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Mapping gas phase dipeptides motions in the far-infrared and terahertz domain.

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Supplementary Material

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Contents

1 Experimental method **3**

2 REMPI spectrum of Ac-Phe-Val-NH_2 **5**

3 Theoretical details for vibrational spectroscopy **6**

4 Conformational assignement of Ac-Phe-Cys-NH_2 **7**

1 Experimental method

A schematic overview of the set-up that is used to conduct IR-UV ion-dip spectroscopy of neutral and cold molecules at the FELIX laboratory is displayed in Figure S1. The key components of the setup are highlighted, starting with the molecular beam expansion which is produced using a pulsed supersonic valve by expanding the gas into vacuum. The sample molecules are seeded into the expansion using the laser desorption technique. The sample molecules are desorbed from a graphite sample bar and are brought intact into the gas phase. A skimmer transmits the central part of the expansion into the differentially pumped interaction chamber, where the molecules are irradiated with IR and UV light to vibrationally excite and consecutively ionize them via resonant enhanced two photon ionization (RE2PI). Finally, the ions are directed into the reflectron TOF-MS detector assembly, where they are directed towards a microchannel plate (MCP) charged particle detector.

The experimental cycle is synchronised to the FELIX pulse generation timing using a digital delay generator, to ensure that the sample molecules are irradiated by the UV laser pulses directly following their interaction with the IR radiation.

