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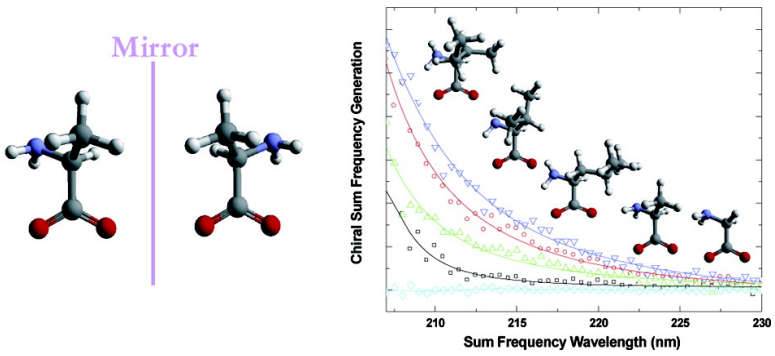

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Optically Active Sum Frequency Generation from Molecules with a Chiral Center: Amino Acids as Model Systems

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It is hardly necessary to stress the importance of molecular chirality, which is present in almost all natural products (e.g., proteins, sugars, and nucleic acids). Since the nineteenth century,[1] molecular chiroptical properties, such as natural optical activity, have been systematically studied, and much insight has been gained by studying the correlation between chiroptical properties and molecular structures.[2] Recently, optically active second harmonic generation (SHG) and sum frequency generation (SFG) have been developed to probe molecular chirality.[3] Since optically active SFG (OA-SFG) is allowed within the electric dipole approximation, it intrinsically has higher sensitivity than linear optical techniques, such as circular dichroism (CD), and is capable of yielding chiroptical spectra from a monolayer of chiral molecules.[3d,e] It has also been shown that the structural information provided by OA-SFG is different from that from CD.[3c] However, the possibility of applying the technique to molecules with a chiral center and an intrinsically achiral chromophore, such as amino acids, has never been investigated, although linear optical activity of such molecules has been well studied. Given the monolayer sensitivity of OA-SFG, it is of great interest to extend its use to molecules of this type. In this paper, we report our study of the OA-SFG near electronic resonance of amino acid molecules. We show that while the chiral signals of SFG and CD are both induced by extra-chromophoric perturbation from the chiral molecular structure, their relative strengths among different amino acids are different because of different perturbations coming into play in OA-SFG and CD.

All naturally occurring amino acids, except glycine (Gly), are chiral, having a carbon atom as the chiral center connecting a carboxyl group, an amino group, a hydrogen atom, and a side chain (R). The lowest electronic resonances originate from the carboxyl group, which is achiral by itself. In neutral and basic solutions, it is deprotonated ($-COO^-$) and has C_{2v} symmetry. The ground state

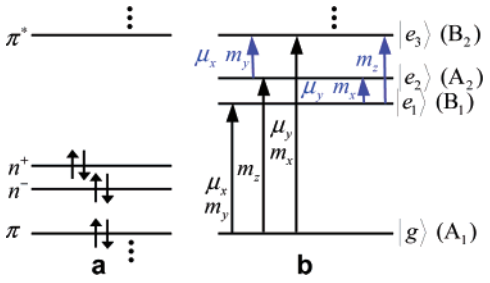

Figure 1. (a) Molecular orbitals of the $-COO^-$ group. The ground state $|g\rangle$ of $-COO^-$ corresponds to the three lowest orbitals fully occupied. (b) Energy level diagram showing the ground and excited electronic states $|g\rangle$, $|e_1\rangle$, $|e_2\rangle$, and $|e_3\rangle$, with their respective symmetry attributions in parentheses. The black arrows denote transitions between $|g\rangle$ and $|e_1\rangle$, $|e_2\rangle$, and $|e_3\rangle$, while the blue arrows denote transitions between the excited states. Labeled on the left of each arrow are the allowed electric ($\vec{\mu}$) and magnetic ($\vec{m}$) dipole transition moments for each transition.

$|g\rangle$ has the electronic configuration with molecular orbitals, n^+, n^-, and π, fully occupied (Figure 1a), while the three lowest excited states, $|e_1\rangle$, $|e_2\rangle$, and $|e_3\rangle$, can be approximated as having one of the electrons in n^+, n^-, and π promoted to the antibonding π^* orbital, respectively.[4−6] As denoted in Figure 1b, they have A_1, B_1, A_2, and B_2 symmetry, respectively. The allowed electric ($\vec{\mu}$) and magnetic ($\vec{m}$) dipole transition moments between the ground and excited states are indicated in Figure 1b, where the $-COO^-$ group is assumed to lie in the *yz* plane and its C_2-symmetric axis along the *z*-coordinate axis.

