Amino Acids (2010) 38:45–50
DOI 10.1007/s00726-008-0220-9

MINIREVIEW ARTICLE

Spectroscopic and structural elucidation of amino acid derivatives and small peptides: experimental and theoretical tools

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Received: 11 October 2008 / Accepted: 19 November 2008 / Published online: 14 December 2008

Abstract This mini review deals with the modern aspects of the spectroscopy and structural elucidation of amino acid derivatives and small biologically active compounds. Free peptide bond rotation in these systems yields various conformers, which possess differing biological activities. Another phenomenon is the intermolecular or intramolecular stacking observed in aromatic small peptides. Specifically, the main aim is to illustrate the successful application of the "complex tool", consisting of a combination of the theoretical approximation methods with experimental linear polarized infrared (IR-LD) and/or Raman spectroscopy of oriented colloid suspensions in a nematic host. The possibilities and limitations of the approach for detailed vibrational assignment and structural elucidation of small peptides are discussed. Having in mind that physical and chemical properties of these systems can be precisely calculated by means of ab initio and DFT methods at Hartee-Fock, MP2 and B3LYP level of theory, varying basis sets, the results obtained allow a precise assignment of many vibrational bands to the corresponding normal modes, electronic structures and conformational state. The validity of the conclusions about the structure or vibrational properties of these systems have been supported, compared and/or additionally proved by the results from independent physical methods. In this respect ^{1}H and ^{13}C-NMR, single crystal X-ray diffraction, HPLC tandem mass spectrometry as well as thermal methods are all employed. A well ordered crystal must first be grown in order to determine the molecular structure by the absolute method of single crystal X-ray diffraction. Although the 3D structures of peptides have been determined over the past decades, peptide crystallization is still a major obstacle to X-ray diffraction work, the presence of chiral centre/s makes for this difficulty. For this reason the "complex tool" presented can be regarded as an alternative method for obtaining of structural information in the solid-state. It is obviously that only absolute crystallographic method can yield geometric parameters, bond lengths and angles, but the spectroscopic method presented can provide information about the dihedral angles for *cis*- and *trans*-configurated amide groups, mutual disposition of the aromatic fragments in peptides. Its validity is illustrated by comparing the theoretical and spectroscopic results obtained with available crystallographic data. The mini review can serve as a useful source of information not only for specialists in IR spectroscopy but, also, for other scientists, working in the field of structural analysis of amino acid derivatives and other small biologically active systems.

Introduction

Free peptide bond rotation yields various conformers, which possess differing biological activities as a result of protonation or coordination processes. The intermolecular aromatic stacking in aromatic amino acids and aromatic-containing small peptides is another interesting phenomenon. This phenomenon with emphasis on its important role in biological systems was first observed and recognized by

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Sunner et al. (1981) and Dougherty (1996) Ma and Dougherty (1996) Kumpf and Dougherty (1993). In this instance they provide a reasonable explanation for functioning and selectivity in variable ion channels (Dougherty 1996). A series of systematic studies with respect to this have been published by Sigel (1981) and also by Yamauchi and Odani (1985).

Infrared and nuclear magnetic resonance are powerful methods for investigating the coordination and protonation ability of such biological samples as well as the stacking effects in aromatic containing peptides. However, in the first case it is difficult to apply conventional IR techniques on account of the complicated IR-spectral patterns of the peptides that result from the presence of more than one amide fragment. The IR-LD of oriented solid samples as a colloid suspension in nematic liquid crystal reduces these difficulties to a significant level (Ivanova et al. 2004, 2006a, 2007; Koleva et al. 2007a, b, 2008a, b). Moreover this latter method allows collection of structural and local structural information about suspended chemicals in solid state independent of their amorphous or polycrystalline character. Its importance in the study of the amino acids, their amides, small peptides and their derivatives is enhanced on account of the difficulty of crystallizing these systems because of their chirality. The systematic investigation of the structure and vibrational properties using the polarized IR and/or Raman spectroscopy described on the systems discussed is carried out with corresponding theoretical calculations. Modern quantum chemical methods with the appropriate level of theory and basic set are used in our studies with a view to performing conformational analysis, elucidating the electronic structures, and predicting the corresponding vibrational properties. Modern vibrational approaches have been applied for these systems (Chou 1983a, b, 1984a, b, 1985, 1988, 1989; Chou et al. 1989). The posibilities of the near-infrared diffuse reflection spectroscopy for the determination of the protein structure has been applied by Bai et al. (2006).

