# Vibrational Circular Dichroism in Amino Acids and Peptides. 8. A Chirality Rule for Methine $C^*_\alpha$–H Stretching Modes

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Vibrational circular dichroism (VCD) has been shown to be sensitive to stereoconformational features in chiral molecules.[1] Although a detailed understanding of VCD spectra requires extensive numerical calculations, in certain cases spectra have been shown to correlate to simple models, such as the coupled-oscillator model,[2] or to vibrations from common molecular groups, such as the $CH_2CH_2C^*H$ ring fragment[3] or the $\alpha$-helical polypeptide backbone.[4]

In this communication we report a methine $C^*_\alpha$–H stretching chirality rule for the $\alpha$-L-amino acids that is based on a new simple mechanism for visualizing the origin of strong monosignate VCD intensity. The empirical basis for the rule is that the VCD in the CH stretching region of the L-amino acids in aqueous solution exhibits a strong positive bias.[5] A mechanism that we propose to explain the source of the bias arises from the formation of an intramolecular hydrogen bond that supports electronic current in the molecular ring fragment $\overline{C^*_\alpha CO \cdots DN}$, induced by the $C^*_\alpha$H stretching motion. As shown for the $C^*_\alpha$H contraction in **1**, the sense of positive current in the ring creates a magnetic dipole

**1** **2**

moment derivative **m** that forms a positive scalar product with the electric dipole moment $\mu$ for this vibration and hence positive circular dichroism intensity.

Theoretical considerations suggest two sources for generating VCD bias. First, nuclear motion can induce electronic charge redistribution at the extremes of the vibrational cycle which contributes to both $\mu$ and **m**. In the localized molecular orbital (LMO) model for VCD,[5e] this charge redistribution results in motion of the LMO centroids that does not perfectly follow the nuclear motion. In charge-flow models of VCD, including the nonlocalized molecular orbital (NMO) model,[6,7] the electronic redistribution enters the magnetic dipole moment expression as charge flows along bonds. For L-alanine-$C$-$d_3$,$N$-$d_3$, using both the LMO and NMO models, the calculated VCD for the lone $C^*_\alpha$H stretch is positive, but the calculated $g$ value is significantly lower than experiment.

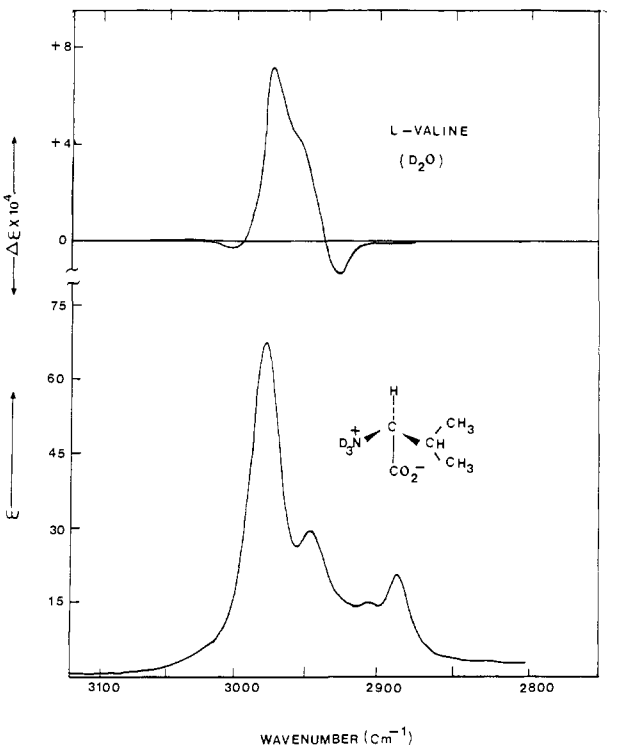


**Figure 1.** VCD (upper curve) and absorption (lower curve) for L-valine-$N$-$d_3$ in the CH stretching region. The spectra were obtained using a dispersive VCD instrument[5d] for a 0.43 M solution in $D_2O$ at a path length of 200 $\mu$m. The uncertainty in $\Delta\epsilon$ is $\pm 0.3 \times 10^{-4}$.

In addition, if a closed molecular ring is present, oscillating electronic current around the ring can be induced by the momenta of the vibrating nuclei[8] that does not redistribute charge. Such a current can contribute to **m** but not $\mu$. The LMO and NMO calculations for alanine do not include this source of VCD intensity; however, the determination of bond charge flows in the NMO model contains an indeterminant parameter for a molecular ring[7] which corresponds to such a ring current. If a ring for alanine is assumed, the calculated NMO-VCD intensity can be increased to yield agreement with the experimental $g$ value by adding a positive ring current of the sense indicated in **1**.