The general theory for SFG at frequency $\omega = \omega_1 + \omega_2$ in chiral liquids near electronic resonance was described in ref 3b,c. Briefly, the OA-SFG intensity is proportional to $|\chi^{(2)}_{\text{chiral}}|^2$, where $\chi^{(2)}_{\text{chiral}}$ is related to the hyperpolarizabilities, $\alpha^{(2)}$, of the chiral molecules by

$$\chi^{(2)}_{\text{chiral}} \propto N\alpha^{(2)}_{\text{chiral}}$$

$$\alpha^{(2)}_{\text{chiral}} \equiv \frac{1}{6}[\alpha^{(2)}_{xyz} - \alpha^{(2)}_{yxz} + \alpha^{(2)}_{yzx} - \alpha^{(2)}_{zyx} + \alpha^{(2)}_{zxy} - \alpha^{(2)}_{xzy}] \qquad (1)$$

$$= \frac{1}{6\hbar^2\epsilon_0}\sum_n \frac{(\omega_1 - \omega_2)}{(\omega - \omega_{ng} + i\Gamma_{ng})}\sum_{n'} \frac{\vec{\mu}_{gn}\cdot(\vec{\mu}_{nn'} \times \vec{\mu}_{n'g})}{(\omega_1 - \omega_{n'g})(\omega_2 - \omega_{n'g})}$$

where N is the number density of the molecules; x, y, and z define the molecular coordinate system, and ω_{ij} and Γ_{ij} denote the transition frequency and damping constant for the transition between the $|i\rangle$ and $|j\rangle$ states, respectively. From eq 1, we see that in order for the chiral response to be nonzero, there should exist at least one nonzero term with three electric dipole transition moments, $\vec{\mu}_{gn}$, $\vec{\mu}_{nn'}$, and $\vec{\mu}_{n'g}$ noncoplanar. For an isolated $-COO^-$ group, the above condition cannot be satisfied. For the four levels[7] in Figure 1b, the allowed electric dipole transition moments are only along the *x* and *y* directions. Chiral perturbation on $-COO^-$ caused by side chain R, however, breaks the C_{2v} symmetry. The perturbed $|g\rangle$, $|e_1\rangle$, $|e_2\rangle$, and $|e_3\rangle$ make $\langle g|\mu_z|e_2\rangle$ and $\langle e_1|\mu_z|e_3\rangle$ nonzero and result in the nonvanishing $\chi^{(2)}_{\text{chiral}}$ and OA-SFG signal.[8]

To study how the different side chains, R, affect $\chi^{(2)}_{\text{chiral}}$, we measured the OA-SFG spectra of alanine (Ala), valine (Val), leucine (Leu), and isoleucine (Ile). The experimental setup was similar to that described elsewhere,[3] with ω_1 tunable from 250 to 340 nm, ω_2 fixed at 1064 nm, and the SF signal at ω detected in the transmission direction. The samples were L-enantiomers dissolved in a 4 M NaOH solution.[9] The SPP (denoting S-, P-, and P-polarized SF output at ω, UV input at ω_1, and IR input at ω_2, respectively) polarization combination was used. The concentration-normalized OA-SFG spectra for Ala, Val, Leu, and Ile, are plotted in Figure 2, together with that of the achiral Gly showing no signal, as expected. The signal increases with a decrease of the SF wavelength because of resonant enhancement as ω approaches the electronic resonances of the $-COO^-$ group.[3]

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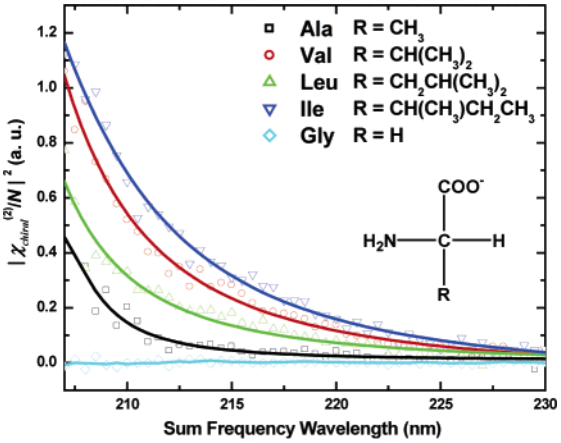

Figure 2. Normalized OA-SFG intensity $|\chi^{(2)}_{chiral}/N|^2$ versus SF wavelength from aqueous solutions of Ala, Val, Leu, Ile, and Gly. Solid lines are the guides for the eye. Polarization combination is S(ω)P(ω_1)P(ω_2).

