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Review article

Lanthanide and transition metal complexes of bioactive coumarins: Molecular modeling and spectroscopic studies

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ABSTRACT

The present paper summarizes theoretical and spectroscopic investigations on a series of active coumarins and their lanthanide and transition metal complexes with application in medicine and pharmacy. Molecular modeling as well as IR, Raman, NMR and electronic spectral simulations at different levels of theory were performed to obtain important molecular descriptors: total energy, formation energy, binding energy, stability, conformations, structural parameters, electron density distribution, molecular electrostatic potential, Fukui functions, atomic charges, and reactive indexes. The computations are performed both in gas phase and in solution with consideration of the solvent effect on the molecular structural and energetic parameters. The investigations have shown that the advanced computational methods are reliable for prediction of the metal–coumarin binding mode, electron density distribution, thermodynamic properties as well as the strength and nature of the metal–coumarin interaction (not experimentally accessible) and correctly interpret the experimental spectroscopic data. Known results from biological tests for cytotoxic, antimicrobial, anti-fungal, spasmolytic and anti-HIV activities on the studied metal complexes are reported and discussed.

1. Introduction

Natural [1] and synthetic coumarins (known as 2H-chromen-2-one (IUPAC), 1,2-benzopyrone et al.) and their derivatives possess great therapeutic potential and pharmacological activities [2] as antibacterial [3], anti-oxidant [4] anti-coagulant [5–7], anti-mutagenic [8], antibiotic [9], anti-cancer [10–15], antimicrobial [16], anti-inflammatory [17,18], anti-HIV [19,20] and anti-leukemic [21] agents. Additionally, coumarins have been used as chromophores of fluorescent ion indicators in biological systems [22], additives to food and cosmetics [23], optical brightening agents [24], dyes for lasers and dye-sensitized solar cell [25].

The functionalized coumarin derivatives possess more than one reactive group (OH, COOH, NO_2) and act as monodentate, bidentate chelate, mono- and bidentate bridging ligands toward lanthanide and transition metal ions. Depending on the metal ion and on the reaction conditions various metal–ligand binding modes are realized in mono-, dinuclear or polymeric structures. This ability has reached an increasing interest since the therapeutic efficacy, the specific biological activity and pharmacological properties (high selectivity and less consequent toxic side effects) of the coumarin compounds were found to be improved upon complexation with metal ions [26–32]. The lanthanide complexes of coumarins have attracted additional attention because of their potential applications as luminescent materials in the new technologies as fluoroimmunoassays and as antennas in photosensitive bioorganic compounds [33–35]. For these compounds, it is important to clarify the effects of the metal type and its oxidation state as well as of the metal–coumarin binding mode on the therapeutic or thermodynamic properties of coumarins. Very few studies on coumarin–metal complexes reported data about their molecular structure and the metal–ligand binding mode [36]. The crystal and molecular structures of the coumarin–metal complexes are not easily experimentally accessible due to their bad solubility and difficult monocrystal growths and hence X-ray diffraction analysis data are unfortunately scarce. The structure of many coumarins and their metal complexes was discussed on the basis of experimental spectroscopic studies (IR, Raman, ^1H, ^{13}C NMR and UV–visible (UV–vis) measurements). Although helpful, the spectroscopic data alone are not sufficient to riddle the structure and thus they have to be used carefully for prediction of the metal–ligand binding modes and molecular geometries [37–42]. For example, in the case of coumarin-3-carboxylic acid, (i) the Δ criterion ($\Delta = \nu_{as}(COO) - \nu_s(COO)$) is quite uncertain to suggest the metal–ligand binding mode and (ii) the downshifts of the carbonylic and carboxylic C=O stretching frequencies observed (ongoing from the ligand IR spectrum to the metal complex spectrum) are not a direct indication of a metal coordination to the corresponding groups [40,42]. Moreover, the vibrational spectra of the neutral forms of the hydroxylic and carboxylic coumarin derivatives are not a good basis for comparison with the spectra of their metal complexes when (i) the ligand is affected by intra- and/or intermolecular hydrogen bonding including the carboxylic and hydroxylic groups and (ii) the deprotonated ligand exists in solution and it interacts with the metal ion in a complex. Thus,

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a simple comparison could lead to a wrong interpretation of the metal–ligand binding situation as it was described in Ref. [40].

The investigations on the molecular structures and properties of the lanthanide and transition metal complexes of coumarins as well as on their biological activities are in an early stage and therefore, a basic concept for development of new bioactive metal complexes of coumarins is still missing and the structure–property relationship is not yet clearly understood. The design of potent bioactive metal–coumarin complexes requires firstly detailed knowledge about their geometrical and electronic structure and properties, from one side and about their biological activity and mechanism of action, from the other. To gain deeper insight into the factors controlling the biological activity of the metal complexes, it is necessary to obtain data about their metal–coumarin binding mode, molecular structure and properties. The determination of the binding mode on the basis of physicochemical and spectroscopic methods, when crystal and molecular structure data are not available, is not a trivial task. Molecular modeling including theoretical simulations of the vibrational, electronic and NMR spectra is a powerful tool used to extract reliable structural and electron density information from first principles. These data obtained complement the database for molecular structures and their properties, necessary to draw structure–activity relationship (applying further appropriate quantitative structure–activity relationship (QSAR) method). Descriptors of the molecular properties obtained from quantum chemical computations are metal–coumarin binding type and strength, geometrical parameters (M–coumarin bond length), atomic charges, bond orders, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO) energies, reactivity indices, total energy, ionization potential, electron affinity, energy of protonation, orbital populations, orbital energies, hardness, vibrational, total enthalpy and entropy etc. In the last decade a great number of studies making use of modern quantum chemical methods (ab initio and density functional theory (DFT)) have shown that the computational methods could successfully be applied i) for prediction of reliable molecular structures of 3d, 4d and 4f metal complexes, various molecular properties and thermodynamic stabilities; (ii) as a supporting tool for a reliable assignment and interpretation of the experimental IR, Raman, NMR and UV–vis spectra; and (iii) for better assessment of inter- and intramolecular hydrogen bonds and metal–ligand interactions [39,40,42,43]. To our best knowledge no specific survey was performed in the literature on molecular modeling and spectral simulation of bioactive metal complexes of coumarin derivatives applying modern quantum chemical methods, especially DFT.