The X-ray technique is often used for determining the 3D structure of proteins/peptides, however not all proteins/peptides can be easily crystallized, particular for membrane proteins. As a complement, NMR is indeed very powerful means in determining those structures (Schnell and Chou 2008; Call et al. 2006; Oxenoid and Chou 2005; Schnell et al. 2005) that are difficult to crystallize, however it is time-consuming and costly. Although using various structural bioinformatics tools (Chou 2004a), particularly the homologous technique (Chou 2004b, c, 2005) can help acquire protein 3D structures, unfortunately the number of templates for homologous modelling is quite limited. In view of this, it would be very useful to develop a complex tool by combining many different techniques as introduced in this review paper.

The IR-LD spectroscopic and structural elucidation of more then 150 small peptides has been performed using the method presented (Kolev et al. 2006a, b, 2007; Kolev 2007; Ivanova 2006; Ivanova and Arnaudov 2006; Ivanova et al. 2006b, c). The series of glycyl-, L-methionyl, L-trpyptophyl, L-phenylalanyl, L-methionyl, L-seryl, L-threonyl, L-alanyl-, L-histidyl-, L-valyl containing di-, tri- and tetra-peptides, some L-arginyl-containing tetrapeptides, selected pentapeptides, their protonated forms and metal complexes have also been investigated. The background of the linear-polarization IR-method of colloid suspensions in nematic host can be find in Ivanova et al. (2004, 2006a, 2007) Koleva et al. (2008a), while the theoretical approximation tools—in Kolev et al. (2007) Koleva et al. (2008b), respectively. Series of small biologically active compounds have been analyzed in Kolev et al. (2008a, b, c, d).

Example on the spectroscopic and structural elucidation of small peptides

The successful application of the experimental polarized IR method and theoretical approximation tools for elucidation of the spectroscopic properties and these systems include full vibrational characterization comparing the theoretical and experimental IR and Raman characteristics. In all cases the characteristic IR and Raman bands and their assignments have been tabulated (Kolev et al. 2006a, b, 2007; Chou 1983b, 2007; Ivanova et al. 2006b, c). In the cases of the hydrochloride salts, where the strong overlapped IR-spectral curves are obtained, the data about the peak positions and integral absorbances are obtained after preliminary procedures of deconvolution and curve-fitting (Ivanova et al. 2004, 2006a, 2007; Koleva et al. 2008a, b). This also applies to the corresponding IR-spectra of hydrogensquarate salts. It is of interest to note that inspire of the equivalent side chains included in the structures of di-, tri- or tetra-peptides or their protonated forms, the IR-spectral characteristics differ, because of different type of intermolecular interactions in solid-state. The disappearance of ν^{as}_{COO-}, ν^{s}_{COO-} bands and the observation of new peak about 1,750 cm^{-1}, associated with the $\nu_{C=O}$ stretching peak of COOH group formed is common for all the hydrochlorides.

In order to illustrate of the application of the method to peptide systems the IR-LD analysis is compared with corresponding Raman spectroscopic data and crystal structures of some of the systems studied. Raman spectra (Fig. 1) contain non-overlapping peaks, which makes identification often easier, than in the corresponding IR spectra. In accordance with theory, the ν^{as}_{NH3+} and δ^{as}_{NH3+} stretching and bending vibrations of NH_3^+ group in each of the zwiterrionic peptides are low-frequency

