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Modulation of an *n*→π* interaction with α-fluoro groups

Amit Choudhary, **Charles G. Fry**, and **Ronald T. Raines**
Graduate Program in Biophysics, Department of Chemistry, and Department of Biochemistry, University of Wisconsin, Madison, Wisconsin 53706

Ronald T. Raines: rtraines@wisc.edu

Abstract

Noncovalent interactions play an essential role in biological and chemical processes. In the main chain of common protein secondary structures, the lone pair (*n*) of a carbonyl oxygen is delocalized into the antibonding orbital (π*) of the subsequent carbonyl group. Herein, experimental and computational data reveal that this *n*→π* interaction can be attenuated by the inductive electron withdrawal of one or two α-fluoro groups in the donor. The steric effect of three α-fluoro groups, however, overcomes the inductive withdrawal. These data evoke a means to modulate the *n*→π* interaction in peptides, proteins, and other systems.

Keywords

Inductive effect; non-covalent interaction; *n*→π* interaction; prolyl peptide bond; stereoelectronic effect

Introduction

Non-covalent interactions play an essential role in many biological processes.1 Yet, the precise nature of many non-covalent interactions is debated actively. For example, the nature of the hydrogen bond has been a subject of debate between proponents of "electrostatic"2 and "partial covalency"3 models. Only recently was the partial covalency of the hydrogen bond established by a direct X-ray measurement4 and NMR *J*-couplings.5

A second non-covalent interaction encountered in many protein secondary structures6 and protein–ligand interactions7 is the carbonyl–carbonyl interaction (C=O…·C=O). Analogous to a hydrogen bond, this interaction was postulated initially to have an electrostatic origin.7,8 We recently presented experimental and theoretical evidence for its partial covalency6b,c and showed that this interaction arises primarily from the delocalization of the carbonyl oxygen lone pair (*n*) into the antibonding orbital (π*) of the carbonyl group. Such *n*→π* electronic delocalization is reminiscent of the Bürgi–Dunitz trajectory for nucleophilic additions to carbonyl groups,9 and is accompanied by pyramidalization of the acceptor carbonyl group.6b

We have continued to explore the nature of the *n*→π* interaction by using an Ac-Pro-OMe model system. In this system, the *trans* amide-bond isomer is stabilized differentially over the *cis* isomer by the *n*→π* interaction (Figure 1). This differential stabilization is reflected in the value of $K_{trans/cis}$, which can be measured experimentally with NMR spectroscopy. We and others have shown that the *n*→π* interaction alters the value of $K_{trans/cis}$.6,9,10 For example, amplifying the *n*→π* interaction by replacing the donor oxygen with sulfur

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increases the population of the *trans* conformation.6b We speculated that attenuating the $n \rightarrow \pi^*$ interaction should reduce the population of the *trans* conformation. Such attenuation can be achieved by reducing the electron-donating ability of the donor oxygen. We anticipated that replacing an acetyl hydrogen in the Ac-Pro-OMe system with the more electronegative fluorine would attenuate the $n \rightarrow \pi^*$ interaction.

The inductive electron withdrawal of fluorine can, however, be contravened by two other factors. First, electron donation from its lone pair into the antibonding orbital (π^*) of the adjacent carbonyl group is an important conformational determinant in many α-halocarbonyl compounds.11 Second, the large size of fluorine relative to hydrogen (r_F = 1.47 Å, r_H = 1.20 Å) makes the monofluoromethyl group more demanding sterically than a methyl group. Indeed, the Taft steric parameters indicate that the monofluoromethyl group (H_2FC–; E_s = 1.48) is larger than an ethyl group (E_s = 1.31), though smaller than an *n*-propyl group (E_s = 1.60).12 As the *cis* conformation in the Ac-Pro-OMe model system is more sensitive than the *trans*-conformation to steric interactions, the larger size of the monofluoromethyl group will increase the value of $K_{trans/cis}$. The steric requirements of the difluoromethyl (HF_2C–) and the trifluoromethyl groups (F_3C–) will be even greater than that of a monofluoromethyl group.