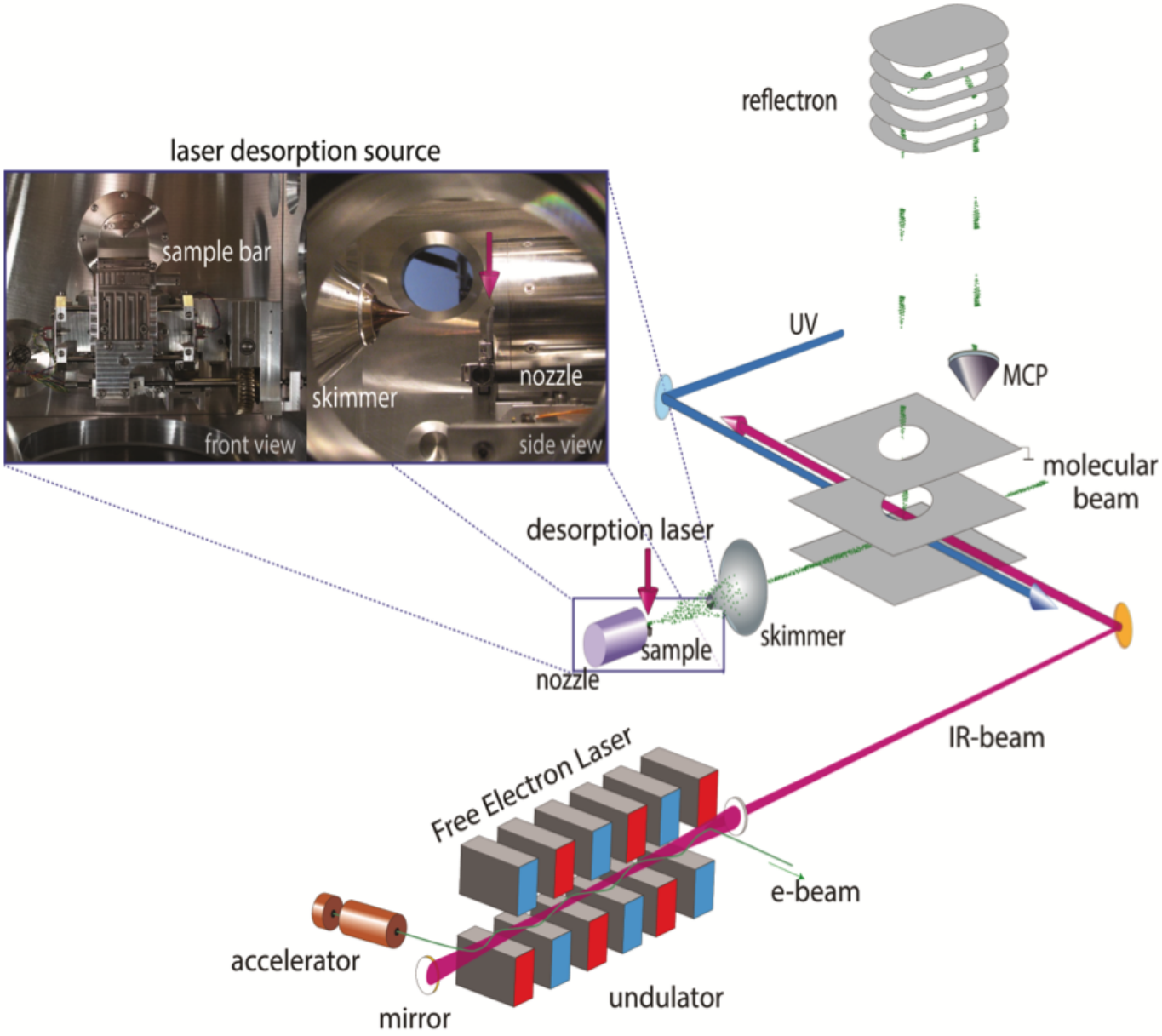

Fig. 1 Schematic representation of the set-up used for IR-UV double resonance spectroscopy. The key components that make up the Free Electron Laser (FEL), laser desorption sample preparation and Time-of-Flight mass spectrometer are highlighted. The translation stage used to precisely position the sample bar with respect to the desorption laser, and the relative positions of the pulsed valve nozzle and the skimmer are displayed in the photos in the inset (Reproduced with permission from "Gas phase IR spectroscopy and structure of biological molecules"[1]).

2 REMPI spectrum of Ac-Phe-Val-NH_2

In table 1 are gathered the wavelengths of the $S_0 \rightarrow S_1$ transitions used for the IR-UV ion dip spectroscopy experiments conducted here.

As an example, the REMPI spectrum of the Ac-Phe-Val-NH_2 system is presented in figure S2.

