Supporting information for "Identifying the Cu(II)-Amyloid  $\beta$  peptide binding intermediates in the early stage of aggregation by Resonance Raman Spectroscopy: A simulation study"

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## I. THEORETICAL PROTOCOLS

We used a linearly displaced two-state harmonic nuclear Hamiltonian for the spectroscopic calculations (see Fig. 1), where the Hamiltonian is given by,

$$H = |g\rangle H_g \langle g| + \sum_e |e\rangle H_e \langle e|$$
(S1)

with

$$H_g = \sum_j \frac{1}{2} \omega_j \left( p_j^2 + q_j^2 \right), \qquad (S2a)$$

$$H_e = \varepsilon_e + \sum_j \frac{1}{2} \omega_j \left[ p_j^2 + \left( q_j + \Delta_j^e \right)^2 \right].$$
 (S2b)

Here  $q_j$  and  $p_j$  are the dimensionless coordinate and momentum of the *j*-th normal mode with the frequency  $\omega_j$ .  $\varepsilon_e$  is the 0-0 excitation energy corresponds to electronic transition  $|g\rangle \rightarrow |e\rangle$ , and  $\Delta_j^e$  is the dimensionless displacement between the potential energy minima of the states  $|e\rangle$  and  $|g\rangle$ . These displacements were calculated using the excited state gradient method, where the difference in energy derivative with respect to the dimensionless normal mode was evaluated.<sup>1,2</sup> The UV-vis absorption spectra were calculated using the cumulant expression,<sup>3</sup>

$$\sigma_e(\omega) = \frac{1}{\pi} \Re \int_0^\infty dt \, \exp\left[i(\omega - \omega_{eg})t - g(t) - \Gamma t\right]$$
(S3)

with the line broadening function given by

$$g(t) = \sum_{e,j} \frac{(\Delta_e^j)^2}{2} \left\{ \coth\left(\frac{\beta\omega_j}{2}\right) \left[1 - \cos(\omega_j t)\right] + i\left[\sin(\omega_j t) - \omega_j t\right] \right\}$$
(S4)

here,  $\beta = 1/k_B T$  is the inverse temperature and  $k_B$  is the Boltzmann constant. We used T = 300K and electronic linewidth  $\Gamma = 100 \text{ cm}^{-1}$  in the calculations. The electronic excitation energy is evaluated by

$$\varepsilon_{eg} = \varepsilon_e + \frac{1}{2}\omega_j \left(\Delta_e^j\right)^2. \tag{S5}$$

The Raman intensity is described by the differential Raman scattering cross section,<sup>4</sup>

$$\frac{\mathrm{d}\sigma}{\mathrm{d}\Omega} = \frac{I_{fi}}{I_0} = \frac{\pi^2}{\epsilon_0^2} \tilde{\nu}_0 \tilde{\nu}_{fi}^3 |\alpha_{fi}|^2 f_i(T) \tag{S6}$$

where  $I_0$  and  $I_{fi}$  are the incident and outgoing wave intensities, respectively.  $\epsilon_0$  is the vacuum permittivity,  $\tilde{\nu}_0$  is the incident frequency (in wavenumber) and  $\tilde{\nu}_{fi}$  is the scattered

wavenumber corresponds to a scattering process with the initial state  $|i\rangle$  and final state  $|f\rangle$ .  $f_i(T)$  is the occupation probability of state  $|i\rangle$  at the temperature T, and  $\alpha_{fi}$  is the transition polarizability. At resonance, the transition polarizability is given by,

$$\alpha_{fi} = \frac{1}{\hbar} \sum_{r} \frac{\langle f | \boldsymbol{\mu} | r \rangle \langle r | \boldsymbol{\mu} | i \rangle}{\omega_{ri} - \omega_1 - \mathrm{i} \Gamma_r}.$$
(S7)

