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REGULAR ARTICLE

A B3LYP investigation of the conformational and environmental sensitivity of carbon–deuterium frequencies of aryl-perdeuterated phenylalanine and tryptophan

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Abstract Carbon–deuterium labeled amino acids can serve as sensitive probes for biophysical characterization. Although multiple research groups have used infrared spectroscopy in conjunction with alkyl backbone or side-chain deuterated amino acids for the biophysical characterization of conformational and/or environmental changes, it was not entirely clear to the authors that perdeuterated aryl rings would demonstrate a similar sensitivity toward conformational or environmental changes. In an effort to evaluate the sensitivity of aryl carbon–deuterium (C–D) IR frequencies, a B3LYP investigation of the sensitivity of aryl C–D frequencies toward conformational and environmental changes was conducted for phenylalanine (Phe) and tryptophan (Trp). To compensate for the low molar absorptivity of C–D frequencies, perdeuterated aryl rings were investigated, which are commercially available and can be readily compared to experimental data. B3LYP results suggest that aryl-deuterated Phe and Trp will exhibit moderate sensitivities toward conformational and environmental changes with frequency shifts upward of 13 and 26 cm^{-1} for Phe and Trp, respectively. B3LYP predicts that conformational sensitivity arises from dipole changes and not orbital alignment changes. In an effort to mimic what might be observed experimentally, simulated IR spectra were created and show absorption band changes with conformational and environmental changes, which indicate that IR characterization of perdeuterated aryl rings in amino acids could serve as a biophysical tool.

Keywords Tryptophan · Phenylalanine · C–D · Deuterium · Frequency · Infrared

1 Introduction

Carbon–deuterium labeled amino acids can serve as sensitive probes for biophysical characterization. Using isotope-edited infrared spectroscopy (IR) [1–3] and taking advantage of an unobscured region in a peptide or protein's IR spectrum (Fig. 1), carbon–deuterium (C–D) labeled peptides can report on local conformational or environmental changes [1]. Although multiple research groups have used IR spectroscopy in conjunction with backbone-deuterated [4–14] or alkyl side-chain deuterated [15–30] amino acids for the biophysical characterization of conformational and/or environmental changes, it was not entirely clear to the authors that the perdeuterated aryl rings of phenylalanine (Phe) [31] or tryptophan (Trp) would demonstrate a similar sensitivity toward conformational or environmental changes.

With alkyl backbone or side-chain deuteration, conformational changes modify the alignment between alkyl C–D bonds and adjacent σ-bonds, π-bonds, or lone pairs of electrons. This change in orbital alignment often has a large impact on frequency shifts [13–15, 19, 32, 33]. However, aryl C–D bonds are rigidly held perpendicular to the π-bonds of an aromatic ring. With conformational changes, the whole ring moves while the orbital alignment with respect to the C–D bonds is held in place, which

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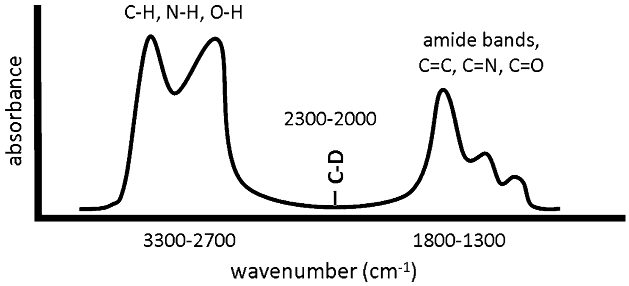


Fig. 1 Cartoon of a peptide IR spectrum highlighting the region for which C–D absorptions are unobscured by peptide chromophores

means any observed effects that might arise from orbital alignment likely arise from an impact on the π electrons. However, this effect might be negligible, and it was not clear to us the degree to which aryl C–D frequencies would shift when the ring undergoes conformational changes. Our specific interest in the aryl C–D frequencies of Phe and Trp results from experimental studies in our lab concerning alpha- and gamma-melanocyte-stimulating hormone neuropeptides (α-MSH and γ-MSH), where Phe and Trp exist in a conserved sequence [34, 35].