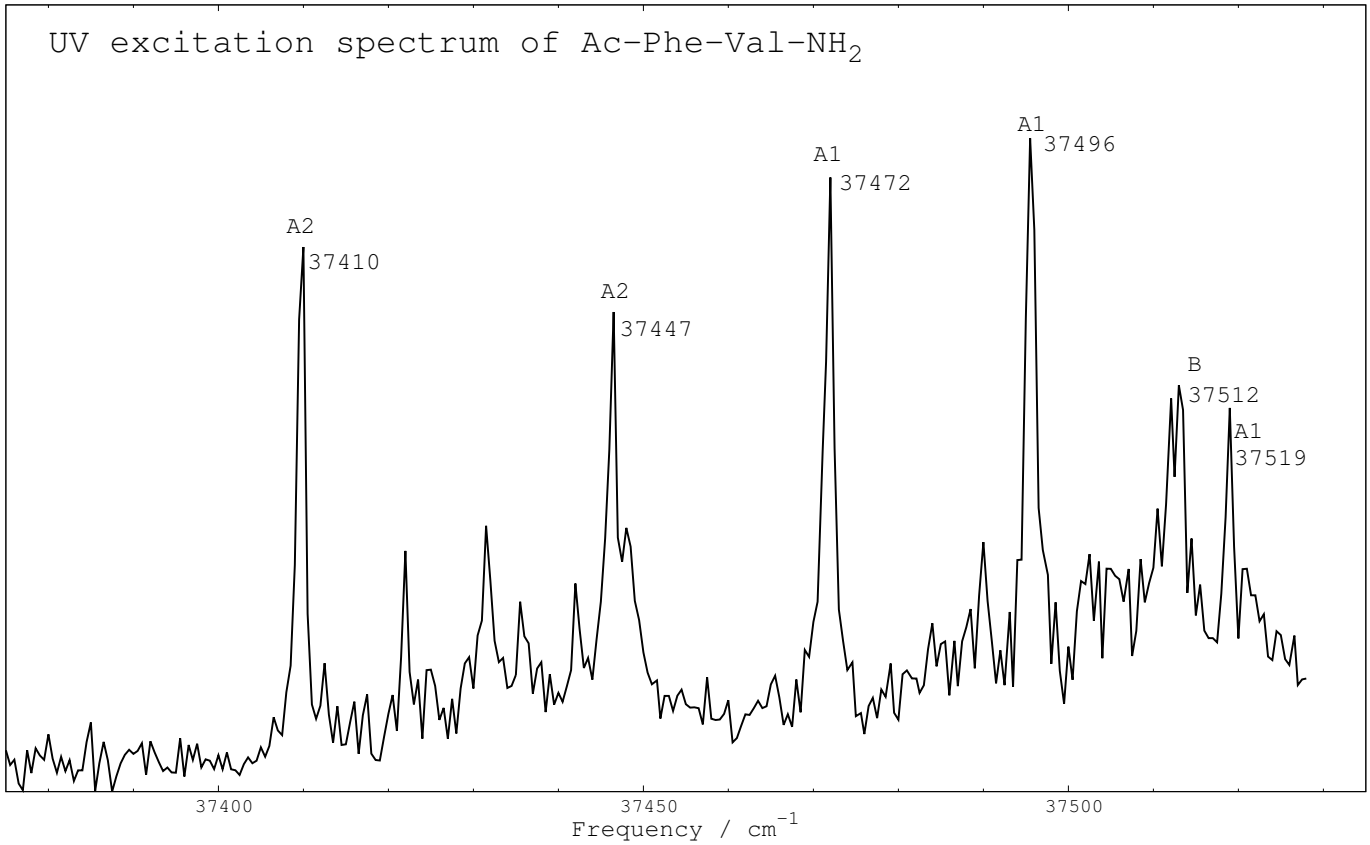

Fig. 2 REMPI spectrum of Ac-Phe-Val-NH_2. Note that this spectrum has not been averaged and has been scaled of +18 cm^{-1} to compensate the lack of calibration of the UV laser.

Molecule	Conformation	λ_{UV} (cm^{-1})	Reference
Ac-Phe-Gly-NH_2	γ-turn	37486	REF[2]
Ac-Phe-Ala-NH_2	γ-turn	37464	REF[2]
Ac-Phe-Pro-NH_2	γ-turn	37435.5	REF[3]
	β-turn	37409	REF[3]
Ac-Phe-Cys-NH_2	γ-turn	37325	REF[4]
	β-turn	37450	REF[4]
Ac-Phe-Ser-NH_2	γ-turn	37390	REF[4]
Ac-Phe-Val-NH_2	γ-turn A1	37472	Present work
	γ-turn A2	37410	Present work

Table 1 $S_0 \rightarrow S_1$ transition used to select each conformation of each single molecule investigated in the work.

3 Theoretical details for vibrational spectroscopy

Within Statistical Mechanics, the Fermi Golden Rule for calculating an infrared spectrum can be reformulated using Linear Response Theory[5,6], and can thus be rewritten as the Fourier Transform of the time correlation function of the fluctuating dipole moment vector of the absorbing molecular system[7,8]:

$$I(\omega) = \frac{2\pi\beta\omega^2}{3cV} \int_{-\infty}^{\infty} \mathrm{d}t \ \langle \delta\mathbf{M}(t) \cdot \delta\mathbf{M}(0) \rangle \ \exp(i\omega t) \tag{1}$$

