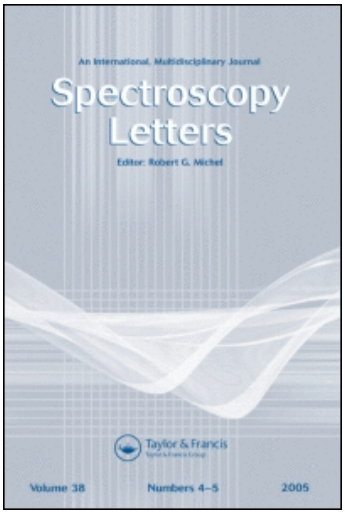

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Dipeptide $_L$-Seryl-$_L$-Methionine—Linear Dichroic IR and Theoretical Characterization

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ABSTRACT The dipeptide $_L$-seryl-$_L$-methionine is elucidated structurally by means of solid-state linear dichroic infrared spectroscopy of oriented samples as a colloidal suspension in nematic liquid crystal as a part of our systematic study of OH-containing small peptides. Vibrational analysis supports the experimental data as well. Quantum chemical *ab initio* calculations are performed in order to obtain the electronic structure and vibrational characteristics of the system studied, where a *cisoide*-configuration of the C=O–NH amide fragment is predicted.

KEYWORDS *ab initio* calculations, linear dichroic infrared spectroscopy, $_L$-seryl-$_L$-methionine, solid-state

INTRODUCTION

The interaction of Au(III) and Pt(II) with peptides and proteins has been widely investigated in light of the potential antitumor effect of their corresponding coordination compounds.[1–9] In order to understand the *in vivo* manner and coordination mechanism of these ions with DNA, a systematic examination of their coordination ability with small peptides is necessary.[1–14] The donor ability of the thioester groups in the methionine side chains is of particular interest. IR spectroscopy and nuclear magnetic resonance methods are powerful tools for studying these interactions, but the comparison of the spectroscopic properties of the pure ligands and their complexes requires knowledge of the corresponding spectroscopic characteristics. However, peptides possess complicated spectroscopic IR patterns requiring the application of specific, unconventional analytical techniques. The possibility of linear-polarized IR spectroscopy (linear dichroic infrared [IR-LD]) or oriented solid samples as a colloidal suspension in nematic liquid crystal address these difficulties to a significant degree. This method has been applied to peptide systems, their complexes, and salts.

A study of the $_L$-seryl-$_L$-methionine (*Ser-Met*) dipeptide (Scheme 1) is justified, and this article focuses on a preliminary structural analysis of the neutral ligand. In this analysis, theoretical *ab initio* calculations and solid-state IR-LD spectroscopy of oriented colloid suspensions have been applied.

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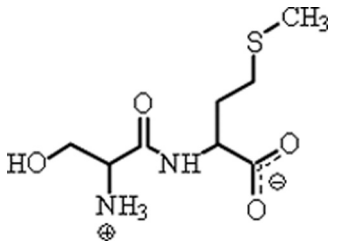