Here, we seek to modulate the $n \rightarrow \pi^*$ interaction by inductive electron withdrawal of α-fluoro groups. We report on the synthesis and $K_{trans/cis}$ values o f Z-C(O)-Pro-OMe compounds with Z = H_3C– (**1**), H_2FC– (**2**), HF_2C– (**3**), and F_3C– (**4**) (Figure 1A). Additionally, we employ hybrid density functional theory and Natural Bond Orbital (NBO) analysis13 to reveal the origins of the conformational preferences. We conclude that α-fluoro groups alter the $n \rightarrow \pi^*$ interaction by the mingling of other electronic effects, as well as steric effects.

Results and Discussion

Geometry optimization and frequency calculations were carried out on various conformations for each model compound (**1**–**4**) at the B3LYP/6–311+G(2d,p) level of theory using Gaussian ’03.14 The frequency calculations indicated that these conformations were true stationary points on the potential energy surface. Each of these optimized geometries was then analyzed with NBO 5.0 at B3LYP/6–311+G(2d,p) level of theory to determine the contribution of specific donor–acceptor orbital interactions to the conformational stability.

Conformational analyses of compound 2

Our *ab initio* calculations indicate that in the low energy conformations of compound **2**, the C–F bond can be oriented either *antiperiplanar* (*ap*) or *synperiplanar* (*sp*) to the amide carbonyl group (C_i=O_i) (Figure 2). The strength of the $n \rightarrow \pi^*$ interaction is greater in the *ap* conformation than in the *sp* conformation (Table 1). It is known that the fluorine lone pairs can donate electron density into the antibonding orbital (π^*) of the adjacent carbonyl group (C_i=O_i) in the *ap* conformation, but not in the *sp* conformation.11 Our NBO analysis suggests that this electron donation is worth 0.51 kcal/mol in the *trans–ap* conformation. Such electron donation enhances the ability of the carbonyl group to partake in the $n \rightarrow \pi^*$ interaction.

It is noteworthy that our calculations predict that the enhanced $n \rightarrow \pi^*$ interaction in the *trans–ap* conformation will not be reflected in the value of $K_{trans/cis}$. Close inspection reveals that the *cis–ap* conformation is stabilized by an $n \rightarrow \pi^*$ interaction wherein the fluoro group rather than the carbonyl group acts as the electron-pair donor. Thus, although the energy difference between the *trans*– and *cis–sp* conformations is −1.21 kcal/mol in the gas

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phase, the energy difference for the *ap* conformations is only −0.36 kcal/mol. Such interactions of fluoro groups with carbonyl groups have been reported previously.7,15

The lower value of $K_{trans/cis}$ for compound **2** than **1** indicates that steric effects do not play an important role. Instead, $K_{trans/cis}$ is diminished, at least in part, because of the attenuation of the $n\rightarrow\pi^*$ interaction in the *trans–sp* conformation.

Conformational analyses of compound 3

In the low energy conformations of compound **3**, the C–H bond can be *sp*, *ap*, or anticlinal/synclinal (*ac*/*sc*) to the amide carbonyl group (Figure 3). Interestingly, the inductive effect of a difluoromethyl group does not attenuate significantly the strength of the $n\rightarrow\pi^*$ interaction in the *trans* conformations of **3** (Table 1), as expected from the aforementioned delocalization of the fluorine lone pair into the antibonding orbital (π*) of the carbonyl group (C_i=O_i). Additionally, our NBO analysis indicates that all the *trans* conformations of **3** have higher amidic resonances than do those of **1**. The inductive effect exerted by the difluoromethyl group tends to polarize the electron density away from the donor carbonyl oxygen and the amidic nitrogen. The former polarization attenuates the $n\rightarrow\pi^*$ interaction, whereas the latter polarization strengthens the $n\rightarrow\pi^*$ interaction via amidic resonance. The electron donation by the fluorine lone pair and the amidic resonance attenuate the effect of inductive electron withdrawal on the strength of the $n\rightarrow\pi^*$ interaction.

