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Theoretical-computational modelling of infrared spectra in peptides and proteins: a new frontier for combined theoretical-experimental investigations

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The state-of-the-art of theoretical-computational modelling of infrared (IR) spectra in peptides and proteins is able to reproduce the main spectral features involved in the secondary-structure organisation. The results so far collected, clearly show that the complexity of the atomic processes inherent to the IR spectra makes the often used empirical secondary-structure/frequency correlations inaccurate and possibly misleading. The use of extended configurational sampling as provided by, for example, molecular dynamics simulations and of a physically coherent treatment of both the quantum degrees of freedom and their coupling with the semiclassical atomic motions, promises to open the way to interpret and predict IR temperature-dependent and time-dependent spectral signals, in particular for the study of folding/unfolding transitions.

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Introduction

In the last two decades a vigorous impulse has been experienced in the field of biochemistry and molecular biophysics, as following from the use of new advanced spectroscopic techniques such as the time-resolved diffraction, UV–vis and infrared (IR) spectroscopies as well as the bi-dimensional (2D) NMR and IR spectroscopies. These methods are providing an extraordinary amount of new information on biomacromolecules' function, structural transitions and dynamics, opening the way to a deeper understanding of the mechanisms involved in biochemical activity, conformational equilibria and folding/unfolding processes of peptides and proteins. In particular, time-resolved [1] and 2D [2] IR spectroscopy, given its high sensitivity to local structural variations, enabled to characterise ligand migration in proteins [3,4] and folding/unfolding kinetics in peptides [5–11]. However, the complexity of the spectroscopic signal emerging from the structural/conformational fluctuations of the polypeptide and from its interaction with the solvent, makes it difficult to properly interpret the spectra in terms of structural features and transitions of the solvated peptide or protein, that is, the assignment of a specific structure to IR absorption at a given frequency is difficult and possibly misleading. Theoretical-computational methods may provide essential information on the complex absorption–structure relation, shedding light on the IR spectroscopic effects of structural transitions, of the polypeptide sequence and of the solvent interaction. In the last decade several theoretical-computational approaches, typically based on mixed quantum-classical models, have been proposed [12–14,15•,16•,17•,18,19•,20,21•,22•] to reconstruct in detail the IR spectra of solvated peptides and hence to clarify the main atomistic determinants of peptide/protein IR signals.

Modelling vibrational excitations in liquid-state systems

Modelling of complex systems at electronic level has been representing, in the last years, one of the major challenges of theoretical physical chemistry. Beyond the intrinsic, that is, dimensional, difficulties because of the presence of a huge number of quantum and classical degrees of freedom, theoretical characterisation of such systems is further complicated by the not always straightforward comparison with experimental data. As a matter of fact the measurement of an observable for a complex system may sometimes result from the average of a huge number of events taking place within the observation time, for example, overall kinetic rate constants. One of the most immediate observables which could be theoretically modelled in a relatively simple fashion, is the absorption spectrum at the equilibrium conditions (stationary spectrum). In this case, in fact, a significant sampling of the configurational space associated with a coherent description of the spectroscopically interesting subregion of the system, may provide good results directly comparable with experimental data.

Several studies have been concentrated in the reproduction of UV–vis spectra [23–26] of molecules in

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solution and it is nowadays possible to approach the problem using different theoretical-computational strategies which share the primary assumption of predefining a portion of the system to be explicitly treated at electronic level (the quantum centre). Relatively less investigated, in this area, is the modelling of vibrational spectra in condensed phase [27]. For UV and NMR spectroscopic equilibrium signals, in fact, a schematic differentiation between classical (nuclei) and quantum (electrons) degrees of freedom may well work if correctly supported by a good statistics and a proper electronic treatment. On the contrary, IR spectra explicitly deal with the quantum character of the nuclear degrees of freedom and the perspective of the model should inevitably change [28]. Nevertheless, in the last years several strategies have emerged either based on a classical view of the process, that is, using the dipole autocorrelation function as obtained by the classical atomic motions provided by molecular dynamics (MD) trajectories [29–32], possibly achieving an extended sampling of configurational space [33], or based on a fully quantum description of the chromophore at expenses of the classical sampling [34].

