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Experimental and computational Raman spectroscopies applied to 2-methoxy-2-methylpropylisonitrile (MIBI) ligand of the ^{99m}Tc-sestamibi radiopharmaceutical

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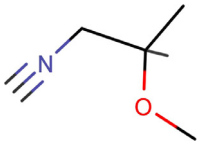
ABSTRACT

Hexakis (2-methoxy-2-methylpropylisonitrile (MIBI)) Technetium (^{99m}Tc) (^{99m}Tc-sestamibi) is a radiolabeled drug used for myocardial, breast and parathyroid imaging. Although commonly used in nuclear medicine clinical practice, data about the exact geometric and electronic structure of the MIBI ligand is missing in the literature.

In this study we present a joint experimental Raman and computational DFT study of the MIBI ligand. The conformational landscape analysis of the compound is followed by a careful vibrational study based on Raman spectroscopy, assisted by DFT calculations performed within both, harmonic and anharmonic approximations, at B3LYP/6-311+G(d,p) level of theory.

It is shown that the contributions from the most stable conformers of the molecule, weighted by their Boltzmann populations, have to be considered for explaining the subtle features of the experimental Raman spectrum. Moreover, for the molecule investigated here, the harmonic and anharmonic approximations have their own particular advantages and shortcomings.

The excellent agreement between the experimental and theoretical spectra allowed for a detailed and reliable description of the vibrational properties of the investigated molecule.



Scheme 1. Molecular structure of MIBI

1. Introduction

The 2-methoxy-2-methylpropylisonitrile (MIBI) compound (Scheme 1), is a molecule mainly used in nuclear medicine, particularly in the radiolabeled compound ^{99m}Tc hexakis MIBI (^{99m}Tc-sestamibi), a lipophilic cation [1], consisting of a ^{99m}Tc core bound to six MIBI ligands. This radiopharmaceutical is commonly used for myocardial perfusion imaging, breast cancer imaging and parathyroid adenoma identification [2]. Beside the well-established uses in clinical practice, ^{99m}Tc-sestamibi has been shown to be a substrate for the P-Glycoprotein transmembrane pump, which plays a critical role in multi-drug resistant tumors [3–6].

In spite of its extensive use in nuclear medicine, information related to the molecular and electronic structure of the MIBI ligand is missing. Quantum chemical calculations as well as Raman spectroscopy were proven to be very useful for structural characterization of biomedical compounds. Previous studies have shown that accurate description of the tridimensional structure of such compounds is crucial [7–10]. Furthermore, the analysis of the conformational space of a drug or radiopharmaceuticals' ligand is essential not only for an exact description of its spectroscopic properties but also for better understanding the uptake mechanism of the investigated compound [11–13].

Thus, the aim of this work was to characterize the conformational landscape of MIBI and the structure of its possible conformers, based on Density Functional Theory (DFT) calculations. Moreover, spectral characteristics of the compound might be useful for

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