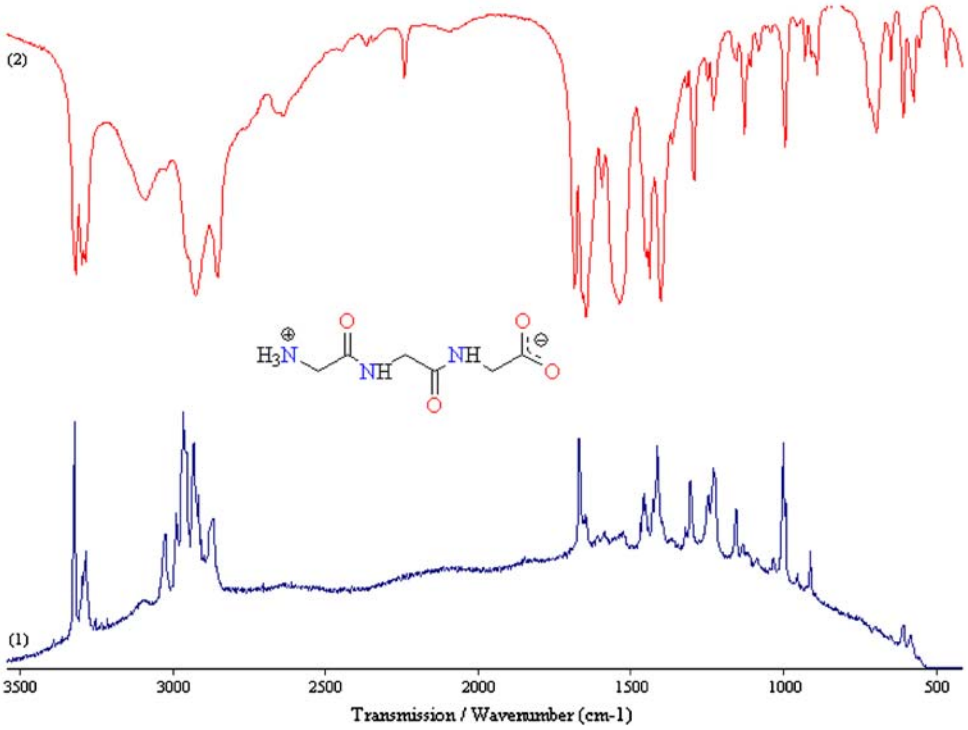

Fig. 1 Raman (*1*) and IR (*2*) spectra of *H–Gly–Gly–Gly–OH* in solid-state

absorbtion bands observed with a difference less then 2 cm^{-1} compared to the corresponding IR-bands. The same applies to the Amide I stretching vibrations.

If we analyze the dipeptide glycyl-glycine (*H–Gly–Gly–OH*) and recorded the corresponding polarized IR-LD spectra in manner described in Kolev et al. 2006a, b, 2007; Kolev 2007; Chou 1984a, 1996; Ivanova 2006; Ivanova and Arnaudov 2006; Ivanova et al. 2006b, c, then with using reducing-difference procedure we have demonstrated a successful application of our method. As for example the elimination of 3,288 cm^{-1} peak (ν_{NH}) provokes a disappearance of Amide I mode at 1,656 cm^{-1} [Fig. 2(2)], indicating a flat *trans*-configurated amide fragment in the frame of *H–Gly–Gly–OH* molecule [Fig. 2(2)]. According the theory given IR-bands is eliminated at equal dichroic ratio, when their transition moments are co-linear (see Fig. 2). Simultaneously with the peak at 1,409 cm^{-1} ($\nu^{\mathrm{s}}_{\mathrm{COO-}}$), a vanishing of 1,679 cm^{-1}, 1,673 cm^{-1} ($\delta^{\mathrm{as}}_{\mathrm{NH3+}}$) and 1,533 cm^{-1} ($\nu^{\mathrm{as}}_{\mathrm{COO-}}$) maxima are obtained [Fig. 2(3)], which is in accordance with known crystallographic data for *H–Gly–Gly–OH* indicating a flat C(=O)–NH amide fragment with torsion angle at 178.7°.