where $\beta = 1/kT$, T is the temperature, c is the speed of light in vacuum, V is the volume. The angular brackets represent a statistical average of the correlation function of the molecular dipole moment vector $\mathbf{M}(t)$, where $\delta\mathbf{M}(t) = \mathbf{M}(t) - <\mathbf{M}>$ is the dipole fluctuation, with $<\mathbf{M}>$ the time average of $\mathbf{M}(t)$. The calculation in equation 1 is done in the absence of an applied external field. For the prefactor in eq. 1, we have taken into account an empirical quantum correction factor multiplying the classical line shape of the form $\beta\hbar\omega/(1-\exp(-\beta\hbar\omega))$, which was shown previously to give accurate results on calculated IR intensities[9–11]. For more detailed discussions on quantum corrections, see for instance refs.[12? –14]. In eq. 1, there are no harmonic approximations made (on the dipole moment, on the potential energy surface, and vibrational modes are coupled by construction), this equation gives the whole infrared spectrum of a molecular system in one single calculation (i.e. band positions, band intensities and band shapes), all conformations populated over time are taken into account in the final spectral calculation.[7,8]

Assignment of the absorption peaks in terms of internal motions is done with two complementary analysis tools, ICDOS (Internal Coordinates Density of States) and PCA (Principal Component Analysis). ICDOS analysis was already applied in our previous work on the far-IR spectroscopy of the Ac-Phe-Pro-NH_2 peptide[3]. It is based on the Fourier transform of the time-dependent autocorrelation of given internal coordinates denoted IC (chosen as a distance, an angle or a dihedral angle):

$$I_{ICDOS}(\omega) = \int_{-\infty}^{\infty} \langle IC_i(t) \cdot IC_i(0) \rangle \ \exp(i\omega t) \, dt \tag{2}$$

thus providing signatures arising from one given IC_i internal coordinate. These reflect rather localized motions.

As the far infrared domain is also expected to be dominated by more delocalised modes and/or combination of large amplitude motions (over the peptide backbone), which are not expected to be well described by one single local internal coordinate, PCA analysis has also been applied. This is a dimension reduction technique from which few principal components are extracted and explain a large proportion of the total sample variance of the n chosen variables (here selected internal coordinates). To that end, a covariance (n,n) matrix is built upon the chosen internal coordinates, with each matrix element being $cov_{ij} = \left\langle (IC_i(t) - \overline{IC_i})(IC_j(t) - \overline{IC_j}) \right\rangle$ (t is time, $\overline{IC_i}$ is the time-average of the time-dependent internal coordinate $IC_i(t)$, $< ... >$ is a time average over the trajectory). The matrix is diagonalized and provides n eigenvalues also known as principal components (PC). Only few PCs are relevant for the description of the total motion built on the chosen $IC(t)$ coordinates, and only the first and second PCA are commonly used without redundancy. Trajectories are subsequently projected onto the identified PCs, and the resulting projections $\rho(t)$ are time-correlated and Fourier transformed

in order to provide the final spectral assignment in terms of delocalized and large amplitude motions.

4 Conformational assignement of Ac-Phe-Cys-NH_2

In two recent papers from Yan *et al.*[4] and Alauddin *et al.*[15], the structure of the β-turn conformation of Ac-Phe-Cys-NH_2 is discussed. It is assigned to a β-turn conformation by both groups, but they do not agree about the orientation of the CH_2-SH residue with respect to the backbone, i.e. SH interacts with the C=O function in ref.[15] (denoted conformer FC1) while it interacts with the aromatic ring in ref.[4] (denoted conformer FC2). These two structures are shown in Figure S3.