A comparison of the value of $K_{trans/cis}$ for compound **3** with those for **1** and **2** indicates that both inductive and steric effects are important. Apparently, the inductive effect is strong enough to lower slightly the value of $K_{trans/cis}$for **3** with respect to that of **1**, but not strong enough to overcome the steric effect imposed by the difluoromethyl group. Thus, the value of $K_{trans/cis}$ for **3** is slightly less than that for **1** but greater than that for **2**.

It is interesting to note that in some *cis* conformations of compounds **2** and **3**, a weak *inverse* $n\rightarrow\pi^*$ interaction is observed. In the inverse $n\rightarrow\pi^*$ interaction, the roles of the donor and the acceptor carbonyl groups are reversed—the acceptor carbonyl acts as a donor while the donor carbonyl acts as an acceptor. This inverse $n\rightarrow\pi^*$ interaction could stabilize the *cis* conformation of the prolyl peptide bond, which is the basis for a polyproline I helix,16 and certain conformations of peptoids.17

Conformational analyses of compound 4

The strength of the $n\rightarrow\pi^*$ interaction in compound **4** (Table 1) is nearly identical to that of **1** and the *trans–sp* and *trans–ac* conformations of **3**. It follows that in the *trans* conformation the inductive electron withdrawal by the $-CF_3$ group is compensated by the electron donation of the fluorine lone pair into the antibonding orbital (π*) of the carbonyl group (C_i=O_i) and enhanced amidic resonance. Based on the strength of the $n\rightarrow\pi^*$ interaction alone, one would expect the $K_{trans/cis}$ of **4** to be identical to that of **1**. Yet, the steric requirement of a trifluoromethyl group ($-CF_3$) is greater than that of a methyl group. *A* strain values indicate that the CF_3– (2.10 kcal/mol) is at least as large as an isopropyl group (2.15 kcal/mol), whereas Taft parameters indicate it to be as large as an isobutyl group.10 As the value of $K_{trans/cis}$ for **4** (Figure 4) is greater than that for **1**, it follows that the large size of the trifluoromethyl group destabilizes the *cis* conformation significantly with respect to the *trans* conformation.

Conclusions

We have explored the conformational effects of attenuation of the $n\rightarrow\pi^*$ interaction in model compounds **1**−**4**. Our data suggest a dichotomous relationship between the inductive and the steric effects: the inductive effect tends to lower the value of $K_{trans/cis}$ by attenuating

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the $n \rightarrow \pi^*$ interaction, but the steric effect tends to increase the value of $K_{trans/cis}$. The *cis–trans* conformational equilibrium is dominated by the inductive effect in **2**, and by the steric effect in **4**. Our data also suggests that the attenuation of the $n \rightarrow \pi^*$ interaction by the inductive effects of fluorine in α-fluorocarbonyl compounds can be compensated by the electronic delocalization of the fluorine lone pair into the antibonding orbital (π*) of the carbonyl group and by enhanced amidic resonance.

Experimental Section

General

Commercial chemicals were of reagent grade or better, and were used without further purification. Anhydrous THF, DMF, and CH_2Cl_2 were obtained from CYCLE-TAINER ® solvent delivery systems (J. T. Baker, Phillipsburg, NJ). Other anhydrous solvents were obtained in septum-sealed bottles. Reactions were monitored by thin-layer chromatography with visualization by UV light or staining with $KMnO_4$ or I_2. In all reactions involving anhydrous solvents, glassware was either oven- or flame-dried. Flash chromatography was performed with columns of silica gel 60, 230–400 mesh (Silicycle, Québec City, Canada). The removal of solvents and other volatile materials "under reduced pressure" refers to the use of a rotary evaporator at water-aspirator pressure (<20 torr) and a water bath of <45 °C. All reported yields are unoptimized.

