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Minimising conformational bias in fluoroprolines through vicinal difluorination†‡

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Monofluorination at the proline 4-position results in conformational effects, which is exploited for a range of applications. However, this conformational distortion is a hindrance when the natural proline conformation is important. Here we introduce (3*S*,4*R*)-3,4-difluoroproline, in which the individual fluorine atoms instil opposite conformational effects, as a suitable probe for fluorine NMR studies.

Proline is the only proteinogenic amino acid with a secondary amino group, resulting in the *cis*-peptide bond (Xaa–Pro) being significantly populated (Fig. 1a).[1] The proline amino group is part of a pyrrolidine ring, and its five-membered ring pucker is thus closely connected with the backbone ϕ-dihedral angle. In addition, its cyclic nature inherently restricts this dihedral angle such that it enhances the importance of n → π* interactions between subsequent carbonyl groups in peptides. This in turn has further implications for peptide conformation and influences the Xaa–Pro *cis*:*trans* ratio.[1,2] These peculiar chemical features result in specific conformational and dynamical properties that are central to a number of biological mechanisms behind protein folding, protein aggregation or protein–protein interactions.[3] The existence of peptidyl-prolyl *cis–trans* isomerases, a class of enzymes able to accelerate proline *cis–trans* isomerization, highlights the functional importance of this dynamical property in biology.[4] Furthermore, post-translational modifications of the pyrrolidine ring by hydroxylation confer mechanical properties to proline-rich proteins such as collagen by further enhancing these n → π* interactions.[3c] Incorporation of a fluorine atom at the proline 4- (or γ-) position strongly affects both its dynamical and conformational properties. Because of the highly polar C–F bond, a destabilisation of the planar charged amide resonance structures results, which manifests itself in an increased amide isomerisation rate. Ring pucker is affected through the *gauche* effect, which is a favourable $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation interaction.[5] This stereoelectronic effect requires the C–H and C–F bonds to be antiperiplanar, and the stereogenicity of the fluorine substituent thus leads to one of the two puckers being favoured (Fig. 1a).[1] Furthermore, C–F introduction affects the overall dipole moment, which also influences conformational stabilities (with a strong solvent effect).[6]

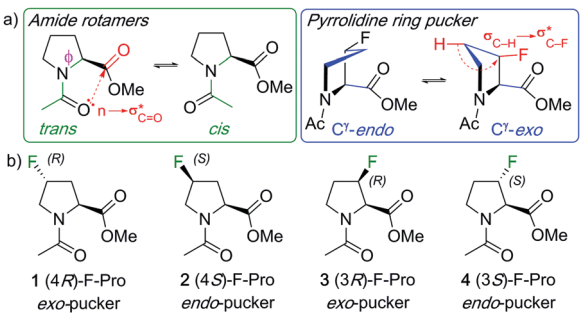

Fig. 1 Illustration of amide rotamer and pyrrolidine pucker structures (a), and typical monofluorinated L-proline models with their conformational bias (b).

N-Acylated proline esters such as **1**–**4** (Fig. 1b) are typical models to investigate the influence of fluorination on proline conformation.[7] In a landmark study, Raines and Markley demonstrated, through NMR studies in 1,4-dioxane, that the *exo*-pucker is dominant in the (4*R*)-fluoroproline derivative **1** (75% population for the *trans*-isomer), while the *endo*-pucker is the most populated one for the 4*S*-isomer **2**.[7] Originally investigated for its effect on collagen stability,[3c] proline fluorination is now applied for a variety of purposes in the biosciences

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including stability and activity studies of peptides and proteins, protein engineering,[8] as well as in medicinal chemistry applications.[1,9]

Fluorinated amino acids are of interest for biological ^{19}F NMR applications, due to its high intrinsic sensitivity, its increased sensitivity to chemical exchange processes due to the broad chemical shift range, and the absence of background signals in biological fluids.[10,11] Also, ^{19}F labelling of single residues in a peptide or protein can afford easy access to site-specific information. Given the pivotal role of prolines in protein folding, stability and binding, and the biological importance of interactions with proline-rich motifs in signalling proteins,[3a] prolines would be a judicious choice to introduce a ^{19}F reporter. Yet, while fluoroprolines have been a much-used tool to study peptide/protein structure and dynamics, or interactions between peptides and receptors,[3b,9b,12] their potential use as ^{19}F NMR probes has, to the best of our knowledge, never been exploited.