As an example of the positive bias in the CH stretching VCD of L-amino acids we show spectra in Figure 1 for L-valine-$N$-$d_3$ in $D_2O$ solution. The methine $C^*_\alpha$–H stretching mode cannot be distinguished in the absorption spectra; however, on the basis of earlier work in alanine, serine, and other amino acids we know this mode to be located at $\sim$2970 $cm^{-1}$ as a broad band with a maximum $\epsilon$ value of $\sim$3–5 $cm^{-1}$ L $mol^{-1}$. In the VCD spectrum, the intensity is due almost entirely to the $C^*_\alpha$–H mode. The valine side group serves only to modify the shape of the overall spectrum. The valine VCD spectrum is similar in general appearance and intensity to most of the L-amino acids. In Table I we list the values of $\Delta\epsilon_{max}$ for the L-amino acids that we have measured thus far. These VCD spectra will be published at a future date.[5f,g] Further evidence for intramolecular hydrogen bonding as a source of VCD is the loss of both positive bias and positive $C^*_\alpha$H VCD intensity in the CH stretching VCD of cysteine·hydrochloride[5f,g] for which

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Table I. Maximum Vibrational Circular Dichroism Intensity for L-Amino Acids[a]

| amino acid | $10^4\Delta\epsilon$, cm$^{-1}$ L mol$^{-1}$ | frequency, cm$^{-1}$ |
|---|---|---|
| alanine | 11.3 ± 0.2 | 2968 |
| serine | 3.3 | 2963 |
| cysteine | 8.8 | 2972 |
| histidine | 5.1 | 2979 |
| phenylalanine | 5.0 | 2975 |
| valine | 7.3 | 2972 |
| penicillamine | 8.9 | 2963 |
| methionine | 6.5 | 2975 |
| proline | 7.3 | 2995 |
| hydroxypyroline | 9.1 | 2989 |
| *allo*-hydroxyproline | 7.6 | 2968 |
| threonine | 11.0 | 2978 |
| *allo*-threonine | 4.9 | 2968 |
| leucine | 16.0 | 2963 |
| isoleucine | 15.3 | 2972 |
| aspargine | 5.9 | 2972 |
| glutamine | 5.3 | 2976 |
| lysine hydrochloride | 5.1 | 2976 |
| arginine hydrochloride | 4.7 | 2966 |

[a] The absorption strength for the $C^*_\alpha$–H modes is estimated to be $\epsilon \gtrsim 3$–5 on the basis of spectra for alanine-*C*-$d_3$, serine, cysteine, and aspargine.

hydrogen bonding would be disrupted.

The methine $C^*_\alpha$–H stretching chirality rule can also be extended to α-L-hydroxy acids, such as L-lactic acid[9] and (*S*,*S*)-tartaric acid,[10] and to bis(L-amino acid)copper(II) complexes[5f,g] where currents are induced by $C^*_\alpha$–H motion in the ring fragments $\overline{C^*_\alpha CO \cdots DO}$ (**2**) and $\overline{C^*_\alpha CO\text{–}Cu\text{–}N}$, respectively. The ring fragment in the hydroxy acids is isoelectronic and nearly equivalent in mass distribution to the amino acid ring. The VCD bias in the hydroxy acids is approximately the same as in the amino acids whereas the Cu complexes show a bias that is approximately twice as large.[5f,g]

The anisotropy ratio $\Delta\epsilon/\epsilon$ for the methine $C^*_\alpha$–H stretching mode in the molecules discussed here and in Table I is either measured or estimated to be greater than $+1 \times 10^{-4}$. Molecules that cannot form intramolecular hydrogen bonds for which $C^*_\alpha$H stretching VCD is available show intensity with $\Delta\epsilon/\epsilon$ less than $10^{-4}$. Examples are 2,2,2-trifluoro-1-phenylethanol (neat and in $CCl_4$ solution),[11] neopentyl-*1*-*d* chloride,[11a] deuterated phenylethanes,[12] and other phenylethane derivatives.[13] The CH stretching VCD of (*S*,*S*)-dimethyl tartrate[1d] is predominantly $C^*_\alpha$–H stretch and has a $\Delta\epsilon/\epsilon$ for this mode of $\sim+1.5 \times 10^{-4}$, equal in sign and magnitude to (*S*,*S*)-tartaric acid and L-lactic acid.[14] This strongly implies a conformation comprised of two isolated hydrogen-bonded rings rather than the interlocking hydrogen-bonded ring conformation,[2b-d] since, in the latter, two opposing ring currents would cancel.