N-Trifluoroacetyl–(2*S*)-proline methyl ester (4)

To an ice cooled solution of Boc-ProOH (1.0 g, 4.7 mmol) in anhydrous MeOH (15 mL) was added AcCl (15 mL) dropwise. The mixture was stirred for 6 h, concentrated under reduced pressure, and dried overnight. The residue was then dissolved in dichloromethane and cooled to 0 °C. To this solution was added dropwise Hünig's base (1.2 g, 9.30 mmol), which was followed by trifluoroacetic anhydride (1.5 g, 7.10 mmol). After stirring for 0.5 h, the reaction mixture was quenched with MeOH, concentrated under reduced pressure, dissolved in 10% w/v citric acid solution, extracted with dichloromethane (4 × 100 mL), and dried over anhydrous $MgSO_4$(s). Column chromatography using hexane/EtOAc afforded **4** as a pale yellow liquid (0.85 g, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz, 4.6:1 mixture of two rotamers): δ 4.75-4.67 (m, 0.18H), 4.62-4.52 (m, 0.82H), 3.91-3.57 (m, 5H), 2.43-1.82 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 4.6:1 mixture of two rotamers): δ 171.5, 171.1, 156.1, 155.7, 117.6, 114.7, 105.0, 60.1, 59.3, 52.8, 52.6, 48.0, 47.2, 31.7, 28.5, 24.9, 21.2. ESI–MS: $[M + Na]^+$ calcd. 248.0510; found 248.0512 (<1 ppm).

N-Difluoroacetyl–(2*S*)-proline methyl ester (3)

To an ice cooled solution of Boc-ProOH (0.75 g, 3.5 mmol) in anhydrous MeOH (15 mL) was added AcCl (15 mL) dropwise. The mixture was stirred for 6 h, concentrated under reduced pressure, and dried overnight. The residue was then dissolved in dichloromethane and cooled to 0 °C. To this solution were added difluoroacetic acid (0.4 g, 4.1 mmol), EDC–HCl (0.83 g, 4.4 mmol), HOBt (0.58 g, 4.4 mmol), and triethylamine (1.0 g, 10 mmol). The reaction mixture was stirred overnight, quenched with water, extracted with dichloromethane (4 × 100 mL), and dried over anhydrous $MgSO_4$(s). Column chromatography using hexane/EtOAc afforded **3** as a colorless liquid (0.58 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz, 3.2:1 mixture of two rotamers): δ 6.72-5.91 (t, J = 53.2 Hz, 0.76H), 6.12-5.86 (t, J = 53.6 Hz, 0.24H), 4.80-4.73 (m, 0.24H), 4.59-4.49 (m, 0.76H), 3.92-3.58 (m, 5H), 2.36-1.84 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 3.2:1 mixture of two rotamers): δ 172.0, 171.7, 161.4, 161.1, 112.5, 112.3, 109.9, 109.8, 107.4, 107.3, 59.5, 58.5, 52.7, 52.5, 47.5, 46.1, 31.5, 28.5, 24.9, 21.3. **ESI–MS**: $[M + Na]^+$ calcd. 230.0605; found 230.0602 (1.3 ppm).

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N-Monofluoroacetyl–(2*S*)-proline methyl ester (2)

To an ice-cooled solution of Boc-ProOH (0.75 g, 3.5 mmol) in anhydrous MeOH (15 mL) was added dropwise AcCl (15 mL). The mixture was stirred for 6 h, concentrated under reduced pressure, and dried overnight. To this solution were added sodium fluoroacetate (0.4 g, 4.2 mmol), EDC–HCl (0.82 g, 4.4 mmol), HOBt (0.59 g, 4.4 mmol), and triethylamine (1.0 g, 10 mmol). The reaction mixture was stirred overnight, quenched with water, extracted with dichloromethane (4 × 100 mL), and dried over anhydrous $MgSO_4$(s). Column chromatography using hexane/EtOAc afforded **2** as a colorless liquid (0.4 g, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz, 2.6:1 mixture of two rotamers): δ 5.04-4.81 (m, 2H), 4.65-4.60 (m, 0.28H), 4.59-4.53 (dd, *J* = 8.7, 3.6 Hz, 0.73H), 3.80-3.49 (m, 5H), 2.35-1.79 (m, 4H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, 2.6:1 mixture of two rotamers): δ 172.4, 172.2, 165.9, 165.8, 81.9, 80.8, 80.1, 79.0, 59.1, 58.5, 58.4, 52.6, 52.4, 47.5, 45.9, 45.8, 31.6, 28.5, 24.9, 22.6. **ESI–MS**: $[M + Na]^+$ calcd. 212.0699; found 212.0691 (3.8 ppm).