In an effort to evaluate the sensitivity of aryl carbon–deuterium (C–D) IR frequencies, a B3LYP investigation of the sensitivity of aryl C–D frequencies toward conformational and environmental changes was conducted for Phe and Trp. To compensate for the low molar absorptivity of C–D frequencies, commercially available perdeuterated aryl rings were investigated. Since this study focused on relative frequency shifts, efforts toward an accurate determination of absolute IR intensities and frequencies were not pursued [36, 37] nor was any attempt made to accurately predict relative populations of conformational isomers [38–41]. Solvent effects were treated implicitly, not explicitly [42], since relative effects were the focus. Observed experimental intensities are a function of both the intrinsic intensity for a stretching mode of a given conformation and the relative amount of that given conformation, but accurate predictions of intensities and relative populations of species were not pursued. Consequently, emphasis was placed on the relative magnitudes of frequency shifts. We chose to evaluate the neutral, non-zwitterionic forms of Trp and Phe as model compounds in the gas phase without and with a solvent or dielectric field. Although zwitterionic forms are not readily calculated in the gas phase without inclusion of a solvent field, they were not required due to the focus on relative affects. Because B3LYP performs acceptably with the computationally inexpensive 6-31G(d) basis set [43], we chose to use that level of theory for this exploratory study.

2 Methods

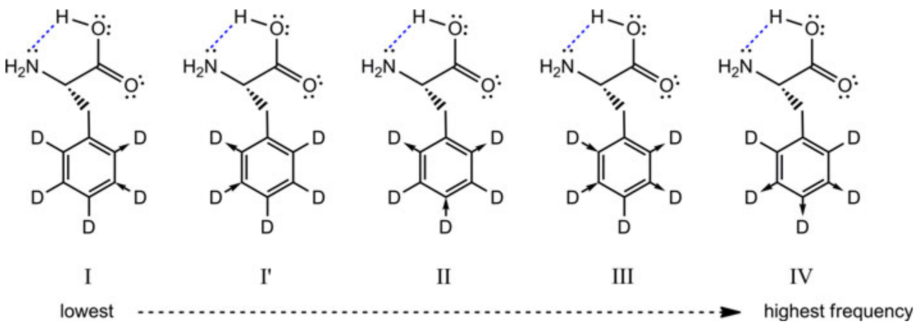
Geometry optimizations for each conformation of Phe [44] and Trp as well as harmonic frequency calculations for each Phe-aryl-d_5 and Trp-aryl-d_5 conformation were performed using GAMESS [45] at the B3LYP/6-31G(d) level of theory [43, 46–49]. C–D stretching frequencies were scaled by 0.9614 [50] and used as the predicted frequencies. Predicted intensities were normalized. A polarized continuum model for water was used to approximate the dielectric effects of water on the frequencies [51–55]. Raman intensities were approximated using the protocol in GAMESS [56, 57]. IR spectra were simulated in MATLAB R2008b by summing individual Gaussian functions for each of the scaled frequencies and normalized intensities; full widths at half maximum were arbitrarily set to 7.5 cm^{-1}.

3 Results and discussion

3.1 Phenylalanine results

Stretching frequencies of neutral, non-zwitterionic phenylalanine (Fig. 2) did not change their relative order with conformational or solvent-field (gas to water) changes (Fig. 3). For each mode, the maximum range of frequency shifts due to conformational changes spanned 0.5–13 cm^{-1}, while the average was 4.9 cm^{-1} (Table 1). Shifts due to solvent-field changes spanned 2.9–10.9 cm^{-1}, while the average was also 4.9 cm^{-1}. Phe mode I′ (Fig. 2) was more sensitive to conformational and solvent-field changes than the other modes. Without this mode, the maximum range of shifts would be 0.5–4.8 cm^{-1} (average 2.8 cm^{-1}) for conformational

