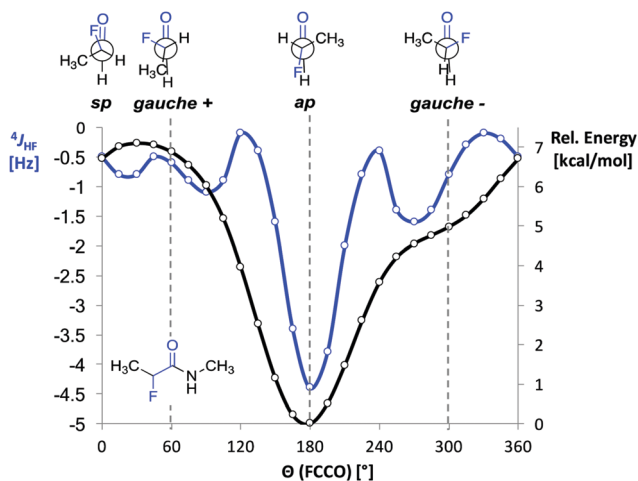


Fig. 2 DFT calculated  $^4J_{\text{HF}}$  coupling constant and relative B3LYP/AUG-cc-pVTZ energies as functions of the dihedral angle F–C–C=O ( $\theta$ ) in **1**.

Table 1 Experimental and calculated values of  $^4J_{\text{HF}}$  (Hz) for **1–5**<sup>a</sup>

Entry	Solvent	$^4J_{\text{HF}}$ [Hz]				
		1	2	3	4	5
1	Calc. (ap)	-4.3	n.d.	-7.0	-3.3 <sup>b</sup>	n.d.
2	CDCl <sub>3</sub>	-4.4	-4.6	-6.8	-3.3	-4.5
3	CD <sub>2</sub> Cl <sub>2</sub>	-4.3	-4.3	-6.5	-2.7	-4.2
4	d <sub>6</sub> -Acetone	-2.9	-2.8	-3.9	-1.5	-1.8
5	CD <sub>3</sub> OH	-2.4	> -2	n.d.	> -2	n.d.
6	d <sub>6</sub> -DMSO	-1.7	-1.7	-1.8	-0.7	> -1

<sup>a</sup> Determined at 50 mM. <sup>b</sup> The calculations were performed on the N-methyl analogue of **4**.

minimum (strongest coupling) at the ap conformation where NH and F are closest in space ( $^4J_{\text{HF}} = -4.3$  Hz,  $\theta = 180^\circ$ ). For the *gauche* conformation the coupling strength is significantly attenuated ( $^4J_{\text{HF}} = -0.8$  Hz,  $\theta = 300^\circ$ ). The calculated dependence of  $^4J_{\text{HF}}$  on  $\theta$  is in agreement with experimental observations by Jaun and Seebach for 2-fluoro- $\beta^3$ -alanine in peptides.<sup>17</sup> For  $\theta$  close to 180° the absolute value of  $^4J_{\text{HF}}$  was reported to be 3.7 Hz whereas for  $\theta$  close to 90° no resolved coupling could be detected ( $|^4J_{\text{HF}}| < 0.5$ ).

We also performed unrestrained geometry optimization *in vacuo* of the ap conformations for **1**, **3**, and the N-methyl analogue of **4** using the same basis set and functional. The resulting minimum energy conformations were then used to predict the values of  $^4J_{\text{HF}}$ . These calculated  $^4J_{\text{HF}}$  coupling constants of **1**, **3**, and **4** differ significantly from each other. The absolute value for anilide **3** is greater ( $^4J_{\text{HF}} = -7.0$  Hz) and that of **4** with an electron withdrawing ester group next to the C–F bond is smaller ( $^4J_{\text{HF}} = -3.3$  Hz) compared to the one of reference compound **1** ( $^4J_{\text{HF}} = -4.3$  Hz, Table 1, entry 1).