Alternative methods [35–37] combining electronic structure/molecular dynamics calculations make use of an empirical relation providing the instantaneous frequency of a solute as obtained by fitting *ab initio* vibrational frequencies of a solute–solvent cluster either to a linear combination of the electrostatic potentials [35] or to the components of the electric fields [36,37] acting on the solute atoms. A recent approach for calculating IR spectra of bi-atomic molecules in condensed phase [38,39] has been proposed on the basis of the Perturbed Matrix Method (PMM) [40,41] whose main aim is to keep the configurational complexity of the system with a proper treatment of the quantum degrees of freedom of the quantum centre. Such a method, extended to treat IR spectra of polyatomic molecules in condensed phase [42], makes use of atomistic MD simulations in explicit solvent providing the instantaneous perturbation to be included into the quantum centre Hamiltonian operator.

These methodologies, although limited to rather small molecules, clearly showed that it is possible to model at atomistic level the vibrational behaviour in liquid state with reasonable quantitative accuracy. Moreover, evidence was provided for IR bands of liquid-state systems being often well defined by the solute vibrational modes, with no significant variation with respect to the corresponding solute gas-phase modes, that is, the isolated solute Hessian eigenvectors. Examples are the bending mode in liquid water [42,43], the stretching mode in solvated carbon monoxide [33,39] and the amide I mode in aqueous *trans-N*-methylacetamide (*trans*-NMA) [35,36].

Modelling the amide infrared bands in peptides and proteins

The understanding of protein-mediated processes at the atomic level requires the use of techniques monitoring protein structural changes. IR absorption spectra of amide modes have long provided a tool for determining the secondary structure of peptides and proteins due to the high sensitivity of amide vibrational frequencies and intensities (particularly for the amide I mode, mostly corresponding to the C=O stretching) on local atomic organisation (e.g. hydrogen bonds, solvation effects, and hydrophobic interactions) [44–46]. However, the complexity of IR signals of solvated peptides and proteins does not allow a detailed frequency-structure assignment to be determined experimentally.

In the last years many different theoretical-computational methods have been proposed to model protein and peptide IR spectroscopic behaviours, the development and parameterisation of which is at present an active area of research. Fully *ab initio* methods for the determination of the vibrational frequencies do not allow to scale up to biologically relevant biomolecules and to properly include the complexity of the solute–solvent interplay, which would require the construction and diagonalisation of the solute–solvent Hessian matrix of the quantum vibrational degrees of freedom at each representative liquid-state configuration. Therefore, hybrid approaches are commonly used to reproduce the band positions and line shapes of structurally well-defined molecules [12–14,15•,16•,17•,18,19•,20,21•,22•].

Many of these [12–14,15•,16•,17•,18,19•] employ quantum mechanical (QM) calculations to determine the vibrational frequencies and eigenstates for single amides which are, then, transferred to the full peptide and/or protein and coupled by dipole-dipole interactions and empirical terms (see below). An alternative approach [20,21•,22•] makes use of Hessian calculations on the whole isolated peptide/protein in a given configuration which are, then, used to reconstruct the local, single-residue, vibrational frequencies via the Hessian matrix reconstruction method [20]. In these approaches coupling effects are included by adding in the Hamiltonian a simplified electrostatic term typically based on dipole-dipole interaction, possibly providing excitonic coupling, and commonly termed transition dipole coupling — TDC (coupling through space) and an empirical term providing the frequency variations due to first-neighbours relative rotations (coupling through chemical bonds). In addition, the solvatochromic and residue-residue interaction effects, beyond the previously mentioned coupling terms, are empirically modelled via relating the single-residue frequency to the perturbing electric potential exerted by its environment, as obtained by calculations on solute–solvent clusters and MD simulation. Diagonalisation of the resulting effective Hamiltonian matrix

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(often defined as local amide Hamiltonian — LAH) provides the vibrational eigenstates and energy of the whole peptide, for each considered structure.

The application of such kind of approaches to different peptides/proteins including β-hairpin peptides [17•,19•], ubiquitin [47•] and globular proteins [3,16•] provided the characterisation of IR spectral features of individual secondary-structure elements, allowing the computational spectrum decomposition into secondary-structure contributions. One of the most striking results emerging from these studies is that the often used empirical secondary-structure/frequency correlations are at best approximated and at worst misleading (for example Ref. [16•]). The subbands from helices, sheets, turns, and loops are much broader and more overlapped than is commonly assumed. In fact, the amide IR bands correspond essentially to the combination of the excitations of localised modes, that is vibrational modes defined in a single peptide group. Therefore, the actual signal as arising from the combined excitation of all the modes is dramatically affected by the local perturbing field acting on each residue. In particular, the over-position of peptide and solvent perturbation effects may cause that different peptide structural features be associated with similar IR signals, not easily distinguishable.