It is obviously how is possible relatively easy to obtain an information about the *cis*- or *trans*-configuration of the amide fragments only using two polarized IR-LD spectra. The presented tool posses underlined advantages but the limitations as well. Using the large number of our systematic investigations part of which we are cited here (Kolev et al. 2006a, b, 2007; Kolev 2007; Chou 1984a, 1996; Ivanova 2006; Ivanova and Arnaudov 2006; Ivanova et al. 2006b, c), we could summarize the possibilities and limitations of the tool, for analysis of small biologically active systems in a following way. (1) The determination of the molecular structure by the absolute method of single crystal X-ray diffraction requires the growing of a well ordered crystal. Although in recent decades numbers of the reports of the 3D structures of the peptides has increased, the crystallization of these systems is still a major obstacle to X-ray diffraction work. For these reason the development of the alternative tools for obtaining the structural information in solid state is still attractive for the structural chemistry of peptide systems. The idea for obtaining of structural information (determination of α- and β-helix) by means of linear-polarized IR-spectroscopy of oriented polymers has been illustrated by Frushour et al. 1976; Jasse and Koening 1979; Scheller et al. 1981. However the limitation of this orientation tool is obvious, it cannot be applied to amorphous or polycrystalline peptide samples, i.e., the method is limited for the large number of small peptides, their salts or metal complexes. In the recent years a new orientation method for solids has been developed by Ivanova et al. (2004, 2006a, 2007) Koleva et al. (2008a, b), which allow the investigation of the solids independently of their amorphous or polycrystalline character and of their melting points. It involves a useful combination of the possibilities of linear-polarization IR-spectroscopy and modern quantum chemical approximation methods for prediction of the electronic structures and vibrational

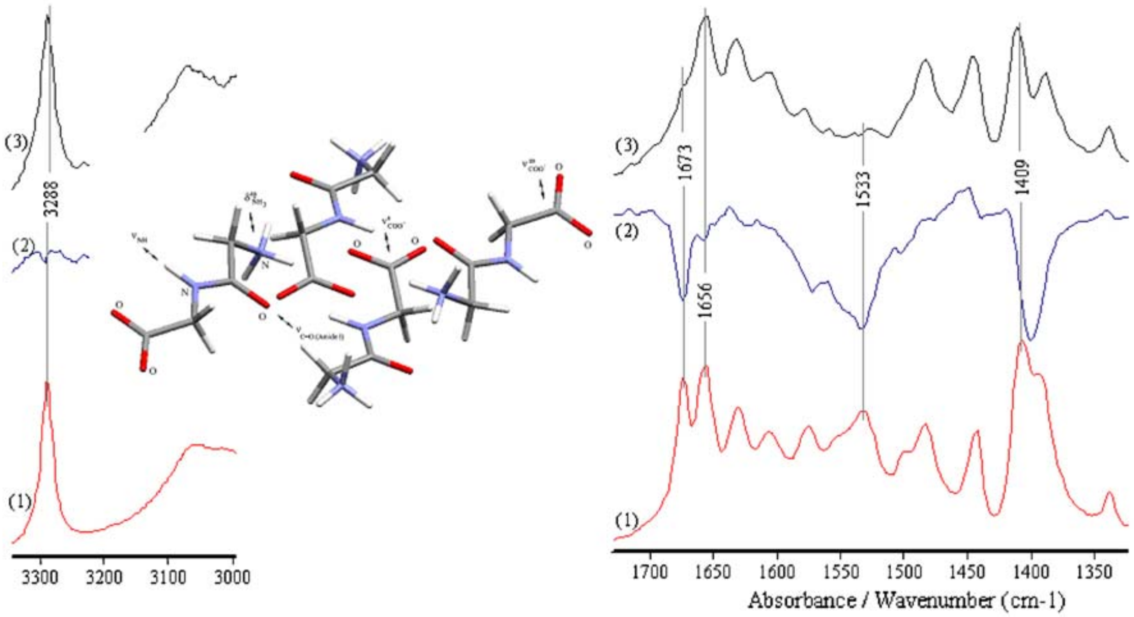

Fig. 2 Non-polarized IR (*1*) and reduced IR-LD spectra of *H–Gly–Gly–OH* after elimination of 3,288 cm^{-1} (*2*) and 1,409 cm^{-1} (*3*) peaks

