Raman technique and Density Functional Theory the "R" & "D" in Research and Development of antibiotics

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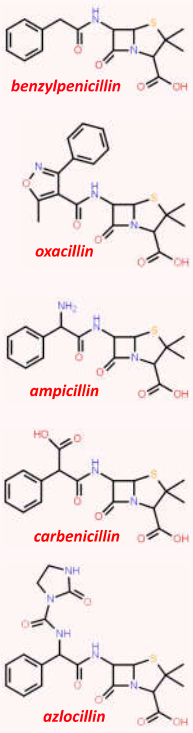
INTRODUCTION

Antibiotics are still a hot topic for research mainly because most of them tend to be bacterial resistant after a period of intensive use. Development of new and more effective antibiotics is requested increasingly more often. Raman spectroscopy is a powerful molecular investigation tool, which provides valuable information regarding geometrical and electronic structure of such molecules to design new drugs.

Even though each molecule has a unique finger-print like raman spectrum, reliable assignments are very challenging, particularly for medium and large-size molecules with a common component of their molecular structure (in the case of penicillins, a penam core, represented by a 6-aminopenicillonic acid (6-APA)). Subtle features, due to the various R side-chains attached to the sixth position of the penam core, require sophisticated theoretical methodologies and considerable computational resources (CPU time and memory).

When it comes to vibrational spectroscopy, harmonic frequency calculations performed with Density Functional Theory (DFT) and coupled with suitable scaling factors yield to results having a good agreement with experimental frequencies. On the other hand, anharmonic calculations employing second order vibrational theory provide very good results, with high accuracy and no need of using scaling factors but on the behalf of high computational costs.



OBJECTIVES

Frequency calculations using DFT were performed in order to obtain theoretical Raman spectra and the corresponding normal modes. By comparing experimental Raman and SERS spectra of the same compound (paying attention to in/decrease of peaks' intensity or shifts) and assigning the normal modes, the position of each molecule relative to the Ag surface is to be revealed.

EXPERIMENTAL AND COMPUTATIONAL DETAILS

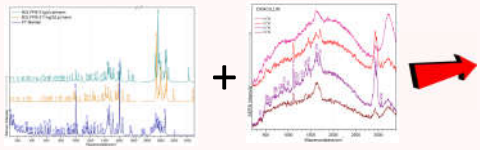
FT-Raman spectra were registered using a Raman Bruker FRA 106/S accessory attached to a FT-IR Equinox 55 spectrometer (Bruker Optik GmbH, Ettlingen, Germany). The Ge detector used is cooled with liquid nitrogen. Laser's wavelenght used is 1064nm, having a power of 250mW.

Raman in aqueous phase and SERS spectra were registered using a compact, dispersive Delta NU Advantage 532 Raman spectrometer, with a 532 nm exitation laser line, and a resolution of 8 cm^{-1}. The final spectrum is the result of 5 accumulations of 60 seconds each.

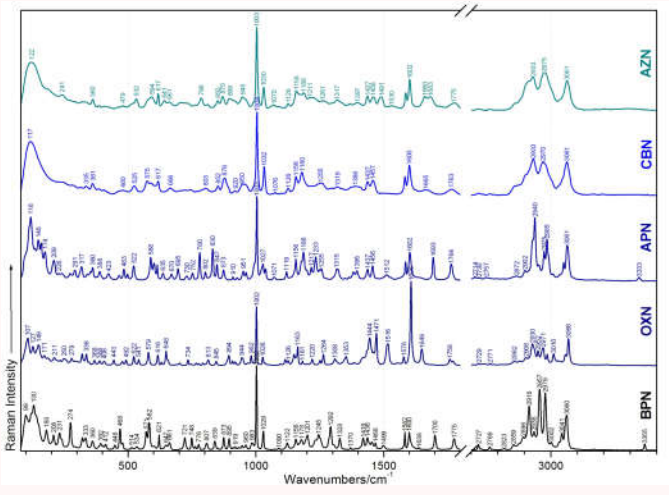
Silver colloid was obtained following Leopold's recipe[1]. Aqueous solutions of each antibiotics were further diluted directly in Ag colloid. 20µl 1M of Na Cl was added to final solutions for SERS.