The models briefly outlined above are based on the explicit treatment of the amide modes coupling (i.e. excitonic coupling), providing detailed information on the coupling effects (i.e. vibrational delocalisation) due to the peptide structural organisation, although the role and relevance of excitonic coupling involved in the amide I band is still not fully clear, hence leading to possible debates [15•,21•,19•]. In such models, however, the effects due to the perturbation field acting on each localised vibrational mode are included by a simplified description, typically involving empirical terms and/or adjustable parameters. The role of the fluctuating perturbation due to the atomic-molecular environment of each residue on the main IR spectral features, is much less investigated and hence the use of a physically coherent approach based on explicitly modelling, at atomistic level, such perturbation effects might provide, beyond the known excitonic coupling, important information to further understand the complex IR signal [17•,22•].

In such a context, in our group, the PMM/MD based procedure previously utilised for modelling simple solute IR spectra [38,39,42], was applied to describe in detail the IR amide I bands of peptides in aqueous solution. Such a procedure proved to be not only rather accurate in reproducing the main quantitative features of the experimental spectra, see Figure 1 (Daidone et al., unpublished data), but also very promising to describe the conformation-absorption relation essential to interpret the IR spectrum variations due to the folding/unfolding process (see last section).

Modelling 2D infrared spectra

Two-dimensional IR spectroscopy [2] has become an important tool to characterise peptides and proteins, allowing to pinpoint the coupling and correlation of vibrational modes. Therefore, 2D IR spectroscopies may in principle collect detailed information on the spatial relative organisation of the modes which in turn might provide a detailed description of the peptide/protein structure. This advanced experimental method, taking advantage of using two subsequent photon pulses allowing (via the second pulse) the IR characterisation of the molecular subpopulations selected by the excitation due to the first pulse, promises to provide data on solvated biomacromolecules not achievable by other techniques, especially when time-dependent or temperature-dependent spectra are concerned. However, the signal arising from the molecular response to the combined pulses involves several complex phenomena including frequency correlation, modes (excitonic) coupling, and anharmonicity of localised modes, making very difficult to interpret such spectra. In the last decade a limited number of theoretical-computational attempts [10,46,47•,48–51] have been presented, utilising models based on the excitonic coupling of amide modes, along the lines of the methods described in the previous section (i.e. using the LAH matrix approach).

Such methods have identified specific 2D IR spectral features, arising from the amide modes coupling, which may be considered as signatures of specific secondary-structure elements [10,47•,49–51], thus possibly allowing experimental predictions and frequency region assignment as it is well illustrated in a recent paper [10] for a set of β-hairpin peptides, including Trpzip *2* (see Figure 2). However, the complexity of the 2D signal may require not only a detailed and unbiased treatment of the mode–environment interaction, but also an extended configurational sampling of the peptide–solvent system which is typically not achieved by the methods presented in literature. Such possible limitations are of particular relevance when the modelling of IR spectra variations due to the folding/unfolding transition is concerned.

Toward a theoretical-computational description of IR spectra variations due to the folding/unfolding transition

A rather recent challenge that goes beyond the application of the IR spectroscopy to structurally well-defined polypeptides, is its use to follow protein folding/unfolding kinetics and thermodynamics. Time-resolved and temperature-dependent IR spectroscopies have been applied to a number of α-helical [5–7] and β-hairpin peptides [8–10], the basic secondary-structural elements of proteins. However, given the lack of a simple and clear frequency assignment to different structures and the complexity of the conformational transitions involved in folding/unfolding processes, a general interpretation