Here  $\mu$  is the dipole moment operator;  $\hbar\omega_1$  and  $\hbar\omega_{ri}$  are the energies of incident photon and the energy difference between the intermediate state  $|r\rangle$  and the initial state  $|i\rangle$ . In this work, we only consider the first order Franck-Condon(FC) contribution to the RR signals. This treatment is also referred as the Albrech's "A term" approximation.<sup>5</sup> The transition polarizability can be written as,

$$\alpha_{fi} = \frac{1}{\hbar} (\mu_{eg})^2 \sum_{\nu^r \in |r\rangle} \frac{\langle \nu^f | \nu^r \rangle, \langle \nu^r | \nu^i \rangle}{\omega_e + \omega_{\nu^r \nu^i} - \omega_1 - \mathrm{i}\Gamma_r}.$$
(S8)

where the electronic part of the transition dipole  $\mu_{eg}$  is factored out by using the Born-Oppenheimer approximation.  $|\nu^i\rangle$ ,  $|\nu^f\rangle$  and  $|\nu^r\rangle$  are the initial, final and intermediate vibrational states, respectively.  $\hbar\omega_e$  is the 0-0 transition energy of the corresponding electronic transition, and  $\hbar\omega_{\nu^r\mu^i}$  is the vibrational part of the excitation energy.

Generally speaking, for electronically allowed transitions as considered here, the higher order Herzberg-Teller terms would only contribute maginally to the spectra. Usually only minor changes in the overall line shapes could be found by incuding these terms. <sup>6–8</sup> The higher order terms have the most significant effect on the electronically (near) forbidden transitions, where the 'A term' vanishes due to (near) zero electronic transition dipoles. This would pronounce only when the electronically forbidden transitions are energetically far away from any allow transition. Otherwise the higher oder contributions would be overwhelmed by the nearby 'A term' contributions, which is the case in the current work.

The Franck-Condon integrals can be obtained by evaluating the overlap between wavefunctions of displaced harmonic oscillators,

$$\langle n|m\rangle = \sqrt{(n-1)!(m-1)!} \exp\left(-\frac{\Delta^2}{2}\right) \sum_{k=0}^{m-1} \sum_{l=0}^{n-1} \frac{(-\Delta)^k \Delta^l}{k! \, l! \, \Gamma(-k+m)} \delta(n-l,m-k).$$
(S9)

where  $|m\rangle$  and  $|n\rangle$  denote the vibrational states of the displaced oscillators with quantum numbers m and n,  $\Gamma(z)$  is the Euler gamma function, and  $\delta(i, j)$  is the Kronecker delta function. The number of Franck-Condon integrals required in the evaluation of Eq. S8 increases exponentially with the number of vibrational modes. We used a multimode expression based on the cumulant expression for linearly displaced harmonic vibrations to avoid the summation.<sup>2</sup> The vibrational linewidth  $\Gamma_r = 10 \text{ cm}^{-1}$  is used for the intermediate vibronic states.

The one-dimensional stimulated resonance Raman (1D stRR) signals are conducted by a two-pulse pump-probe experiment, where the electric field is represented as,

$$E(\mathbf{r},t) = \mathbf{e}_1 \mathcal{E}_1 \exp(i\mathbf{k}_1 \cdot \mathbf{r} - i\omega_1 t) + \mathbf{e}_2 \mathcal{E}_2(t-\tau) \exp(i\mathbf{k}_2 \cdot \mathbf{r} - i\omega_2(t-\tau)) + \text{c.c.}$$
(S10)

Here  $\mathbf{k}_j$ ,  $\omega_j$ ,  $\mathbf{e}_j$ , and  $\mathcal{E}_j$  are the wavevector, carrier frequency, polarization vector, and complex envelope of the *j*-th pulse, respectively. The system is excited by a pump pulse and the the arrival of the probe pulse is recorded after a time delay  $\tau$  (see Fig. S1). The time-domain 1D stRR signals can be evaluated according to the diagram rules in Ref 9,

$$S(\tau) = -\sum_{b,b',c} V_{a,b'} V_{b'c} V_{cb} V_{ba} \int_{-\infty}^{\infty} dt \int_{-\infty}^{\infty} d\tau_3 \int_{-\infty}^{\infty} d\tau_2 \int_{-\infty}^{\infty} d\tau_1 \, \mathcal{E}_2^*(t-\tau) \mathcal{E}_2(\tau_3-\tau) e^{-i\omega_2(\tau_3-t)} \\ \times \left[ \mathcal{E}_1^*(\tau_2) \mathcal{E}_1(\tau_1) \exp(-i\omega_{b'a}t + i\omega_{b'c}\tau_3 - i\omega_{bc}\tau_2 + i\omega_{ba}\tau_1 - i\omega_1(\tau_1-\tau_2)) \right] \\ + \mathcal{E}_1(\tau_2) \mathcal{E}_1^*(\tau_1) \exp(-i\omega_{bc}t + i\omega_{ba}\tau_3 - i\omega_{b'c}\tau_2 + i\omega_{b'a}\tau_1 - i\omega_1(\tau_1-\tau_2)) + c.c.$$
(S11)