SCHEME 1 **Chemical diagram of *Ser-Met*.**

MATERIALS AND METHODS

IR spectra were measured using a Bomem Michelson 100 FT-IR Spectrometer (ABB Bomem, Canada) (4000–400 cm^{-1}, 2.0 cm^{-1} resolution, 150 scans) equipped with a Perkin Elmer (Waltham, MA, USA) wire-grid polarizer. Nonpolarized solid-state IR spectra were recorded using the potassium bromide disk technique. The oriented samples in the IR-LD spectroscopic study were obtained as colloidal suspensions in a nematic liquid crystal (MLC 6815, Merck, Darmstadt, Germany) with the presence of an isolated nitrile stretching IR band at about 2230 cm^{-1}, which served as an orientation indicator. This solid-state orientation method was used for IR-LD spectroscopy and has been validated.[15] It uses a colloidal suspension in nematic liquid crystal, which allows accuracy and precision in measuring the influence of the liquid crystal medium on peak positions and integral absorbances of the guest molecule bands. The experimental conditions and design were optimized for the quantitative evaluation of the impact of the four input factors.[15–17] The number of scans, the rubbing out of KBr plates, the quantity of studied compounds included in the liquid crystal medium, and the ratios of Lorentzian to Gaussian peak functions in the curve-fitting procedure on the spectroscopic signal at five different frequencies were studied. The procedure for determining the position (ν_i) and integral absorbencies (A_i) for each i peak were carried out by deconvolution and curve-fitting procedures at 50:50% ratio of Lorentzian to Gaussian peak functions (χ^2 factors within 0.00066–0.00019 and 2000 iterations). The two treatments are compared using the student t-test. The applicability of this approach of experimentally assigning IR-spectroscopic bands and of obtaining stereo-structural information has been demonstrated in a series of organic systems and coordination complexes (e.g., heterocyclic, Cu(II) complexes, polymorphs, codeine derivatives, peptides their Au(III) complexes, hydrochlorides, and hydrogensquarates[18–23]). The nature and balance of the forces in the nematic liquid crystal suspension system, the mathematical model for their clearance, the morphology of the suspended particles, and the influence of the space system types on the degree of orientation (i.e., ordering parameter) have been previously shown[24] using five liquid crystals and 15 compounds. The theory of IR-LD spectroscopy and the use of polarized IR spectra interpretation difference-reduction procedure are given in the reference literature.[12–24] Quantum chemical calculations were performed with the GAUSSIAN 98 program package.[25] The output files are visualized using the ChemCraft program.[26] The dipeptide *Ser-Met* is a Bachem Organics (Budendorf, Switzerland) product.

RESULTS AND DISCUSSION

This work can be considered as a part of systematic spectroscopic and structural elucidation on small peptides, their responsibility to form metal complexes, and their application as potential anticancer medications.[12–24,27,28]

Theoretical Calculations

The geometries are optimized using two levels of theory: the second-order Moller-Pleset perturbation theory (MP2) and the restricted Hartree-Fock (RHF) theory using a 6-311++G** basis set. The conformational analysis shows several conformers with relative energies (E_{rel}) of less than 5 kJ/mol (Fig. 1) for the zwitterionic and protonated forms of studied peptides. The 3D graph dependence of the E_{rel} as a function of Psi and Phi and angles for the compound studied is shown in Fig. 1, where Psi and Phi describe torsion angles around the Cα–C bond (Psi(ψ)$-NH_3^+-$CH$-$C=O) and bond N–Cα (Phi(ϕ) –O=C–NH–CH), respectively, in this case.

For the purposes of the experimentally determining structure in solid state, this was used only with the E_{rel} value of 4.1 kJ/mol, the geometry of which is depicted in Fig. 2. The perpendicular orientation of the transition moments were established (Fig. 2).

The RHF approximation gives sufficient comparatively structural parameters for protonated peptides: a conclusion valid for other similar systems as

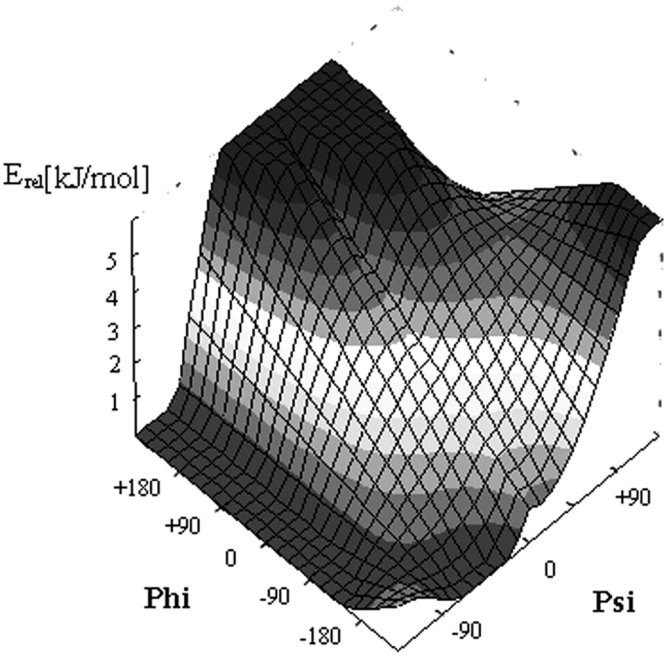

FIGURE 1 **3D graph of E_{rel} (kJ/mol) as a function of Phi and Psi angles for *Ser-Met*.**