Measurement of $K_{trans/cis}$ values for compounds 2–4 with NMR spectroscopy

Each compound (5–10 mg) was dissolved in $CDCl_3$. ^{1}H spectra were acquired and worked up using the software package NUTS (Acorn NMR, Livermore, CA). Values of $K_{trans/cis}$ were determined from the relative areas of the *trans* and *cis* peaks. NOEDIFF experiments were carried out to confirm the proton assignments for **2** and **3**. ^{19}F–^{1}H NOE experiments were carried out for **4**. TOCSY1D experiments were used for assignments of overlapped ^{1}H resonances from the two conformations. The TOCSY1D pulse sequence used was from the standard ChemPack library available for Varian spectrometers with a 5-mm inverse triple PFG-equipped probe. The sequence uses DPFGSE and SEDUCE-shaped RF pulses for multiplet selection, and an MLEV-17 spin lock for mixing. Zero-quantum filtering was implemented. Selection of the 4.705 or 4.570 ppm multiplets were clean, as demonstrated by mix = 0 spectra. The spin lock power equaled 9.4 kHz. Spectra at mix times = 0, 0.015, 0.035, 0.055, 0.080 and 0.150 s were obtained. Other parameters used were: d1 = 4 s, at = 2 s, sspul = 'y' (G_Z–90°–G_Z), ss = −4, and nt = 16. For processing, fn = 4 ×np, and lb = 0.5. TOCSY1D spectra were referenced to TMS, and obtained by using a Varian INOVA spectrometer with ^{1}H resonating at 599.76 MHz. T_1 values measured by standard inversion-recovery methods ranged from 1.5 to 3.2 s. The TOCSY1D spectra showed clean polarization of the two respective conformational spin systems, minor coupled through the 4.705 ppm and major through the 4.570 ppm multiplet.

All experiments involving ^{19}F were performed on a Varian INOVA spectrometer, having resonance frequencies of 470.64 MHz for ^{19}F and 500.23 MHz for ^{1}H. All ^{19}F spectra are referenced by the unified scale,18 with the ^{19}F Ξ value referenced to $CFCl_3$. The unified scale utilizes the ^{1}H spectrum acquired from the same sample, experimentally referenced with TMS set to 0 ppm. A 5-mm dual-coil ^{1}H–^{19}F Varian probe was used.

Standard ^{19}F 1D spectra were obtained without ^{1}H decoupling using *d1* = 4, *at* = 1.5, *nt* = 8, *ss* = 2, *pw* = 30°. The sweep width was reduced from an initial 400 ppm to 181 ppm to improve digital resolution. No peaks were observed except for the three singlets: CF_3 peaks for the minor and major isomers at −71.712 and −72.758 ppm, respectively, and a small peak (<2%) at −75.754 ppm. The ^{1}H–^{19}F dual probe used for these studies did not have PFG capability. Hence, ^{1}H–^{19}F NOEs were obtained by using NOE difference methods as follows. Our INOVA-500 spectrometer has a single high-band AMT transmitter, so re-cabling to allow RF splitting and recombining while retaining high sensitivity for both nuclei was necessary.19

With NOE difference methods, a saturation pulse is applied to one multiplet; in our experiments, we chose the CF_3 singlets. A saturation power between –10 and 0 dB was

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found to work well (that is, the pulse did not affect the nearby multiplet). Saturation equalizes the ±½ spin states of the ^{19}F nuclei, which will then produce NOEs at nearby protons. Acquiring ^{1}H spectra with the ^{19}F saturation pulse applied at the reference position and subtracting that spectrum from another having the saturation pulse at the CF_3 position produces the NOEdiff spectra, as shown in Figure 4. Parameters for these spectra were: *nt* = 1200, *ss* = 16, *dpwr* (=*satpwr*) = −4, *d1* = 10, *at* = 4, *bs* = 16, *il* = 'y'.