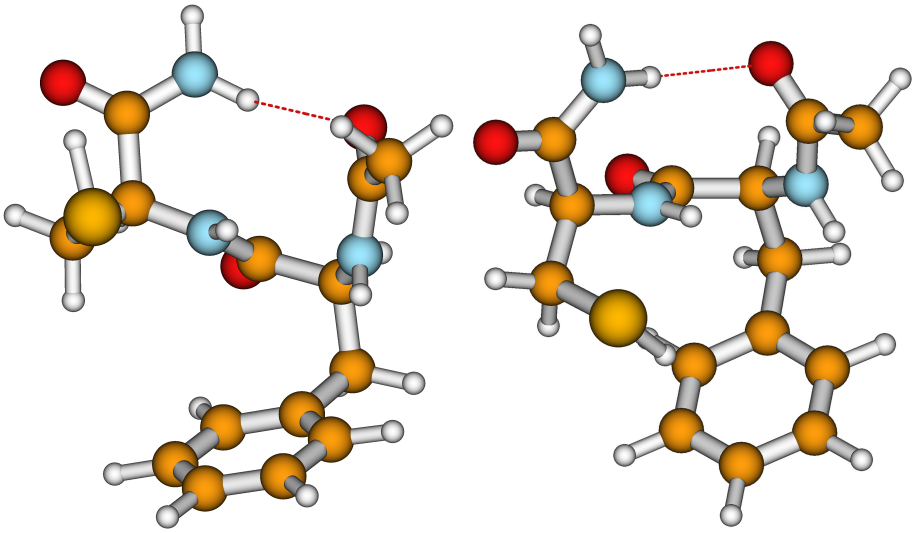

Fig. 3 Structures labelled FC1 (left) and FC3 (right) of the Ac-Phe-Cys-NH_2 dipeptide.

DFT-MD simulations have been performed for both conformers (following the details of section 2 in the paper), and the two IR dynamical theoretical spectra are found almost identical in both the 3000-4000 cm^{-1} (Fig. S4) and 800-1800 cm^{-1} (Fig. S5) ranges. The same comparison has been made in the far IR range (<800 cm^{-1}) and is presented in figure S6. The far-IR experimental spectrum has been recorded in the present work, and is also reported in the main text of the paper.

One can observe small but workable differences between the two theoretical spectra in the far-IR range, reinforcing the idea, discussed elsewhere[2] that the far-IR could indeed be a stronger tool than the other spectral ranges for conformational assignment. One can note two main differences between the two theoretical DFT-MD spectra of FC1 and FC3 conformers. The out of plane wagging motion of the SH function gives rise to two active IR peaks located at 288 and 311 cm^{-1} for the FC1 conformer, while there is only one peak at 295 cm^{-1} for the FC3 conformer. The second difference is visible for the peaks located between 425 and 525 cm^{-1} arising from the out of plane motion of both NH_2 and backbone NH (belonging to the amide group of the phenylalanine residue). For these peaks, differences are mainly in the band shapes.The two peaks located at 288 and 311 cm^{-1} observed for FC1 are found in excellent agreement with the two experimental peaks located respectively at 289 and 304 cm^{-1}, thus providing strong evidence that FC1 is the conformer probed in the experimental conditions. This is the conformer used in the analyses in the paper.