Fig. 2 Cartoon of Phe-d_5 C–D stretching modes. *Arrows* represent large amplitude motions, while small amplitude motions were neglected. Modes I and I′ are very similar



changes and would be 2.9–3.6 cm^{-1} (average 3.4 cm^{-1}) for solvent-field changes. Mode I′ was most sensitive to conformational and solvent-field changes but on average it exhibited the lowest relative IR intensity. Since relative Raman intensities often differ from relative IR intensities, we explored its Raman intensity, which proved to increase its relative intensity from an average of 0.08 for IR to 0.23 for Raman.

3.2 Tryptophan results

Stretching frequencies of neutral, non-zwitterionic tryptophan (Fig. 4) did not change their relative order with conformational or solvent-field changes (Fig. 5). For each mode, the maximum range of frequency shifts due to conformational changes spanned 3.5–25.7 cm^{-1}, while the average was 11.9 cm^{-1} (Table 2). Shifts due to solvent-field changes spanned 1.6–23.2 cm^{-1}, while the average was 9.3 cm^{-1}. Trp mode V (Fig. 4) was more sensitive to conformational and solvent-field changes than the other modes. Without this mode, the maximum range of shifts would be 3.5–11.7 cm^{-1} (average 8.4 cm^{-1}) for conformational changes and would be 1.6–8.7 cm^{-1} (average 5.8 cm^{-1}) for solvent-field changes. Given that mode V was most sensitive to conformational and solvent-field changes, but on average exhibited the lowest relative IR intensity, we explored its Raman intensity, which proved to increase its relative intensity from an average of 0.13 for IR to 0.24 for Raman.

3.3 Phenylalanine and tryptophan discussion

Although our predicted frequency shifts are helpful for better understanding, the probability that aryl-deuterated

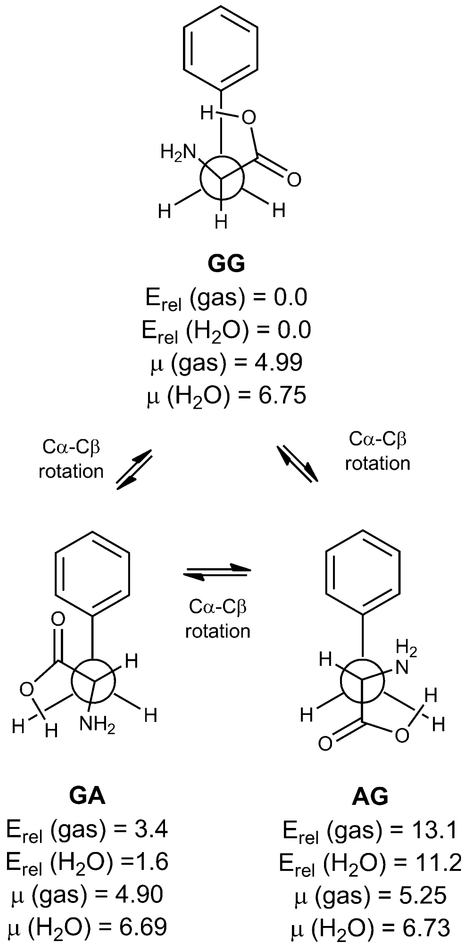


Fig. 3 Phenylalanine conformers with relative electronic energies (kJ/mol) and dipole moments (debye), *GG* gauche ring/CO_2H and gauche ring/NH_2, *GA* gauche ring/CO_2H and anti ring/NH_2, *AG* anti ring/CO_2H and gauche ring/NH_2

Table 1 Phenylalanine conformers with stretching frequencies (cm^{-1}), as well as relative IR and Raman (*italics*) intensities

