J. S. Redinha
J. da Providência
A. J. C. Varandas
Editors

Quantal Aspects in Chemistry and Physics

A tribute to the memory of Professor Couceiro da Costa

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7. The Quantum Aspects of Proteins and Their Biological Function

H. G. Bohr*

Quantum Protein (QuP) Center, Technical University of Denmark (DTU),
Department of Physics, DK-2800 Kgs. Lyngby, Denmark

Peptides, proteins, and especially enzymes, are studied with respect to their quantum behavior which includes electronic states, vibronic states involving the coupling of nuclear and electron motions, excited electronic state dynamics, electron and nuclear tunneling phenomena, bio-Auger processes, charge-density fluctuations and general charge transfer. All these issues are elucidated by quantum electronic calculation of vibrational spectra for small peptides in water solutions, for nucleic acids and finally for protein illustrated by the particular cases of the gene repair processes involving the peptides and then the proteins: Photolyase and Peridinin/ chlorophyll which, respectively, repair UV-radiation damages on genes and harvest light. In the latter two cases the quantum phenomena, such as bio-Auger, are playing a big role.

7.1 Introduction

Vibrational spectroscopies, *e.g.*, vibrational absorption (VA), vibrational circular dichroism (VCD), Raman scattering, and Raman optical activity (ROA), have many virtues, including many of the following: being easily accessible (FT IR/VA and FT Raman instruments are now common in most biospectroscopy laboratories, along with the chiral analogues FT VCD and FT ROA), being non-invasive techniques, being able to be measured on a solution and hence one is able to treat solvent effects and observe the biomolecules in their native or near-native environment, and finally with the addition of colloidal particles, as in SERS, it can detect nano-molar quantities which virtually are single molecules or singular

*Email address: hgbohr@gmail.com

molecular complexes or singular molecular machines in dilute solutions [1–3].

However, the difficulty has been to derive theoretical vibrational spectra from quantum electronic calculations in the case of large molecules with more than 10 atoms in their native or near-native environments. This is due to all the couplings between the involved bonds between the atoms. The vibrations basically all couple to each other and this creates a complex picture of superposition of vibrational modes that are hard to interpret and especially if one has to take into account the harmonic and anharmonic couplings with the solvent.

Another problem is that of the large number of conformational states or conformers (as one calls the stable conformations) which appear during the molecular dynamics simulations of peptides (the time scale during with the experiments are being made). These problems, however, open great opportunities in time-resolved spectroscopy since conformational changes can be monitored in time-resolved fluorescence and VA spectroscopy down to the time-scale of nano seconds.

7.2 Quantum analysis of small peptides

We shall firstly present how to use the quantum mechanical calculations of the electronic structures and properties of biomolecules and biomolecular complexes, especially peptides in their native environments, to interpret and understand vibrational spectra and changes in the vibrational spectra either as a reaction proceeds, or in response to a perturbation. From calculated structures and selected molecular properties, the vibrational absorption (VA) and vibrational circular dichroism (VCD) can be simulated from *first principles* within the mechanical harmonic approximation for the vibrational frequencies and normal modes, the electronic harmonic approximation for the electric dipole moments and their derivatives with respect to the nuclear displacements (the atomic polar tensors, APT), and beyond the Born-Oppenheimer approximation for the magnetic dipole transition moments and their derivatives with respect to the nuclear velocities (the atomic axial tensors, AAT). For amino acids, peptides and polypeptides solvent and environmental effects have been shown to affect even

the stability of the conformational states and species present. In addition, the changes which occur as one perturbs a system can be monitored and followed in time with time resolved vibrational spectroscopy. But to do so requires one to be able to reliably take into account the effects of the aqueous environment. These effects have been shown to stabilize both species (the zwitterionic form of amino acids) and conformers, the P_{II} conformational state of the L-alanine dipeptide (N-acetyl L-alanine N'-methylamide, NALANMA), which are not stable in the isolated state (as single molecular species) in the gas phase or in non-polar solvents. Hence it is fundamental to include explicit water molecules and any other species which are in the first solvation shell (hydration) layer and are responsible for stabilizing the biomolecular complex, the species of interest, and not the so-called isolated biomolecule. Hence not single molecule, but biomolecular complex, or better biomolecular machine or catalyst. Next we present two illustrative cases of our methodology applied to large biomolecules.

The 3 molecules we chose in which to to illustrate the types of problems that can arise and how one can overcome/solve there problems are 1. L-alanine (LA); 2. the di-peptide, L-alanyl L-alanine (LALA); and 3. the L-alanine dipeptide, N-acetyl L-alanine N'-methylamide (NALANMA).

In the following sections we present a brief discussion of each molecule and why it is important. This is followed by the most commonly used methodology for simulating vibrational spectra using density functional theory (DFT). The methodology of how one actually can simulate the VA and VCD spectra is presented, followed by a summary of our work which documents and shows the usefulness of our methodology to solve real life structural and functional problems in molecular biophysics and molecular biology.

7.2.1 L-alanine

L-alanine (LA) is the simplest chiral amino acid with the methyl group replacing one of the two achiral hydrogens in glycine. All other amino acids are more complicated. The chiral nature of 19 of the 20 naturally occurring amino acids gives the preference for right handed α helices over the left hand variant

in peptides and proteins. In addition, the preference of the so-called C_7^{eq} conformer over the so-called C_7^{ax} conformer for small peptides is due to the bulky C_β group of the 19 chiral amino acids. Here we focus initially on the various possible species of the L-alanine in aqueous solution, its native environment, at neutral pH. In the isolated single molecular state in either the gas phase or in non-polar solvents like carbon tetrachloride or carbon disulfide, the species of L-alanine present is the non-ionic neutral species, $NH_2 - CH(CH_3) - COOH$, while in aqueous solution the species present is the ionic neutral species, the so-called zwitterionic species, $NH_3^+ - CH(CH_3) - COO^-$. We and others have shown that to correctly simulate and interpret the VA, VCD, Raman and ROA spectra of the zwitterionic form of LA in aqueous solution, one must include explicit water molecules [4–9]. Hence the molecule or molecular complex of interest is not the individual single molecule, but the hydrated zwitterionic species. Which and how many of the water molecules are not only important, but an integral part of the species of interest is the more relevant question.

7.2.2 L-alanyl L-alanine

On peptide formation, two amino acids interact chemically to form a peptide bond. The species present in aqueous solution at neutral pH is again the ionic neutral zwitterionic species, and not the nonionic species present as a isolated single molecule either in the gas phase or in nonpolar solvents. Here, once again, the species of interest is stabilized by the presence of a finite number of strongly interacting water molecules of the aqueous environment. The isolated single molecular state in either the gas phase or in non polar solvents is the non-ionic neutral species, $NH_2 - CH(CH_3) - CO - NH - CH(CH_3) - COOH$.

To simulate the aqueous environment, we initially added a small number of explicit water molecules to stabile the zwitterionic species of the L-alanyl L-alanine (LALAZ) [4], but subsequently used classical molecular dynamics simulations of LALAZ in a box of water molecules to determine the number and positions of the water molecules in the so-called first solvation shell of water molecule encapsulating and stabilizing the LALAZ. We initially kept only those