properties of molecules. Since this "complex" tool is not an absolute method like single crystal X-ray diffractions its possibilities and limitations in investigation of small peptides and their derivatives must be carefully investigated. The large number of studies of the application of the this new approach for experimental spectroscopic and structural elucidation of small peptides independent methods such as Raman spectroscopy, ^{1}H- and ^{13}C-NMR, tandem mass spectrometry and, etc. have been used to investigate its validity and limits. The conclusions about the application and the limits of the method can be divided into two main parts; the advantages and limits of the method, and the types of small peptides that can be successfully investigated. (2) One of the main advantages of this "complex tool" is its ability to provide structural information concerning the suspended chemicals in the solid state independent of their amorphous or polycrystalline character. For the systems where is difficult or impossible to be obtained high quality single crystal for crystallographic study, the method appears to be unique in providing any structural information at all. The possibility defines precisely the configurations of the amide O=C–NH group/s and corresponding mutual disposition of the amide planes in the frame of the peptide molecules is a great advantage of the method. Moreover, the tendency for distortion of the absolute flat-*trans* configuration of the O=C–NH fragments as a result of protonation of the COO– group or coordination processes with metal ions is experimentally proved by single crystal X-ray diffraction on series of glycyl-containing small peptides. Same is true for the mutual co-planarity of the amide fragments. These last systems are used for confirming of the validity of the conclusions obtained by our method, and those obtained by the absolute method of single crystal X-ray diffraction. (3) Another advantage of the method lies in the possibility for of precise and complete elucidation of the vibrational characteristics of the suspended substances and small peptides in particular. Linear polarized IR-(or Raman) spectroscopy is the one and only method for experimental proving and assignment of the bands to corresponding molecular vibrations. By the method it is possible to correlate structure-vibrational characteristics in the solid-state. The orientation method of colloid suspensions in a nematic host possesses the advantage of making this possible in amorphous systems. In such cases the "single molecule approach" is used, insofar as far as the additional effects observed both in IR and Raman spectra, typical for crystalline compounds are absent. When IR-spectroscopic patterns are complex, a useful approach is a preliminary investigation and assignment of the IR-spectroscopic patterns of the smaller fragments of corresponding peptides or simple amino acid residues. In these cases the complete vibrational assignment must be carried out comparing both IR and Raman spectra. For the purpose for obtaining of the structural conclusions. The accuracy of the method derives from the information is obtained by the interpretation of the well defined and relatively intense bands. The method can be applied successfully to different types of peptide systems, especially aromatic small peptides which are characterized by a large number of employed in the IR-analysis. In the case of tryptophan-containing systems the IR-bands of in-plane stretching ν_{NH} and bending out-ofplane modes about 770 cm^{-1} of indole ring can even be used for quantitative determination of the systems. For aliphatic peptides the method can be used successful for determination of *cis*- or/and *trans*-configuration of the amide fragments, due to their separation in the spectrum from the characteristic bands of other structures. (4) The IR-method is of limited value for peptide systems, where the IR-spectroscopic pattern is characterized by an underlying Evans hole effect, such as some small peptide salts and in these cases polarized Raman spectroscopy is an alternative method. One of the best results is obtained when the systems are from di- to tetra-peptides. (5) The possibilities of the method are limited for amorphous or polycrystalline penta- to deca-peptide. A precise analysis can be carried out if, as a result of the types of intra- or inter-molecular interactions in solid-state well defined bands are observed with relatively little overlap. In these systems it is necessary to find independent confirmation of the structural conclusions.

Acknowledgments We would like to express our sincere gratitude to the *Alexander von Humboldt Foundation (Germany)* for their continuous support of our research. We wish to thank for the research fellowships granted, which provided us with the unique opportunity to work with prominent scientists at recognized educational and research institutions such as the *University of Dortmund, Department of Organic and Structural Chemistry* (*Prof. Paul Bleckmann*, fellowship granted to Prof. Ts. Kolev, (1988–1989 and 1991–1992); *Ruhr University Bochum, Department of Analytical Chemistry* (*Prof. William S. Sheldrick*, fellowship granted to Assoc. Prof. B. Koleva, 2003, 2007–2008), respectively. Personally, we greatly appreciate the kind assistance of *Prof. William S. Sheldrick* and the faculty members of the *Department of Analytical Chemistry at Ruhr University Bochum (Germany)* headed by him for our fruitful collaboration, including the valuable discussions, excellent conditions, provided for research and creative atmosphere. We also greatly acknowledge the several research projects, supported by *Bundesministerium für Bildung und Forschung (BMBF, Germany) and Deutscher Akademisher Austauschdienst (DAAD, Germany)* from 2002 to 2008.

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