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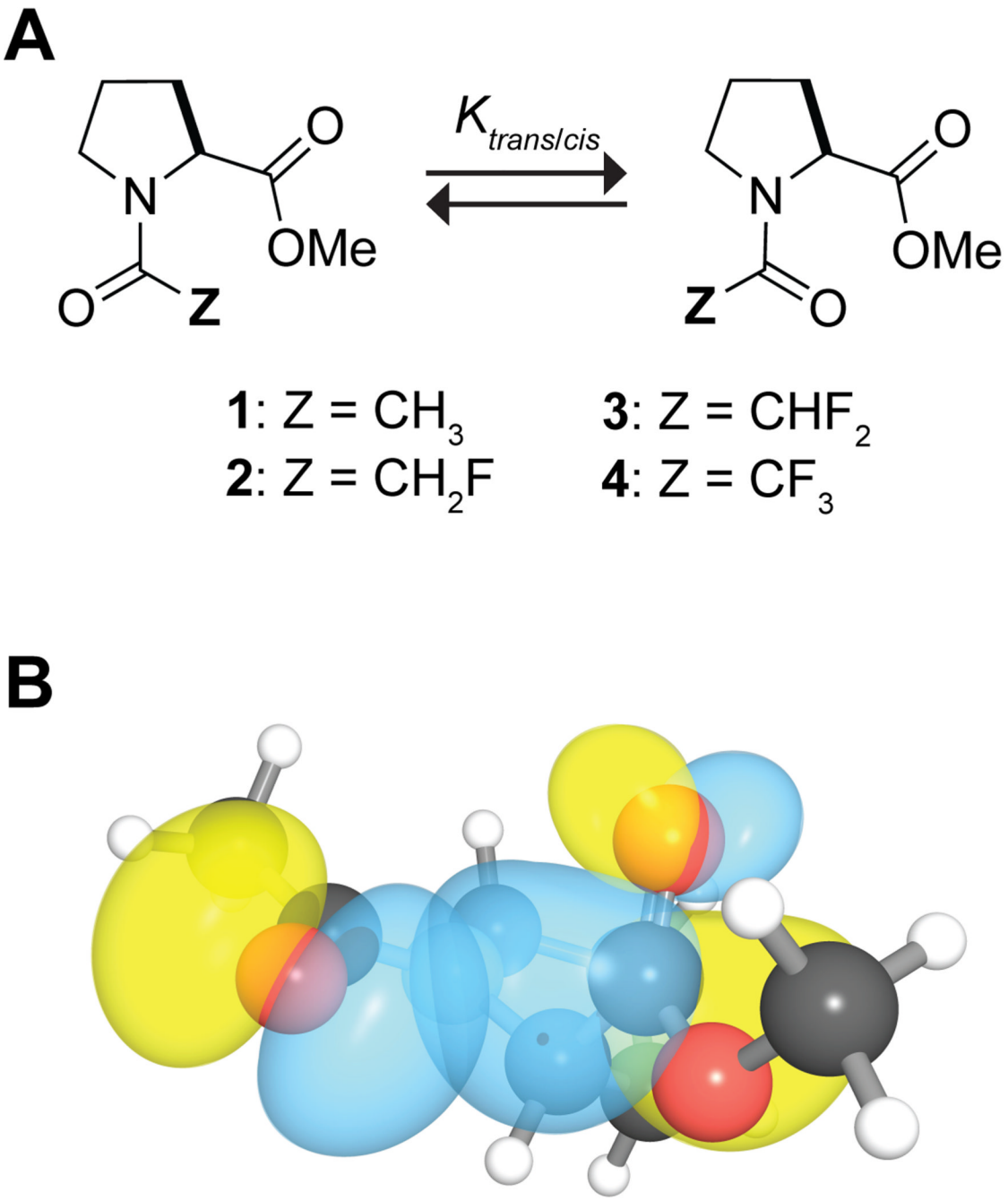