In many cases, the conformational bias caused by the common singly fluorinated prolines is a hindrance for biological ^{19}F NMR purposes, as it distorts the natural proline pucker conformation and/or amide *cis–trans* equilibrium and thus the properties of the system under study. Instead, for this purpose, fluorinated analogues in which two fluorines are introduced in such positions as to offset each other's conformational bias would be of more interest. For example, by combining the 4*S* and 4*R*-fluoro motif to give 4,4-difluoroproline derivatives (*e.g.* **5**, Fig. 2), their respective stereoelectronic effects influencing pucker are expected to cancel out.[1,13] While a detailed conformational analysis of 4,4-difluoroproline is yet to be published,[1] initial analysis indicated that the *exo*- and *endo*-puckers of 4,4-difluoroproline are of similar energy, and that its preorganisational capacity is close to that of proline.[14] However, a CF_2-group in which the two fluorine atoms are diastereotopic is not an ideal ^{19}F NMR reporter group because of the very large geminal F–F coupling (>200 Hz). This leads to severe *J*-modulation distortions in any NMR experiment involving, for instance, spin echoes, which is a key problem. Furthermore, since the fluorines typically have relatively close chemical shifts, strong second order effects are present, which complicate spectral interpretation. In addition, when introducing multiple fluoroproline probes, especially in similar environments (*i.e.* low-complexity peptide sequences such as polyprolines), the availability of a larger set of fluoroproline analogues with minimal conformational bias is desirable to prevent spectral overlap.

We wished to investigate the extent of compensating conformational bias in the proline ring by vicinal fluorine introduction at different ring carbons. For this, proline positions **3** and **4** are the most practical. Such analogues feature vicinal instead of geminal ^{19}F–^{19}F coupling, with $^3J_{F-F} \ll {}^2J_{F-F}$. In addition, CHF groups have very different ^{19}F chemical shift values than CF_2 groups. This leads to **6** and **7** as analogues of interest (Fig. 2). There is some precedent for these structures: syntheses of the (3*R*,4*S*)-difluorinated proline motif,[15] as in **6**, and of the (3*R*,4*R*)-difluoromotif[16] (not shown) have been reported. Unfortunately, many synthetic steps were required to convert 3,4-dehydroproline to Cbz-protected (3*R*,4*S*)-3,4-difluoro-L-proline[16] and 3-deoxy-3-fluoro-1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose to *N*-benzyl protected (3*R*,4*R*)-3,4-difluoro-L-proline.[16]

Here we report a short synthesis of **7** from (4*R*)-hydroxyproline, as well as NMR studies (amide *cis* : *trans* ratio and amide isomerisation rates) and preliminary theoretical calculations (ring pucker). The results are compared to the equivalent data of the 4,4-difluorinated derivative **5**.[14] Given **5** can be regarded as a combination of the 4*R*- and 4*S*-fluoroprolines **1** and **2**, and the 3*S*,4*R*-difluorinated derivative as a combination of the 3*R*- and 4*S*-fluoroprolines **2** and **3**, the corresponding conformational data of **1**–**3**, all of which were synthesised using described methodology,[17] were also obtained.