Conformer	Solvent	C–D v (cm^{-1}) (relative IR and *Raman* intensity)				
GA	Gas	2,241.5	2,260.0	2,271.3	2,281.8	2,291.4
		(0.34, *0.17*)	(0.03, *0.30*)	(0.80, *0.35*)	(0.23, *0.03*)	(0.87, *1.00*)
	H_2O	2,249.6	2,259.3	2,270.7	2,278.9	2,290.4
		(0.29)	(0.03)	(0.52)	(0.56)	(0.68)
GG	Gas	2,241.0	2,261.1	2,271.5	2,281.1	2,293.2
		(0.32, *0.17*)	(0.01, *0.21*)	(0.29, *0.34*)	(0.68, *0.09*)	(0.66, *0.90*)
	H_2O	2,248.6	2,259.1	2,271.0	2,280.4	2,294.0
		(0.24)	(0.02)	(0.08)	(0.91)	(0.50)
AG	Gas	2,241.0	2,248.1	2,266.7	2,277.8	2,293.3
		(0.35, *0.17*)	(0.21, *0.17*)	(0.08, *0.40*)	(1.00, *0.18*)	(0.62, *0.88*)
	H_2O	2,246.0	2,248.4	2,267.4	2,277.5	2,292.7
		(0.35)	(0.20)	(0.06)	(1.00)	(0.48)

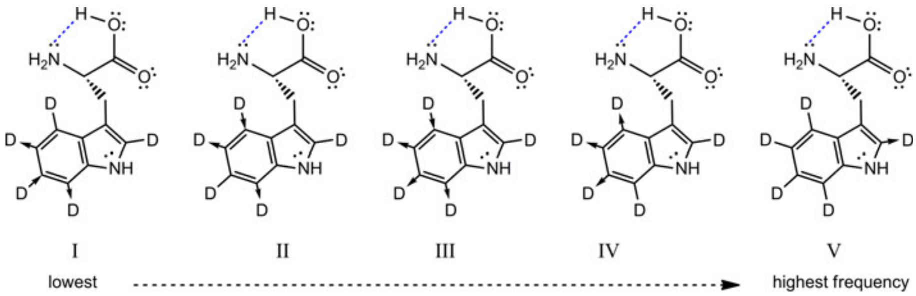


Fig. 4 Cartoon of Trp-d_5 C–D stretching modes. *Arrows* represent large amplitude motions, while small amplitude motions were neglected