Figure 1.
Z-C(O)-Pro-OMe model system: A. *Cis–trans* equilibrium in Z-C(O)-Pro-OMe. B. Overlap of the *n* and π* orbitals in Ac-Pro-OMe generated with NBOView 1.1.20

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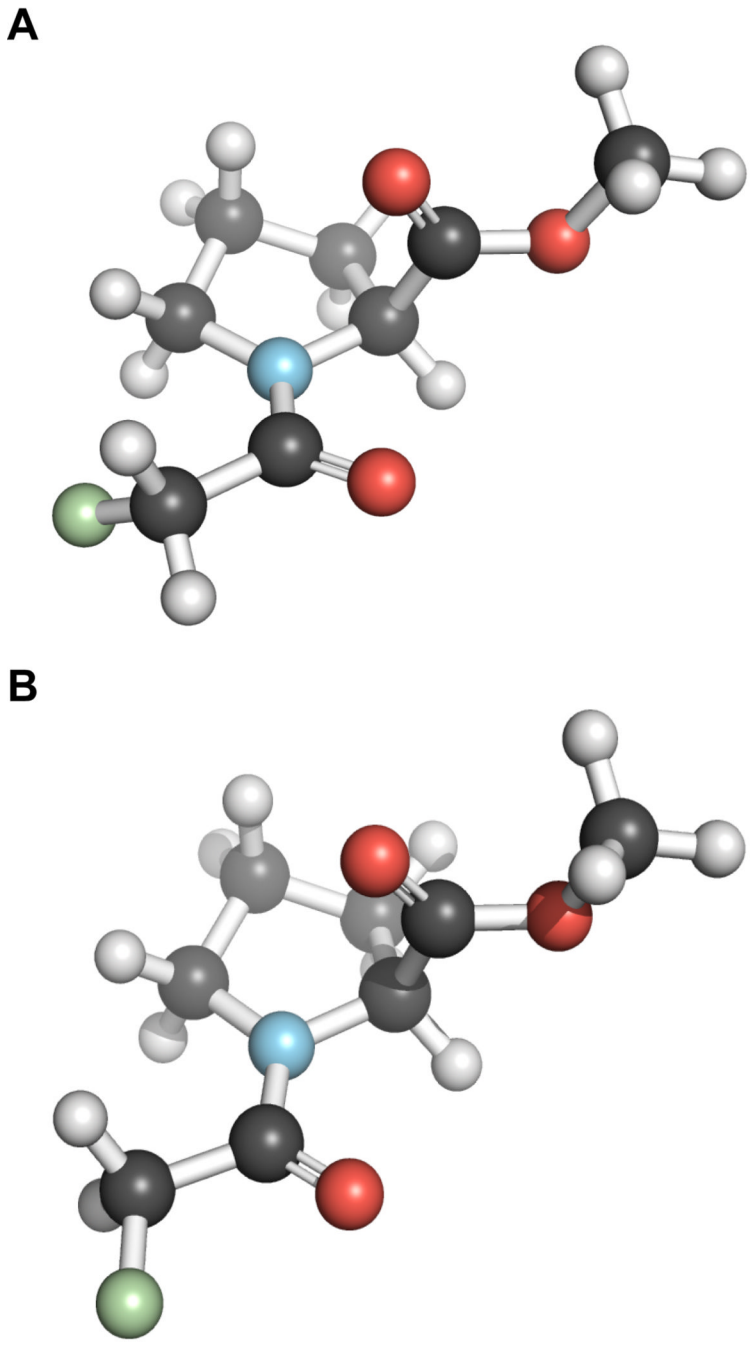

Figure 2.
Conformations of **2**: A. *antiperiplanar* conformation of **2**. B. *synperiplanar* conformation of **2**.