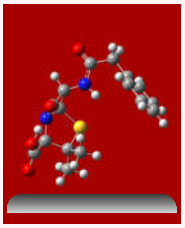
DFT computations were performed using Gaussian software package. B3LYP global hybrid exchange-correlation desity functional combined with 6-311+g(d,p) (harmonic) and 6-31g(d) (anharmonic) basis sets were used as level of theory on monomers of benzylpenicillin (BPN), oxacillin (OXN), ampicillin (APN), carbenicillin (CBN) and azlocillin (AZN). Full optimizations of the geometries were first performed, with very tight convergence and nosymm criteria. All calculations were performed in gas phase. Harmonic frequencies were scaled by 0.967.

[1]N. Leopold and B. Lendl, *J. Phys Chem B*, **2003**, *107* (24), 5723-5727

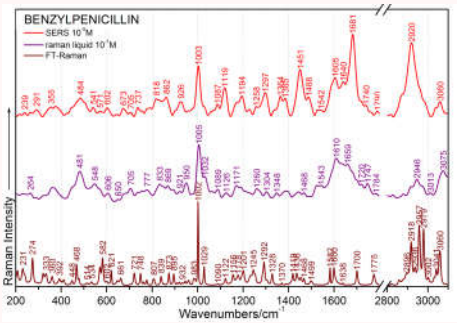


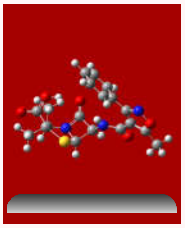
FT-Raman spectra of different penicillins



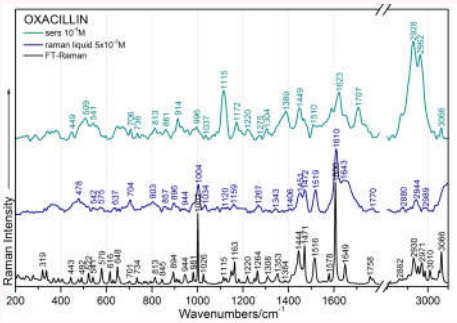


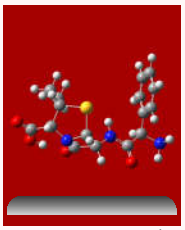
BPN orientation on Ag surface



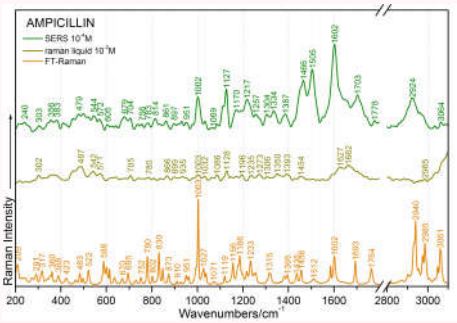


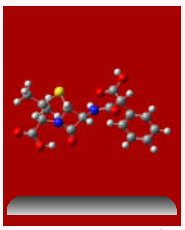
OXN orientation on Ag surface



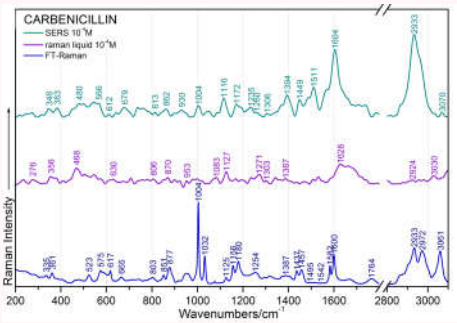


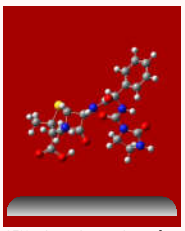
APN orientation on Ag surface



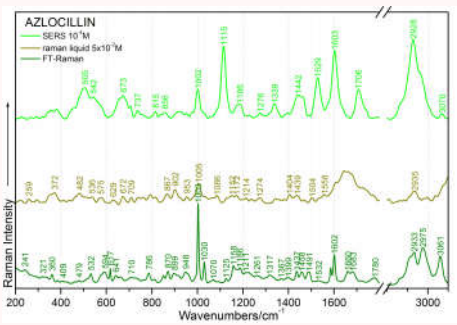


CBN orientation on Ag surface





AZN orientation on Ag surface



ACKNOWLEDGEMENTS

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