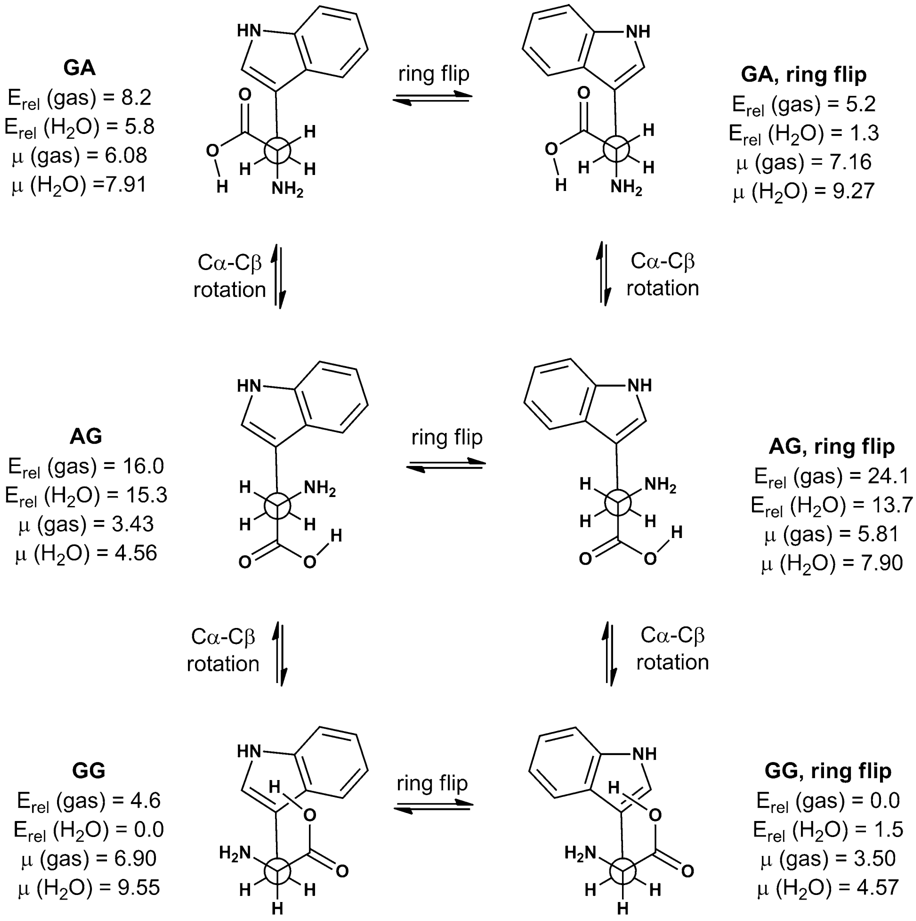


Fig. 5 Tryptophan conformers with relative electronic energies (kJ/mol) and dipole moments (debye), *GG* gauche ring/CO_2H and gauche ring/NH_2, *GA* gauche ring/CO_2H and anti ring/NH_2, *AG* anti ring/CO_2H and gauche ring/NH_2

Trp-d_5 and Phe-d_5 could serve as biophysical probes, the spectra for these compounds exhibit overlapping absorptions as reported by Tokuhisa et al. [31]. To gain a better idea as to whether we would readily observe differences in IR absorption bands, we simulated IR spectra using the data in Tables 1 and 2. Stacked plots of the Phe and Trp simulated spectra (Figs. 6, 7) show that despite the overlapping nature of the predicted absorptions, the resulting absorption bands appear to the naked eye to be distinct from one another. Although band fitting and/or second derivative analysis would be necessary when deconvoluting experimental spectra, the ability to see qualitative differences by eye is helpful for the utility of any probe.

At the B3LYP level of theory, a positive correlation between frequency shifts and changes to the molecular dipole appears, which could explain variable frequency changes with conformational changes. More specifically, Phe conformational changes were predicted to exhibit small molecular dipole changes (0.35 and 0.06 debye; gas and water, respectively) and stretching modes had an average maximum shift of 4.9 cm^{-1}. In contrast, Trp was predicted to exhibit larger dipole changes (4.99 and 3.73; gas and water, respectively) as a function of conformational changes, and its stretching modes had a larger average maximum shift of 11.9 cm^{-1}. Since some Phe and Trp conformational changes produce very small

Table 2 Tryptophan conformers with stretching frequencies (cm^{-1}), as well as relative IR and Raman (*italics*) intensities