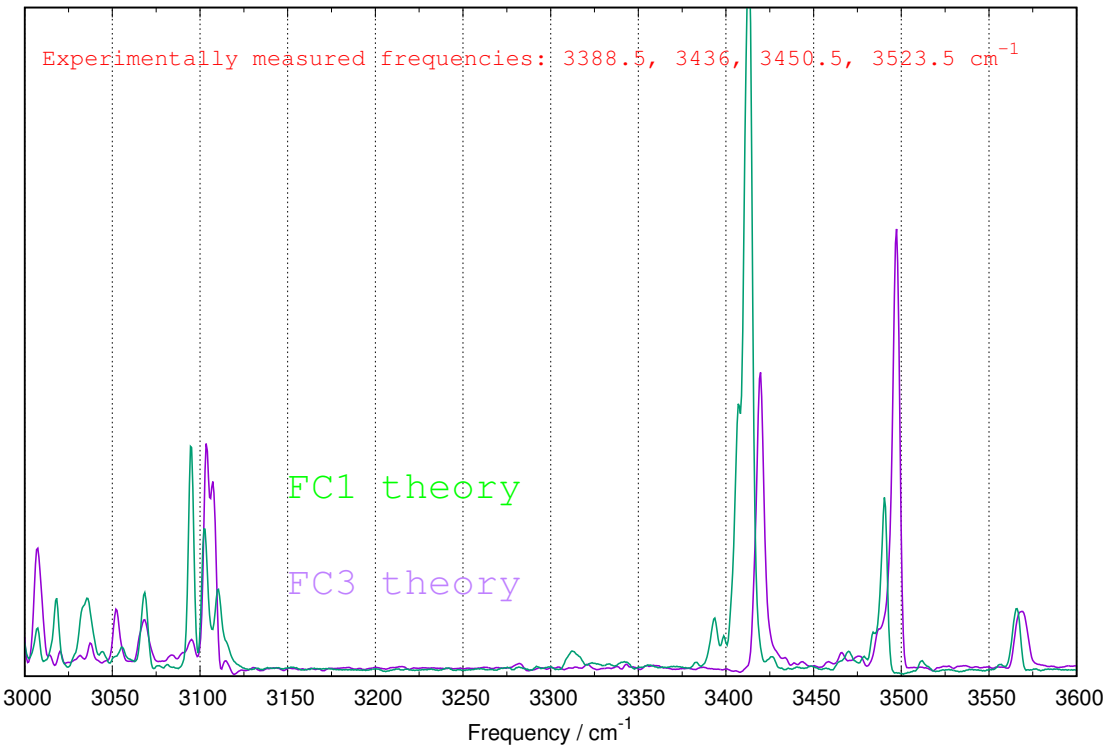

Fig. 4 In green and purple, the DFT-MD theoretical spectra of FC1 and FC3 conformers of Ac-Phe-Cys-NH_2 peptide, respectively, in the range 3000-4000 cm^{-1}. The experimental frequencies reported come from the publication of Alauddin *et al*[15]. See structures in figure 3.