Next, we determined absolute values of the  $^4J_{\text{HF}}$  coupling constants experimentally by recording <sup>1</sup>H and <sup>19</sup>F NMR spectra and started by using CDCl<sub>3</sub> as a solvent. As suggested by the calculations, the sign of  $^4J_{\text{HF}}$  was found to be negative by analysis of the cross-peak fine-structure in a constant-time <sup>13</sup>C-HMBC spectrum. Reassuringly, the experimental  $^4J_{\text{HF}}$  values in CDCl<sub>3</sub> do not deviate by more than 0.2 Hz from the predicted values (Table 1, entries 1 and 2). Such a good agreement is remarkable, in particular in light of the well-known difficulties of DFT calculations to predict coupling constants involving fluorine.<sup>35,36</sup>

Since amide moieties can form intermolecular H-bonds that could disturb the conformational properties of  $\alpha$ -fluoro amides, we recorded NMR spectra of **1–5** at different concentrations in CD<sub>2</sub>Cl<sub>2</sub> (0.8–200 mM). These studies showed that the experimental values of  $^4J_{\text{HF}}$  hardly change upon increasing the concentration. In contrast, the NH chemical shift has a significant concentration dependence, which suggests that intermolecular interactions between the amides occur ( $K_{\text{d}} \sim 0.1$ –1 M). This finding shows that possible intermolecular interactions between the amides do not affect the  $^4J_{\text{HF}}$  coupling constant to a significant extent.

Next, we explored the effect of substituents at the  $\alpha$ -fluoro amide on the value of the  $^4J_{\text{HF}}$  coupling. The NMR spectra of anilides **3** and **5** in CDCl<sub>3</sub> revealed stronger  $^4J_{\text{HF}}$  couplings (–6.8 Hz and –4.5 Hz) compared to those of the analogous benzyl amides **2** and **4** (–4.6 Hz and –3.3 Hz). This observation is in agreement



with the expected higher N–H acidity of **3** and **5** in comparison to **2** and **4**, respectively, and indicates a stronger F···H–N interaction. Conversely, the absolute  $^4J_{\text{HF}}$  values are lower in case of **4** and **5** that bear ester moieties compared to **2** and **3** with methyl groups at C $\alpha$ . This indicates that an electron withdrawing group (ester) at C $\alpha$  lowers the electron density at fluorine and weakens the F···H–N interaction. Thus, in accordance with our expectations, changes in molecular structure designed to modulate the strength of the putative F···H–N hydrogen bond are mirrored in the measured values of the  $^4J_{\text{HF}}$  coupling constant.

We then investigated the influence of the solvent on the value of the  $^4J_{\text{HF}}$  coupling constant by recording  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra of **1**–**5** in  $\text{CD}_2\text{Cl}_2$ ,  $d_6$ -acetone,  $\text{CD}_3\text{OH}$ , and  $d_6$ -DMSO. In the more polar solvents the strength of the  $^4J_{\text{HF}}$  coupling in **1**–**5** decreases (Table 1, entries 4–6). Considering the significant differences in the calculated  $^4J_{\text{HF}}$  coupling constants of *gauche* and *ap* conformations (Fig. 2), these data show that the *ap* conformer becomes less populated in polar solvents, which is expected based on the higher dipole moment of the *gauche* compared to the *ap* conformation.

Compounds **2**, **3**, and **4** crystallized and allowed for their conformational analysis by X-ray crystallography (Fig. 3).<sup>22</sup>  $\alpha$ -Fluoro amides **2** and **3** are in *ap* conformations in the crystalline state. Their interatomic NH–F distances of approximately 2.2 Å are significantly shorter than the sum of the van der Waals radii (2.5–2.7 Å). The F···H–N angles are 102° and 105° for **2** and **3**, respectively. Both, the inter-atom distances and the bond angles, match the criteria for H–F hydrogen bonds as defined by Dunitz and Taylor (F–H distance < 2.3 Å, F···H–X angle > 90°).<sup>37</sup> In contrast, the  $\alpha$ -fluoro amido moiety of **4** adopts a near *gauche* conformation in the solid state ( $\theta = 42^\circ$ ). The crystal packing of **2**, **3**, and **4** reveals that the amide groups are involved in intermolecular chain-type N–H–O interactions. In **4**, these intermolecular hydrogen bonds in the solid state override the favourable *ap* orientation of the F–C–C=O moiety observed in solution.<sup>38</sup>