Conformer	Solvent	C–D v (cm^{-1}) (relative IR and *Raman* intensity)				
GA	Gas	2,254.1	2,259.3	2,275.6	2,289.7	2,338.9
		(0.24, *0.07*)	(0.06, *0.49*)	(1.00, *0.27*)	(0.73, *1.00*)	(0.59, *0.17*)
	H_2O	2,256.8	2,262.7	2,276.3	2,288.5	2,341.5
		(0.08)	(0.09)	(0.95)	(0.65)	(0.32)
AG	Gas	2,251.9	2,259.0	2,276.0	2,289.5	2,321.2
		(0.25, *0.18*)	(0.11, *0.43*)	(1.00, *0.22*)	(0.55, *0.96*)	(0.02, *0.28*)
	H_2O	2,255.3	2,260.1	2,275.6	2,288.9	2,325.9
		(0.20)	(0.09)	(1.00)	(0.55)	(0.02)
GG	Gas	2,250.6	2,268.1	2,285.1	2,301.2	2,314.9
		(0.17, *0.29*)	(0.47, *0.38*)	(0.65, *0.64*)	(0.18, *0.45*)	(0.04, *0.26*)
	H_2O	2,256.8	2,266.1	2,284.3	2,294.9	2,324.6
		(0.03)	(0.46)	(0.58)	(0.34)	(0.02)
GA, ring flip	Gas	2,252.9	2,264.7	2,279.6	2,290.8	2,314.9
		(0.18, *0.24*)	(0.16, *0.38*)	(0.87, *0.24*)	(0.60, *0.89*)	(0.06, *0.28*)
	H_2O	2,256.3	2,263.0	2,276.7	2,287.9	2,324.3
		(0.04)	(0.13)	(0.96)	(0.61)	(0.02)
AG, ring flip	Gas	2,252.1	2,264.2	2,278.2	2,291.0	2,313.1
		(0.19, *0.24*)	(0.09, *0.37*)	(0.79, *0.25*)	(0.56, *0.91*)	(0.02, *0.26*)
	H_2O	2,255.2	2,261.8	2,276.0	2,288.4	2,318.3
		(0.10)	(0.09)	(0.91)	(0.59)	(0.01)
GG, ring flip	Gas	2,252.0	2,259.4	2,275.7	2,289.9	2,331.2
		(0.25, *0.11*)	(0.05, *0.41*)	(0.90, *0.27*)	(0.66, *0.97*)	(0.02, *0.18*)
	H_2O	2,256.8	2,264.8	2,278.4	2,290.0	2,325.5
		(0.11)	(0.07)	(0.93)	(0.59)	(0.002)

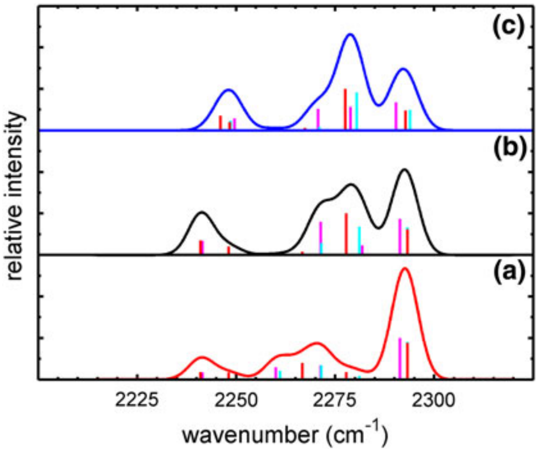


Fig. 6 Simulated IR for neutral Phe in water (**c**), and gas (**b**). Each *stick* shows IR shift and relative intensity for the stretching mode of a single conformer. Raman (*red*) data appears in the *bottom* (**a**)

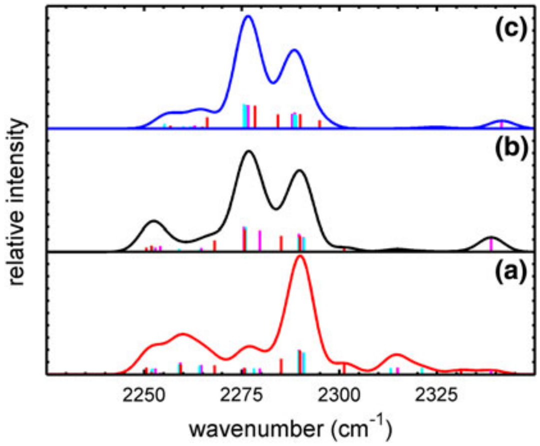


Fig. 7 Simulated IR for neutral Trp in water (**c**), and gas (**b**). Each *stick* shows IR shift and relative intensity for the stretching mode of a single conformer. Raman (*red*) data appears in the *bottom* (**a**)

shifts, while changes to the molecular dipole can produce large shifts, the results suggest that aryl C–D frequency shifts are not dominated by orbital alignment issues as alkyl C–D frequency shifts often are. Rather, they are dominated by the electrostatic environment set by the molecule itself (molecular dipole) or by the solvent (dielectric constant).