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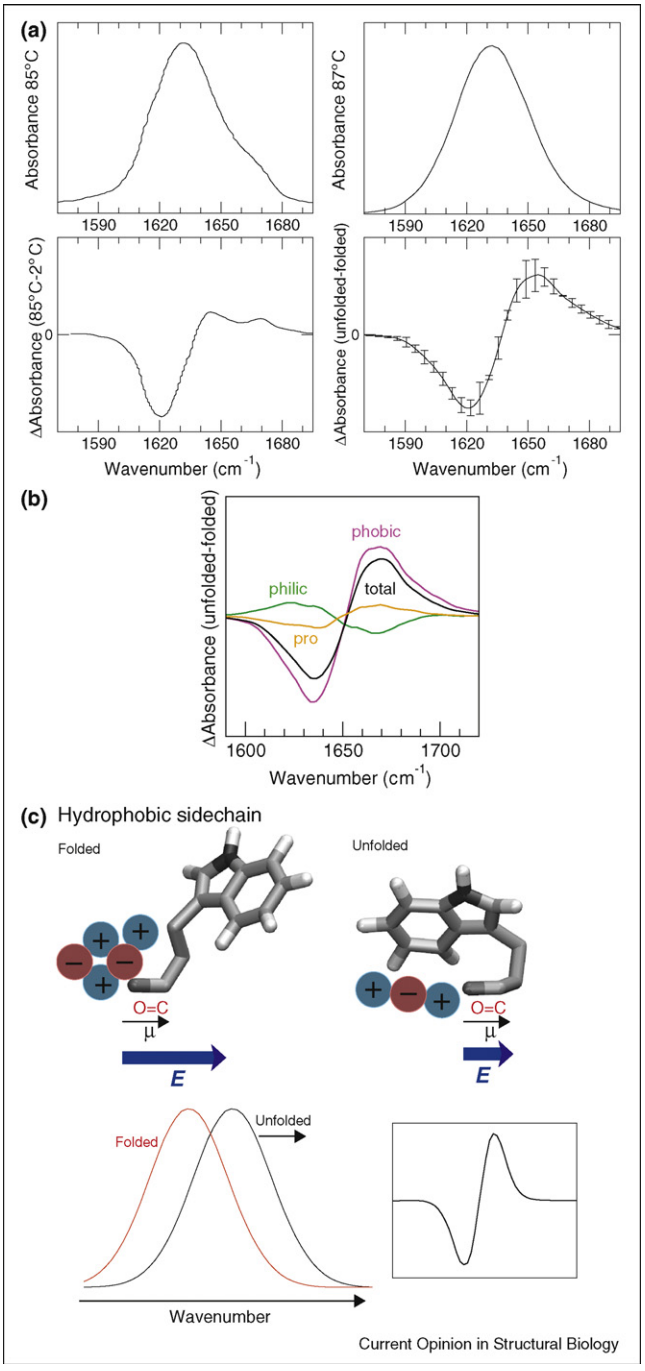
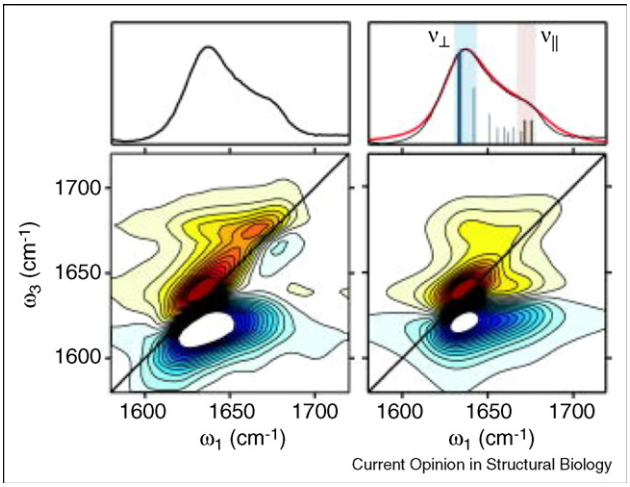
Figure 1



(a) Experimental [9] (left) and computed via PMM/MD (right) infrared spectra in the amide I region of a 10-mer cyclic analogue of Gramicidin S, GS10, in D_2O solution. The experimental difference spectrum was generated by subtracting the spectrum collected at 2.0°C from the one collected at 85.0°C. The computed difference spectrum was generated by subtracting the spectrum of the folded state from the spectrum of the unfolded state. For the sake of comparison, the computed frequencies (right panels) have been uniformly shifted to lower frequencies by 57 cm^{-1} in order to align the computed amide I peak to the experimental maximum at 1632 cm^{-1}. **(b)** Contribution of the single peptide groups to the computed unfolded – folded amide I difference spectrum. The signals from hydrophobic, hydrophilic and amino acids not included into any category (prolines) are grouped into three separated groups. **(c)** Scheme summarising the effect of the hydrophobic sidechain on the amide I mode vibrational frequency of the peptide group, to which the sidechain is attached, in the folded and unfolded states.