well.[18–23] The molecular geometry of the studied dipeptide was fully optimized using the force gradient method employing Bernys' algorithm. For every structure, the stationary points found on the molecule potential energy hyper-surfaces were characterized by using standard analytical harmonic vibrational analysis. The absence of imaginary frequencies confirms that the stationary points correspond to the minima of the potential energy hyper-surfaces. The calculation of vibrational frequencies and infrared intensities were checked to determine which of the performed calculations agreed well with the experimental data. In this case, the RHF method provided enough accurate vibrational data with calculated standard deviations of $11\,cm^{-1}$ (RHF) and $13\,cm^{-1}$ (MP2), respectively. Therefore, the RHF/6-311++G** data are presented. In order to improve the correspondence between the experimental and theoretical values, the results were modified using an empirical scaling factor of 0.8929.

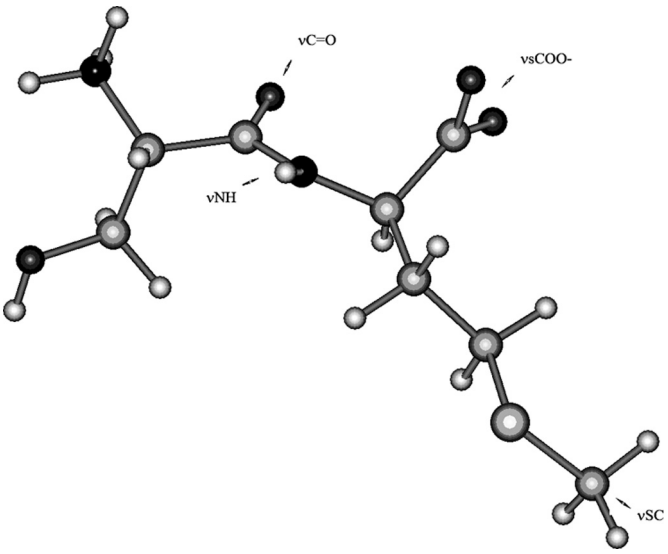

FIGURE 2 **Most stable conformer of *Ser-Met* and visualization of selected transition moments.**

IR and IR-LD Spectral Analysis

The suspended particles in the nonpolarized IR and difference IR-LD spectra of *Ser-Met* (Fig. 3) showed a significant degree of orientation. The observed pairs of maxima at $3207\,cm^{-1}$ and $3070\,cm^{-1}$ correspond to the stretching ν_{NH} and ν_{OH} modes of the NH and OH groups of the dipeptide molecules that participate in very strong hydrogen bonding. The multiple 3100–2300 cm^{-1} peak corresponds to the asymmetric and symmetric stretches $\nu^{as}_{NH_3^+}$ and $\nu^{s}_{NH_3^+}$ vibrations of protonated NH_3^+ groups in the zwiterionic dipeptide. In the 1700–1400 cm^{-1} range, maxima at $1687\,cm^{-1}$ ($\nu_{C=O}$, Amide I), $1610\,cm^{-1}$ ($\delta^{as}_{NH_3^+}$, NH_3^+-asymetric bending vibration), $1563\,cm^{-1}$ (ν^{as}_{COO-}, asymmetric stretching mode), $1482\,cm^{-1}$ (δ_{NH}, Amide II), $1502\,cm^{-1}$ ($\delta^{s}_{NH_3^+}$), and $1396\,cm^{-1}$ (ν^{s}_{COO-}) are observed. The obtained data correlated well with the known theoretical IR spectral for pure amino acids; in methionine, $\delta^{as}_{NH_3^+}$ and $\delta^{s}_{NH_3^+}$ are observed at $1625\,cm^{-1}$ and $1475\,cm^{-1}$,[21–24,26,29] while in glycine, the ν^{as}_{COO-} and ν^{s}_{COO-} modes are at $1575\,cm^{-1}$ and $1417\,cm^{-1}$. In contrast to L–threonyl–L–methionine dipeptides[30] the δ_{NH} is observed in the low-frequency region, which is typical for *cis*- or *cisoide*-configurated O=C–NH amide fragments.[31] A direct experimental confirmation of this assumption is seen in the difference IR-LD spectrum (Fig. 3), where the elimination of the δNH band and reduction, but not the disappearance of the $\nu_{C=O}$ (Amide I) mode, is observed. This result is in accordance with the theoretically predicted value of the amide O=C–NH dihedral angle of 163.2(1)° (Fig. 2). On the other hand, the spectrum in Fig. 3 is characterized by the not elimination of the ν^{as}_{COO-} and ν^{s}_{COO-} bands, which is impossible in the frame of a structural COO– fragment, due to the