Finally, we investigated the origin of the observed  $^4J_{\text{HF}}$  long-range coupling constant by NBO calculations.<sup>39</sup> Second order

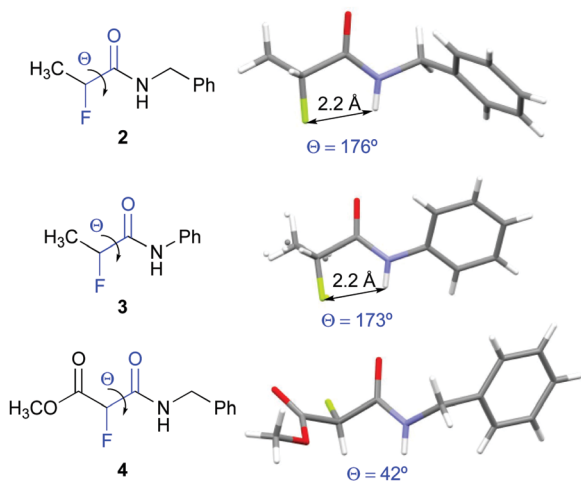


Fig. 3 X-ray crystal structures of **2**–**4**.



Fig. 4 Graphical representation of the  $n_{\text{F}} \rightarrow \sigma_{\text{NH}}^*$  interaction in **1**. (iso value = 0.02 e Å $^{-3}$ ).<sup>††</sup>

perturbation analysis revealed the presence of a favourable electron donation from the fluorine lone pair ( $n_{\text{F}}$ ) to the antibonding N–H orbital ( $\sigma_{\text{NH}}^*$ ) (Fig. 4). This finding suggests that this weak through-space interaction gives rise to the observed  $^4J_{\text{HF}}$  coupling. The calculations predict a contribution of this  $n_{\text{F}} \rightarrow \sigma_{\text{NH}}^*$  interaction of 0.8 kcal mol $^{-1}$  for **1**, 1.3 kcal mol $^{-1}$  for **3**, and 0.6 kcal mol $^{-1}$  for **4** to the stability of the *ap* conformer of these  $\alpha$ -fluoro amides.<sup>\*\*</sup> Thus, the strength of this interaction increases progressively from the *N*-benzyl amides **4** and **1** to the *N*-phenyl amide **3**, in agreement with the observed increase of the  $^4J_{\text{HF}}$  coupling constants.

In conclusion, our results show that the  $^4J_{\text{HF}}$  coupling in  $\alpha$ -fluoro amides depends on the substituents and the solvent. Calculated  $^4J_{\text{HF}}$  couplings for the *ap* conformations of a series of  $\alpha$ -fluoro amides match the experimental values. The  $^4J_{\text{HF}}$  coupling is strongest in the *ap* conformation when F and HN are closest in space. In this conformation the strengths of the observed  $^4J_{\text{HF}}$  couplings and predicted  $n_{\text{F}} \rightarrow \sigma_{\text{NH}}^*$  interactions correlate. This suggests that the  $^4J_{\text{HF}}$  coupling is a genuine through-space coupling concomitant with a F···H–N hydrogen bond.

We are grateful to the Swiss National Science Foundation (grant 200020\_169423) and the Laboratory of Organic Chemistry of ETH Zurich for financial support. We thank Rainer Frankenstein and Michael Solar for recording NMR spectra and X-ray crystal structures. This publication is dedicated to Prof. Bernhard Jaun on the occasion of his 70th birthday.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- ‡ For a similar charge-dipole effect, see ref. 24.  
 § For related examples on F···H–O bonds, see ref. 26.  
 ¶ Such a through space interaction is reminiscent of intrasidual hydrogen bonds within  $\beta$ -sheets formed by peptides, ref. 31.  
 || For details, see the ESI.<sup>†</sup>  
 \*\* In the *gauche* conformation of **1** this stabilizing contribution is absent.  
 †† Note, the relative signs of the  $n$  and  $\sigma^*$  orbitals have no physical relevance.

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