Here  $|a\rangle$  and  $|c\rangle$  are vibrational states in the ground electronic state, and  $|b\rangle$  is a vibronic excited state. Eq. S11 can be recast as,<sup>2,10</sup>

$$S(\tau) = \Re \left[ \left\langle \alpha^{(1)}(0)\alpha^{(2)}(\tau) \right\rangle - \left\langle \left( \alpha^{(1)}(0) \right)^{\dagger} \alpha^{(2)}(\tau) \right\rangle \right]$$
(S12)

where  $\alpha_{ac}^{(i)}$  is the effective transition polarizability between the vibrational states  $|a\rangle$  and  $|c\rangle$  due to the *i*-th pulse,

$$\alpha_{ac}^{(i)} = \frac{1}{\pi} \sum_{b} \langle a|b\rangle \langle b|c\rangle |\mu_{eg}|^2 \int_{-\infty}^{+\infty} \mathrm{d}\omega \; \frac{\mathcal{E}_i^*(\omega)\mathcal{E}_i(\omega+\omega_{ac})}{\omega+\omega_i-\omega_{bc}+\mathrm{i}\Gamma_b}.$$
(S13)

 $\alpha^{(n)}$  is a non-Hermitian operator in the vibrational subspace, but becomes real Hermitian far off-resonance, where Eq. S12 reduces to a commutator. The signal is recorded versus the pump-probe delay and is Fourier transformed to the frequency domain giving the 1D stRR signal,

$$S(\Omega_1) = \sum_{ac} P(a) \frac{i\alpha_{ca}^{(1)} \left[\alpha_{ac}^{(2)} - \left(\alpha_{ac}^{(2)}\right)^*\right]}{\Omega_1 - \omega_{ca} + i\Gamma}.$$
(S14)



FIG. S1. Loop diagrams for the 1D stRR signal.

A detailed derivation of Eqs. S14 and S13 can be found in the appendix of Ref. 2. In the time domain calculations, we used Gaussian pulse envelopes with a full width at half maximum (FWHM) of 1768 cm<sup>-1</sup> (8.33 fs). The center frequencies of the pump pulses are chosen to be  $\delta = 1500$  cm<sup>-1</sup> below those of the corresponding probe pulses.<sup>11</sup> Since the electronic dynamics is much faster than the nuclear relaxation, we use the linewidth parameters of 10 cm<sup>-1</sup> and 100 cm<sup>-1</sup> for the vibrational and electronic spectra to capture the broadening effects originates from intermediate state lifetimes, respectively. These values have been widely used in previous theoretical calculations.<sup>6–8</sup> We adopted parallel polarization configuration for the pump and probe pulses in the time domain simulation.

## II. CHARGE STATES AND SPIN MULTIPLICITIES

	Complex	Charge	Ground state multiplicity	$\Delta E \ (eV)$
	Ι	+2	2	3.495
•	II	+1	2	4.056
	III	0	2	3.642
	IV	-1	2	3.718

TABLE S1. Charge and spin multiplicities of the four complexes. The energy differences between the doublet and quadruplet are listed in the last column ( $\Delta E$ )



FIG. S2. Natural transition orbitals (NTOs) for the complex I. Only strongly allowed electronic transitions are depicted here. Left column: hole states; right column: electron states. The labels  $\varepsilon_i^S$  denotes the *i*-th electronic transition in the system *S*. The NTOs are generated by a script that extends the standard protocol<sup>12</sup> to the open-shell case.<sup>13</sup> All the distributions are rendered by using VMD <sup>14</sup> with the isosurface value of 0.02 a.u.

## **III. NATURAL TRANSITION ORBITALS**



FIG. S3. Same as Fig. S1 except for the complex II.



FIG. S4. Same as Fig. S1 except for the complex III.



FIG. S5. Same as Fig. S1 except for the complex IV.

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