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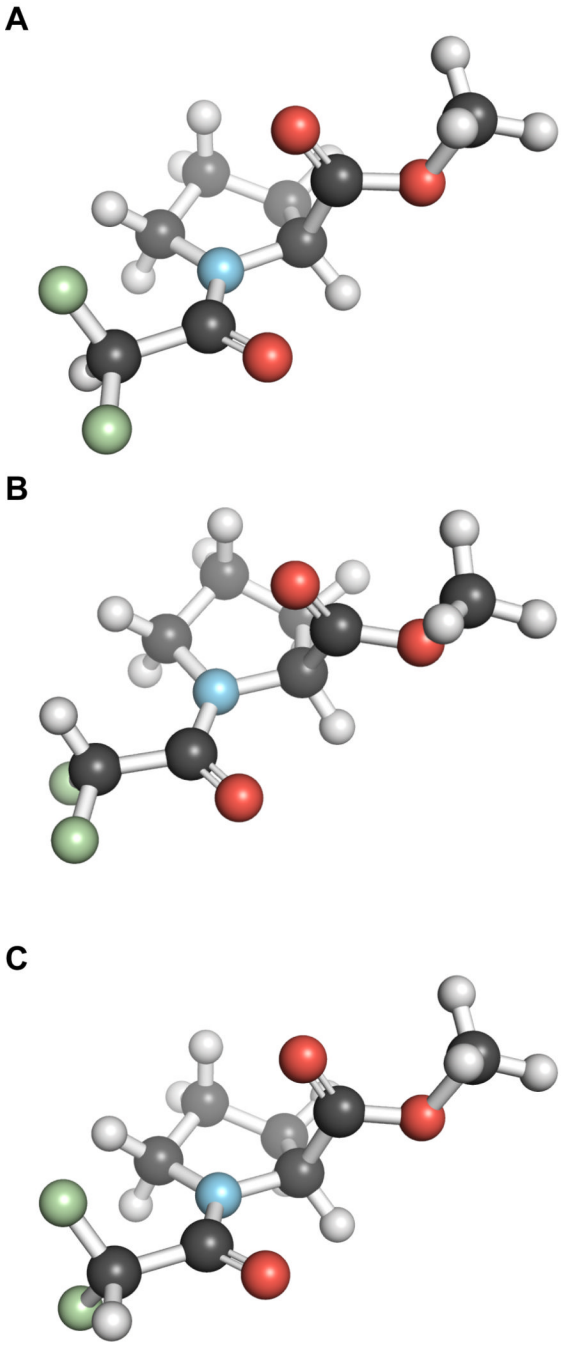

Figure 3.
Conformations of **3**: A. *antiperiplanar* conformation of **3**. B. *anticlinal* conformation of **3**. C. *synperiplanar* conformation of **3**.

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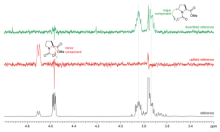

Figure 4.

NOE difference spectra with (top) CF_3 of the *trans* conformation saturated; (middle) CF_3 of the *cis* conformation saturated; and (bottom) baseline region in ^{19}F spectrum saturated. Parameters for the experiments are provided in the text.

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Table 1

Values of $K_{trans/cis}$ and $E_{n\rightarrow\pi^*}$ for compounds **1–4**

Compound	Z	$K_{trans/cis}$[a]	Conformation	$E_{n\rightarrow\pi^*}$ (kcal/mol)
1	H_3C–	4.0[b]	—	0.40
2	H_2FC–	2.7	*anti*-periplanar	0.76
			syn-periplanar	0.29
3	HF_2C–	3.4	*anti*-periplanar	0.30
			anti-clinical	0.38
			syn-periplanar	0.38
4	F_3C–	4.6	—	0.37

[a]Measured in $CDCl_3$ at 25 °C.

[b]from Ref 6a.