The observation that the most conformationally and environmentally sensitive mode for both Phe and Trp also exhibited the lowest relative IR intensity was perhaps

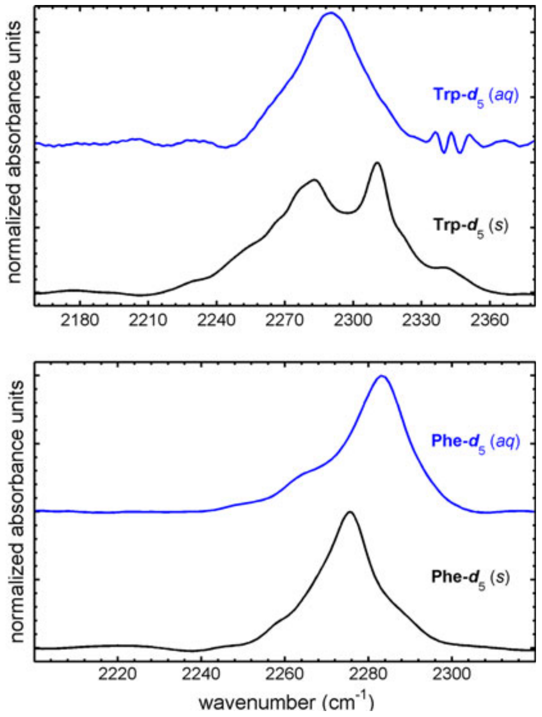


Fig. 8 Experimental IR spectra for Trp-d_5 and Phe-d_5. *Top*: Trp-d_5 in aqueous solution (50 mM Trp, p*H* 7) and out of solution (KBr pellet). *Bottom*: Phe-d_5 in aqueous solution (100 mM Trp, pH 7) and out of solution (KBr pellet). Trp-d_5 is less soluble in aqueous solution than Phe-d_5, has a weaker signal, and exhibits greater interference from CO$_2$ (*g*) that creates a residual in the *top* spectrum near 2,345 cm^{-1}

coincidental. Trp mode V is a stretch predominately localized to the C–D bond adjacent to the indole nitrogen. Given its proximity to the indole nitrogen, this stretching mode might be expected to exhibit behavior different from the four other aryl C–D modes, which are not adjacent to the indole nitrogen. Nonetheless, mode V exhibited a dramatic frequency shift upon conformational or solvent-field changes. Similarly, the predicted sensitivity of mode I$'$ in Phe-d_5 was unexpected. It is not entirely clear to us why mode I$'$ is sensitive, when a very similar mode (I) is not as sensitive. Regardless of the reason, it is clear that both Trp-d_5 and Phe-d_5 could serve as biophysical probes for IR and/or Raman measurements; experimental IR results for Trp-d_5 and Phe-d_5 (Fig. 8, supporting information) support this claim. Figure 8 shows that the aryl C–D absorption bands change as the environment changes from an aqueous to non-aqueous environment.

4 Conclusions

From the B3LYP results, one could conclude that perdeuterated aryl rings of both Trp and Phe showed C–D frequency shifts in response to electrostatic changes (i.e., molecular dipole and/or dielectric constant), which suggests they could be biophysical tools, although Trp-d_5 might be a more sensitive probe than Phe-d_5. However, the experimental IR data suggests that the simpler band of Phe-d_5 might make it easier to employ. Given that Trp fluorescence measurements already provide a sensitive biophysical tool for evaluating Trp environments [58], developing a general tool using IR/Raman spectroscopy of aryl C–D bonds would be valuable in expanding the scope of biophysical tools used to probe questions relevant to aryl rings. For example, C–D frequencies of aryl-perdeuterated tyrosine were shown to exhibit p*H*-dependent shifts during the course of a dihydrofolate reductase study [59]. In collaboration with the Desamero Lab, we are gathering Raman experimental data for Phe-d_5 and Trp-d_5 as well as working toward implementing these biophysical tools for characterization of α-MSH and γ-MSH neuropeptides.

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