The methine chirality rule appears to be a promising interpretive concept for VCD spectra and it reveals that VCD intensities can be particularly sensitive to the presence and strength of intramolecular hydrogen bonds. The rule may likely be further generalized to include any out-of-plane stretching motion associated with an adjacent induced ring current.

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**Registry No.** L-Alanine, 56-41-7; L-serine, 56-45-1; L-cysteine, 52-90-4; L-histidine, 71-00-1; L-phenylalanine, 63-91-2; L-valine, 72-18-4; L-penicillamine, 1113-41-3; L-methionine, 63-68-3; L-proline, 147-85-3; L-hydroxyproline, 51-35-4; L-*allo*-hydroxyproline, 618-27-9; L-threonine, 72-19-5; L-*allo*-threonine, 28954-12-3; L-leucine, 61-90-5; L-isoleucine, 73-32-5; L-aspargine, 70-47-3; L-glutamine, 56-85-9; L-lysine hydrochloride, 10098-89-2; L-arginine hydrochloride, 15595-35-4.

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(14) L-Lactic acid corresponds to "*S*" absolute configuration and is analogous in configuration to (*S*,*S*)-tartaric acid.

## First Experimental Demonstration of Chemical Resonance in an Open System

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The phenomenon of resonance is observed when a damped oscillator is driven by a periodic driving force in such a way that the response amplitude of the oscillator goes through a maximum as a function of driving frequency.[1] The maximum occurs when the driving frequency is close to the endogeneous frequency of the oscillator if the damping constant is smaller than the endogeneous frequency. This is exemplified by many spectroscopic resonance processes familiar to every chemist. The mathematical equation for a damped oscillator is $f(t) = e^{-t/\tau} \cos(\omega_0 t)$ where $1/\tau$ is defined as the damping constant $\gamma$ and $\omega_0$ as the endogeneous frequency of the oscillator. We have asked ourselves whether resonance may also be demonstrated in a chemical reaction, i.e., when the driven system represents a chemical oscillator.[2] We report to our knowledge the first experimental example of chemical resonance as it occurs in the well-known Belousov–Zhabotinsky (BZ)[3] reaction, which is modified by the addition of $Br^-$ and carried out in a continuous-flow stirred tank reactor (CSTR). In order to obtain chemical resonance, it was essential for us to conduct the BZ reaction in the absence of limit-cycle oscillations and to choose conditions that it only shows *damped* oscillations. We found such conditions guided by our computer simulations of chemical resonance in the Oregonator model (and other mechanisms).[2]

The BZ reaction is initiated inside the CSTR and run for a number of periods without inflow of reactants, i.e., $k_f = 0$, where $k_f$ is the inverse mean residence time $\tau_r$ of all species in the absence of a chemical reaction, and $k_f = 1/\tau_r$ where $\tau_r = V/u$, $V$ being the volume of the CSTR (1.70 mL) and $u$ being the volume rate of flow expressed in mL/min. Two solutions are allowed to flow simultaneously from two motor-driven 50-mL syringes into the CSTR, which has been placed into a spectrometer in order to monitor the $Ce^{4+}$ concentration at 350 nm as a function of time inside the reactor. One solution contains potassium bromide ($2.4 \times 10^{-6}$ M) and 0.6 M malonic acid in 0.75 M $H_2SO_4$ and the second solution contains $1 \times 10^{-3}$ M $Ce^{3+}$ and 0.28 M $KBrO_3$. The effective concentrations inside the reactor are half of the input concentrations, since two identical supply syringes and tubes are used. Any interference of the 350-nm light intensity with the kinetics of the present reaction could not be observed. The reaction mixture does not show any fluorescence.

We superimpose a sinusoidal modulation on the total flow through the CSTR. This is achieved by controlling flow frequency and amplitude via a CBM Commodore computer whose analog-converted output drives the step motor of a precise syringe pump (Infors Precidor). The time dependent flow rate is

$$k_f = k_f^0(1 + \alpha \cos \omega t)$$

where $k_f^0$ is the flow-rate constant in the absence of any modu-

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