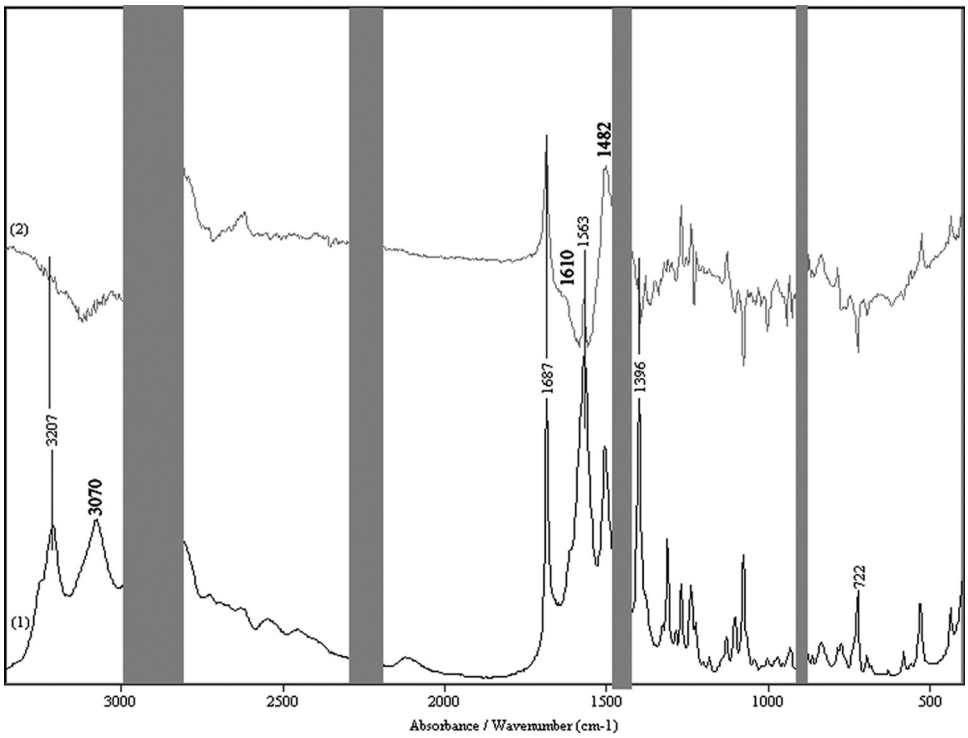

FIGURE 3 **Nonpolarized IR (Line (1)) and difference IR-LD (Line (2)) spectra of *Ser-Met*; self-absorption of the liquid crystal is shown with gray rectangles.**

perpendicular orientation of the discussed transition moments (Fig. 2). This indicates that the unit cell of *Ser-Met* contains mutually perpendicular oriented molecules as a result of the co-linear orientation of the transition moments in the frame of the neighboring disposed molecules. This phenomenon has been observed in a series of small peptides studied with polarized IR-LD spectroscopy,[32–34] where the data space group $P2_12_12_1$ (obtained by single crystal X-ray diffraction) is characterized by perpendicularly oriented molecules in the unit cell.

Previous data related to methionine containing tripeptides shows peaks corresponding to νCS.[14,18–23,29] In pure methyonine, the peak is obtained at 725 cm^{-1}.[29] The elimination of the band at 722 cm^{-1} does not affect the IR characteristic bands and cannot be obtained experimentally, thus providing no proof about its origin. However, it was theoretically predicted that the νCS mode should be observed at 720 cm^{-1}, which means that the band at 722 cm^{-1} corresponds to the stretching νCS vibration.

CONCLUSION

The IR spectroscopic and structural elucidation of the dipeptide *Ser-Met* was performed using IR-LD spectroscopy of oriented colloid suspensions in nematic host, as well as *ab initio* calculations at RHF/6-311++G** and MP2/6-311++G** levels of theory and basis set. Conclusions about the geometry and IR characteristic bands of the dipeptide were obtained. In contrast to *Thr-Met*, where a *trans*-configuration of the C=O–NH amide fragment is preferable,[30] in *Ser-Met*, a *cisoide*-configuration is predicted (with a dihedral angle of 163.2(1)°).

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