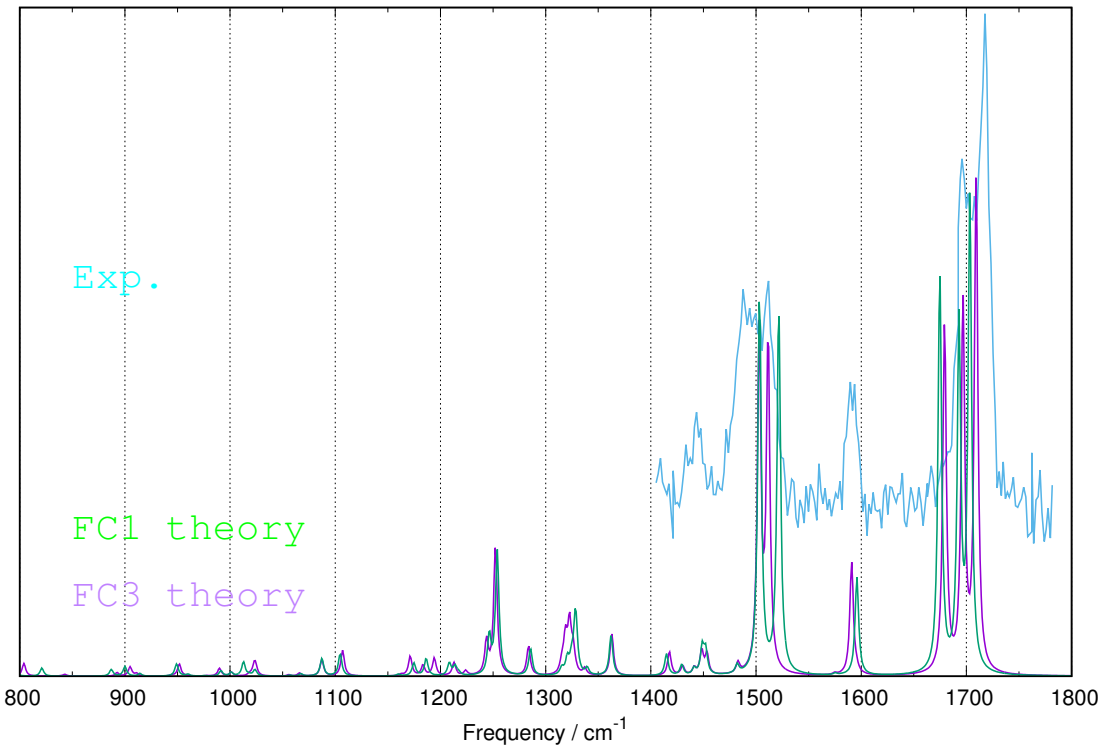

Fig. 5 In cyan, the experimental spectrum of Ac-Phe-Cys-NH_2 dipeptide (β-turn conformation) measured in the range 1400-1800 cm^{-1} [4]. In green and purple, DFT-MD theoretical spectra of FC1 and FC3 conformers of Ac-Phe-Cys-NH_2, respectively. See structures in figure 3.

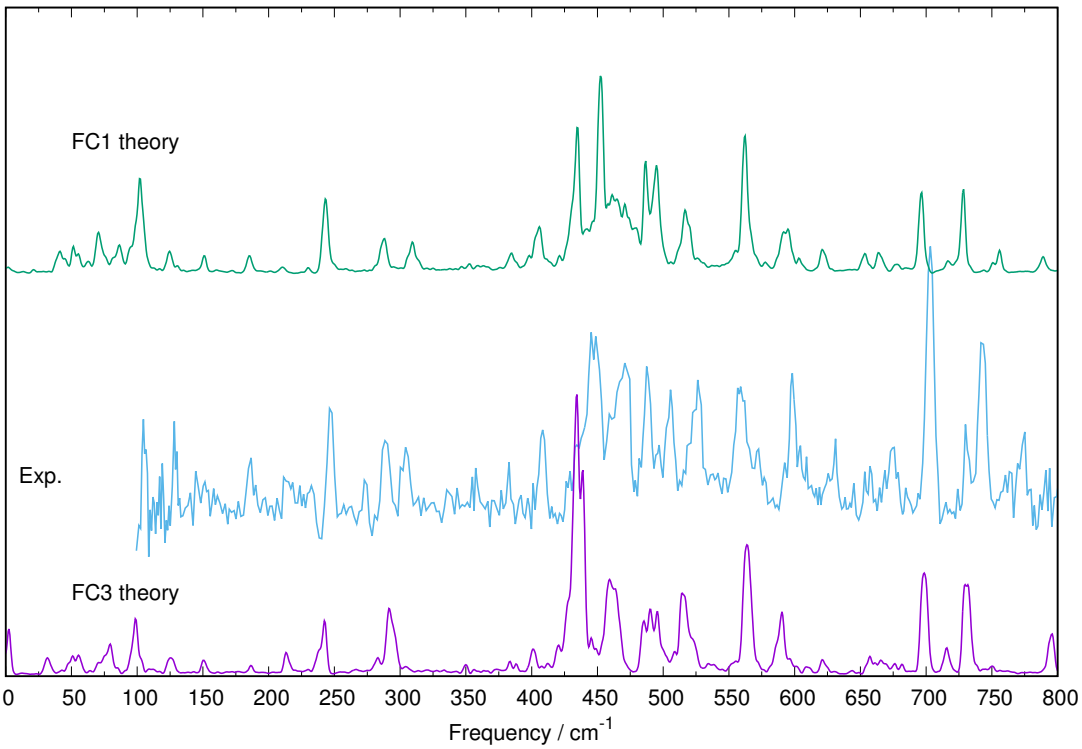

Fig. 6 In cyan, the experimental spectrum of Ac-Phe-Cys-NH_2 dipeptide (β-turn conformation) measured in the present work in the range 100-800 cm^{-1}. In green and purple, the DFT-MD theoretical spectra of FC1 and FC3 conformers of Ac-Phe-Cys-NH_2, respectively. See structures in figure 3.

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