The synthesis of **7** is shown in Scheme 1, and employs a direct deoxyfluorination approach from the known[18] 3,4-diol, which was obtained from a suitably protected 3,4-dehydroproline. Marson has shown that bis-triflation of *N*-alkylated *trans*-3,4-dihydroxypyrrolidines, followed by TBAF treatment led to *trans*-3,4-difluoropyrrolidines with inversion of configuration in excellent yields.[19] Although the methyl ester and *N*-acetyl groups present in **7** could have been introduced from the start, benzyl ester and Boc amine protection was chosen in order to make the process relevant for the synthesis of suitable peptide synthesis building blocks. Given 3,4-dehydroproline is expensive, cheap (4*R*)-hydroxyproline was employed, which was protected to give known[20] **8** (not shown). Elimination of 4-hydroxyproline's hydroxyl group is typically achieved *via* a two-step procedure involving alcohol activation, leading to a mixture of 3,4- and 4,5-alkene isomers.[18a,b,21,22] Pleasingly, it was found that the one-pot Grieco elimination procedure[23] starting from **8** gave the desired alkene **9** in excellent (10 : 1) selectivity. Dihydroxylation of 3,4-dehydroproline with OsO_4 has been reported to form the all-*cis*-diol isomer in small quantities.[18] However, with potassium osmate (0.3 mol%), the *trans*-diol obtained is as the only observable isomer.[22b] Direct conversion of the 3,4-diol to the required 3,4-difluoro motif was best achieved with nonafluorobutanesulfonyl fluoride (NFF) in combination with a triphenyldifluorosilicate salt,[24] which led to **11** as the only 3,4-difluorinated stereomer in 24% yield. The enol

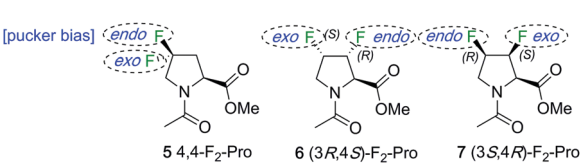
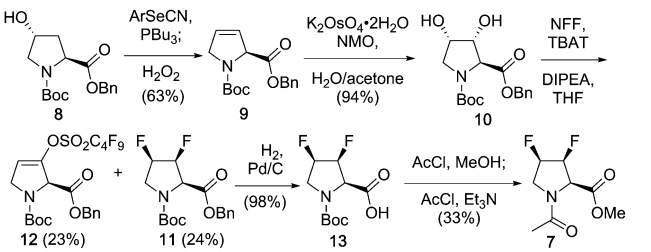


Fig. 2 Proposed difluorinated L-prolines featuring compensating conformational bias towards proline pucker.



Scheme 1 Synthesis of (3*S*,4*R*)-F_2-Pro.

sulfonate **12** was isolated in equal amounts, presumably through fluoride mediated E2 elimination of the corresponding bis-nonaflate intermediate. Only one regioisomer was isolated, which suggests that the bis-nonaflate intermediate preferentially adopted a C^{γ}-*exo* conformation, resulting in antiperiplanar disposition between the C3–H and C4–ONf bonds allowing for a smooth E2 reaction. Given this process essentially involves two separate deoxofluorination reactions, the obtained yield was deemed acceptable, as gram-scale quantities of **11** could be obtained. Finally, the protecting groups were replaced to give the 3,4-difluorinated model **7**.

Unambiguous assignment of the relative stereochemistry proving inversion of configuration in the fluorination step could be obtained by X-ray crystallographic analysis of **11** (Fig. 3), which crystallised in a perfect C^{γ}-*exo* pucker.§

Despite the expected acceleration of the *cis–trans* isomerisation rate, the exchange remains slow on the NMR time scale and both amide rotamers of **5** and **7** are always separately visible in the ^{1}H and ^{19}F NMR spectra. The difference in ^{19}F chemical shift resonances of the *cis* rotamers is larger than that of the *trans* rotamers, both for **5** and **7** (Table 1). As expected the J_{F-F} values for **5** are much larger than these of **7**; the close chemical shifts of the fluorine atoms of *trans*-**5** result in a roofed set of doublets (upon ^{1}H decoupling).

Next, the conformational properties of **5** and **7** were determined, and compared with the non-fluorinated *N*-acetylated proline methyl ester, the 4,4-difluorinated derivative **5**, and the monofluorinated prolines **1–3** (Table 2). The *cis* : *trans* ratio was measured with NMR for all compounds in $CHCl_3$ and D_2O. The ratios of both **5** and **7** in chloroform and water are quite similar to those of Ac-Pro-OMe, clearly cancelling out the marked biases seen in their respective monofluorinated progenitors.