Figure 2



Experimental amide I spectra of Trpzip 2 (left). Simulated amide I spectra (right). Antiparallel β-sheets are predicted to have two dominant IR delocalised modes, $\mu_\perp$ and $\mu_\parallel$. Reprinted with permission from Smith and Tokmakoff [19]. Copyright 2007, American Institute of Physics.

of such spectra in terms of local structural variations and peptide–solvent interaction is still missing. Even a clear assignment of spectral features to the folded and unfolded state conformations may be sometimes doubtful as it is typically based on assuming a completely folded or unfolded peptide population at the lowest and highest temperature, respectively, of the temperature range considered. The use of a reliable theoretical-computational model would then be essential to improve our understanding of the IR signal variations occurring upon folding/unfolding transitions, hence providing a proper framework to evaluate folding/unfolding thermodynamics and kinetics as well as to interpret the time-dependent IR signal in terms of structural rearrangements. In recent papers [50,51] an attempt to model 2D unfolded – folded difference spectra of small proteins has been presented, providing evidences that state-of-the-art calculations may reproduce some spectral features, characteristic of the unfolding process, experimentally observed in 2D IR spectra. However, the limitations of the standard methods employed discussed briefly in the previous section, in particular the poor sampling used, cannot reproduce accurately the spectral line shapes [47•].

Very recently in our group it has been shown that a theoretical-computational model reconstructing the IR signal of solvated peptides from the atomic interactions,

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may be used to quantitatively characterise the IR spectral changes induced by the folding/unfolding transition. The PMM/MD procedure employed, provided a good reproduction of the unfolded − folded IR amide I band difference spectra as shown, for example, in Figure 1 (unpublished data) for the 10-mer cyclic analogue of Gramicidin S (GS10) peptide. From the figure, the typical negative–positive trend of the difference spectrum is evident, which is a common feature of β-hairpin peptides and observed also for α-helices, that is, the amide I band typically shifts to lower frequency in the folded state with respect to the unfolded state with a negative signal at $\approx 1620-1630\,cm^{-1}$ and a positive signal at $\approx 1660-1670\,cm^{-1}$. Dissection of the amide I bands into the individual components arising from the different amino acids shows that the main determinant of the shift of the unfolded state amide I peak toward higher frequencies arises from the hydrophobic sidechains (see Figure 1, panel b). In fact, for the hydrophobic residues the perturbing electric field is found to be lower in the unfolded state than in the folded state, giving rise to the observed shift to higher frequencies of the amide I band with respect to the folded state (negative–positive signal in the unfolded − folded difference spectrum) as shown in the scheme of Figure 1, panel c.

It is worth to note that in the PMM/MD procedure used in our calculations we did not include any excitonic modes coupling effect, although it can be treated within the PMM framework [41], and hence all the perturbation effects were provided by the ground state perturbing field due to the atomic–molecular environment of each localised vibrational mode. Our data, well reproducing the spectral changes induced by the folding/unfolding transition, suggest that excitonic coupling (i.e. vibrational delocalisation) may be less relevant than it has been proposed [47•,51], pointing out the essential role of an extended configurational sampling and a proper atomistic modelling of the interaction between the (localised) vibrational mode and its complex, fluctuating environment, often poorly addressed.

Conclusions and perspectives

Theoretical-computational methods modelling IR spectra in peptides and proteins have recently reached sufficient accuracy to reproduce the spectral features of conventional and 2D IR spectra, allowing a more efficient interplay between experiment and theory. However, the complexity of the atomistic processes contributing to the IR signal makes it still rather difficult to interpret IR absorption patterns in terms of local structural organisation and atomic motions. The results collected so far clearly indicate the essential role of a proper treatment of the interaction effects on quantum vibrational states, including both the perturbation of the atomic environment on the localised modes and their excitonic coupling. The use of models based on extended configurational sampling as provided by, for example, MD simulations and utilising a physically coherent treatment of both the quantum states and their coupling with the semiclassical atomistic motions, promises to furnish a powerful tool to interpret and predict IR temperature-dependent and time-dependent spectral signals, in particular for the study of folding/unfolding transitions.

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