Figure 2 shows that the observed nonlinear chiroptical response per molecule is different for amino acids with different side chains, R. When SF wavelength is at 210 nm, for example, it follows the order Ile > Val > Leu > Ala. On the other hand, CDs of the same molecules at this wavelength follow the order Leu > Ile > Val > Ala.[10]

The difference can be understood by knowing how chirality is induced by side chain R into the $-COO^-$ group through perturbation on the relevant transition moments in the two cases.

As mentioned earlier, OA-SFG from $-COO^-$ results from the perturbation of R that produces nonzero transition moments, μ_z, between states $|g\rangle$ and $|e_2\rangle$ as well as $|e_1\rangle$ and $|e_3\rangle$. Perturbation on the matrix elements of μ_x and μ_y can be neglected because they are already electric dipole allowed in the zeroth order. Thus, the relative strengths of OA-SFG for the four amino acids are directly correlated with the strengths of $\langle g|\mu_z|e_2\rangle$ and $\langle e_1|\mu_z|e_3\rangle$, both of which depend on the spatial characteristics of the perturbation in the same way.[11] For CD near a transition, $|g\rangle \rightarrow |n\rangle$, the strength is given by

$$R_{gn} = \mathrm{Im}\{\vec{\mu}_{gn} \cdot \vec{m}_{ng}\}$$

which is also zero for isolated $-COO^-$ because $\vec{\mu}_{gn}$ is either forbidden or orthogonal to $\vec{m}_{ng}$ (Figure 1b). The induced CD in COO^- at 210 nm, for example, mainly comes from side-chain perturbation that produces nonvanishing $\langle g|\mu_z|e_2\rangle$ as well as nonvanishing $\langle g|\mu_y|e_1\rangle$ and $\langle g|m_x|e_1\rangle$.[12] Although $\langle g|\mu_z|e_2\rangle$ contributes similarly to CD and OA-SFG, $\langle g|\mu_y|e_1\rangle$ and $\langle g|m_x|e_1\rangle$ contribute significantly only to CD near resonance in the UV. They lead to the different sequences of amino acids in the order of chiral signal strength in CD and SFG. In a detailed calculation, assuming van der Waals interactions (through-space interactions)[13] between side chains R and the $-COO^-$ chromophore as perturbations on the wave functions and transition moments, we were able to reproduce the observed sequences of amino acids in CD and OA-SFG.[14]

We can understand the observed sequence of amino acids in OA-SFG from a simple physical argument. Since van der Waals interaction decreases rapidly with distance, perturbation on COO^- is dominated by perturbers in the immediate neighborhood of the chromophore; the more perturbers there are, the stronger the perturbation is. Furthermore, for chiral perturbation, to induce a μ_z transition moment on COO^-, the effective perturbers should have an oscillating dipole component along the *z*-direction. Thus, Ile and Val, having two substitute groups on the β-carbon with strong projection on the *z*-axis, are expected to have a larger OA-SFG response than those of Leu, which has two substitute groups on the more remote γ-carbon, and Ala, which has no substitute group on β-carbon. (The carbon atom at the chiral center is the α-carbon.) Ile and Leu have a stronger chiral response than Val and Ala, respectively, because of the larger number of perturbers.

In summary, we have measured near-resonant OA-SFG from a series of amino acids with similar side-chain structures. This is the first time OA-SFG was used to probe chirality of molecules possessing a chiral center and an intrinsically achiral chromophore. Complementary to CD, the results provide information on how extrachromophoric perturbation induces chirality in a chromophore that shows up in CD and OA-SFG. Knowing OA-SFG responses from amino acids, we can estimate the signal strength of the OA-SFG expected from peptides and proteins since their amide group is isoelectronic with the carboxyl group of amino acids. Experiments on peptides and proteins are currently underway.

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(8) A simple way to see this is through the correlation table of the C_{2v} group and C_2 group. When the chromophore is reduced to C_2 symmetry, the two electric dipole transition moments are then allowed in the *z*-direction.
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