The present work summarizes our theoretical and spectroscopic investigations on bioactive coumarins and their lanthanide and transition metal complexes. Our purpose is to demonstrate the potential and the valuable role of the computational methods for accurate prediction of the metal–ligand binding mode, molecular structures in gas phase and solution, stabilities, nature and strength of the metal–coumarin bonding in the ground electronic state and molecular spectroscopic properties of the metal complexes of coumarins. The calculated values can be used as appropriate molecular descriptors related to the specific biological activities of the metal–coumarin complexes. Preliminary results established from biological tests of the studied metal complexes are also reported and discussed.

2. Results and discussion

2.1. Metal complexes of coumarin-3-carboxylic acid

2.1.1. Molecular structure of coumarin-3-carboxylic acid, intramolecular hydrogen bonds

Coumarin-3-carboxylic acid (HCCA) (Fig. 1(a)) and its derivatives possess various medicinal and fluorescence applications [44]. They are proved to be selective inhibitors of monoamine oxidase [44] and exhibit antibacterial [45] and strong anti-fungal activities [46]. HCCA has been reported as a detector of hydroxyl radical generated chemically or by gamma radiation [47]. The HCCA has been used as a ligand in complexation reactions with transition metal cations — Cu(II) [48], Sn [49,50], Rh(III), Ru(IV), Pt(II), Pd(II), Fe(III), Ni(II) [45,51–53], Ag(I) [26], Ni(II), Co(II), Zn(II), and Mn(II) [54] and lanthanide cations (Dy(III), Eu(III), Gd(III), Tb(III) and Sm(III)) [34,55], Er(III) [36], La(III) [39], Pr(III) [56], Ce(III), and Nd(III) [42]. The metal complexes have shown promising biological activities (in some cases even higher than that of the coumarin ligands) and valuable luminescent properties. The structures of very few metal complexes of HCCA have been obtained using X-ray diffraction measurements [36,49,50]. In many other cases it was predicted on the basis of various comparative spectroscopic studies. The conjugated coumarin structures however, reveal complicated vibrational behavior and electron density distribution upon metal complexation and therefore the interpretation of spectroscopic data only from empirical point of view is uncertain to suggest the metal–ligand binding mode. Using appropriate theoretical methods and approaches the molecular and electronic structures as well as the spectroscopic and binding properties of HCCA to lanthanide (La(III), Ce(III), Nd(III), Pr(III), Sm(III), Eu(III), Tb(III)) [39,42,56,57] and transition metal ions (Ni(II), Co(II), Zn(II), Mn(II)) [54] were examined in details. Available X-ray data of HCCA [58] served as a good basis to test different ab initio (HF and MP2 methods) and DFT methods (using B3LYP, BHLYP, B3P86, B3PW91, PW91P86, MPW1PW91 functionals) in respect to geometry prediction and vibrational spectral simulation of coumarins [39]. The conformational analysis and energy calculations at DFT/B3LYP level showed that the lowest energy conformer coincides with the experimentally determined molecular structure. It is located in a plane and stabilized by intramolecular hydrogen bonding, estimated at ~5 kcal/mol (at B3LYP/6-31G(d) and it is larger by 1 kcal/mol as compared to MP2 energy) (Fig. 1(a)). Among the tested hybrid functionals, the BHLYP/6-31G(d) geometry parameters were in best agreement with the experimental ones (bond lengths and angle deviation is ~0.4 %), whereas PW91P86 best reproduced the experimental vibrational frequencies

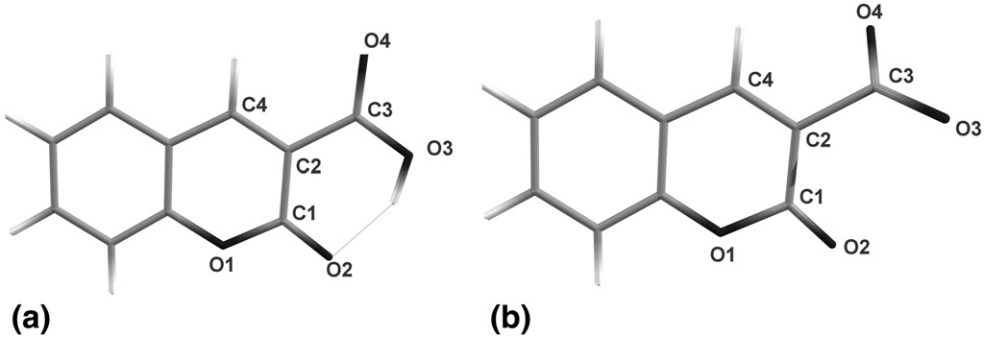

Fig. 1. Molecular structure of HCCA (a) and its deprotonated form CCA (b).