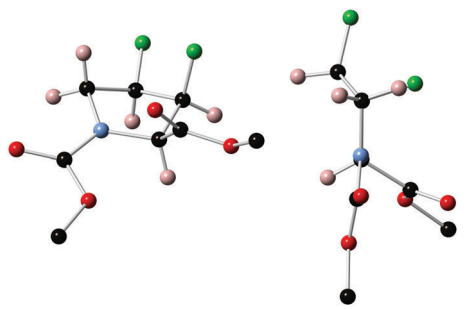


Fig. 3 X-ray structure of **11** (Bn and *tert*-Bu group removed for clarity).

Table 1 Fluorine chemical shift and coupling constant values of **5** and **7**

			5		**7**	
			$CDCl_3$	D_2O	$CDCl_3$	D_2O
δ (ppm)	*cis*	pro-*S*	−96.9	−95.5	F_4 −202.6	−200.3
		pro-*R*	−101.6	−104.7	F_3 −207.2	−208.5
	trans	pro-*S*	−98.4	−98.4	F_4 −206.7	−203.3
		pro-*R*	−99.3	−102.2	F_3 −208.9	−210.4
J_{F-F} (Hz)	*cis*		234.8 ± 0.1	235.8 ± 0.1	5.2 ± 0.1	5.7 ± 0.1
	trans		234.1 ± 0.1	234.8 ± 0.1	4.2 ± 0.1	4.7 ± 0.1

The *trans*-isomer appears in both chloroform and water slightly more favoured in **7** than in **5**. Next, the kinetic rate constants of *cis–trans* isomerisation $k_{cis-trans}$ and $k_{trans-cis}$ were determined in D_2O by 2D ^{1}H–^{1}H or ^{19}F–^{19}F EXSY for **3**, **5** and **7**, while for Ac-Pro-OMe, **1** and **2**, values were calculated based on results reported by Renner *et al.*[13]

Since $k_{cis-trans}$ and $k_{trans-cis}$ depend on the *cis* : *trans* ratios, we define their sum k_{ex} in order to compare isomerization kinetics between the different compounds. Clearly, every fluorinated compound shows accelerated isomerization kinetics compared to proline. When comparing the monofluorinated compounds, there are marked differences depending on the substitution patterns, even between **1** and **2**, showing that inductive effects alone do not explain the change in rate constant. Both doubly fluorinated compounds **5** and **7** show a further increase in isomerization kinetics, and turn out to have very similar rate constants. Interestingly, while **5** shows faster kinetics than its monofluorinated progenitors **1** and **2**, **7** unexpectedly has a slightly lower k_{ex} value than **3** (though markedly higher than **2**).

Finally, the preference of the five-membered ring pucker was assessed by DFT, using the M06 functional with cc-pVDZ basis set and chloroform or water as implicit solvents (Table 2). It is clear that the monofluorinated compounds **1**, **2** and **3** alter the pucker preference profoundly, while doubly fluorinated **5** and **7** display pucker ratios much more similar to the Pro model compound. In chloroform, **7** deviates more from Pro compared to **5**, with higher preference for the *exo*-pucker. In water, the limited deviations to Pro for both **5** and **7** are similar and in opposite sense compared to the *trans* form.

In conclusion, we find that 3*S*,4*R*-difluoroproline, with a vicinal *cis*-difluoromotif, is a proline analogue featuring minimal conformational bias with respect to the *cis–trans* rotamers and ring pucker thanks to the offsetting stereoelectronic effects instilled by the individual fluorine atoms. While the 4,4-difluoroproline variant also displays such characteristics, the 3,4-difluoroproline is superior as a fluorinated proline marker for ^{19}F spectroscopic studies of natural proline containing peptides and proteins due to the much more suitable NMR properties. Furthermore, we suggest that the very different chemical shifts of the 3,4- and 4,4-difluoroprolines offers opportunities for multi-proline labelling in peptides. The short, gram-scale synthesis assures convenient access to the 3*S*,4*R*-difluoro isomer, and the improvements for the hydroxyproline elimination and 3,4-dehydroproline dihydroxylation reactions, will be useful for synthetic proline chemistry. The 3*S*,4*R*-difluoroproline analogue is a valuable addition for applications of fluorinated prolines in medicinal chemistry and structural biology. Applications of these prolines in ^{19}F NMR structural studies are in progress.

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Table 2 Experimental *cis*–*trans* ratio's and amide isomerisation rates, and calculated pucker ratio's

	trans : *cis*, 25 °C		*cis*–*trans* kinetics (D_2O), 35 °C (s^{-1})			*endo* : *exo*[j]			
						$CHCl_3$		H_2O	
	$CDCl_3$	D_2O	$k_{cis-trans}$	$k_{trans-cis}$	k_{ex}[e]	*trans*	*cis*	*trans*	*cis*
Ac-Pro-OMe	79 : 21[b]	82 : 18[b]	0.031[f]	0.007[f]	0.038	81 : 19	90 : 10	66 : 34	83 : 17
5 (4,4)	75 : 25	78 : 22[c]	0.114 ± 0.006[g,h]	0.034 ± 0.002[g,h]	0.148 ± 0.008	64 : 36	93 : 7	77 : 23	89 : 11
7 (3*S*,4*R*)[a]	79 : 21	83 : 17	0.119 ± 0.009[g]	0.025 ± 0.002[g]	0.144 ± 0.011	41 : 59	78 : 22	56 : 44	90 : 10
1 (4*R*)	81 : 19[b]	87 : 13[b]	0.064[f]	0.010[f]	0.074	11 : 89	28 : 72	7 : 93	17 : 83
2 (4*S*)	62 : 38[b]	71 : 29[b]	0.037[f]	0.015[f]	0.052	97 : 3	99 : 1	99 : 1	99.5 : 0.5
3 (3*R*)	84 : 16	89 : 11[d]	0.141 ± 0.021[g,i]	0.019 ± 0.003[g,i]	0.159 ± 0.024	24 : 76	16 : 84	15 : 85	44 : 56

[a] CIP prioritization changes with introduction of the second fluorine atom, so **5** must be compared with **1** and **2**, and **7** with **2** and **3**. [b] In good agreement with reported ratios by Siebler *et al.*[6] [c] In good agreement with reported ratios by Shoulders *et al.*[14] [d] In good agreement with reported ratios by Kim *et al.*[25] [e] k_{ex} is defined as $k_{ex} = k_{cis-trans} + k_{trans-cis}$. [f] Calculated value based on Renner *et al.*[13] [g] Experimental NMR value obtained using similar procedure as Renner *et al.*[13] [h] Corresponding calculated values based on Renner *et al.* at 35 °C: 0.155 s^{-1} and 0.049 s^{-1}.[13] [i] Corresponding values reported by Thomas *et al.* at 37 °C using an alternative experimental procedure: 0.229 s^{-1} and 0.028 s^{-1}.[17c] [j] DFT values, using the M06 functional with cc-pVDZ basis set and $CHCl_3$ or water implicit solvent models.

Conflicts of interest

There are no conflicts to declare.

Notes and references

§ Crystal data $C_{17}H_{21}F_2NO_4$, M_r = 341.35, orthorhombic, *Pna*21 (No. 33), a = 9.3962(3) Å, b = 10.8390(3) Å, c = 33.4374(9) Å, $\alpha = \beta = \gamma = 90°$, V = 3405.45(17) Å^3, T = 100(2) K, Z = 8, Z' = 2, μ(MoKα) = 0.108, 24 677 reflections measured, 8447 unique (R_{int} = 0.0563) which were used in all calculations. The final wR_2 was 0.1201 (all data) and R_1 was 0.0703 ($I > 2(I)$).

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